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A newborn female has a cardiac murmur. Before the cardiologist arrives to evaluate her, she has a seizure. Results of laboratory testing include a serum calcium level of 5.0 mg/dL (1.25 mmol/L). Subsequently, echocardiography reveals an aortic arch anomaly.

Of the following, the MOST appropriate test to obtain now is:

1	brainstem auditory evoked responses
2	electroencephalography
3	fluorescent in situ hybridization analysis of chromosome 22
4	peripheral blood chromosome analysis
5	thyroid function testing

You selected 1, the correct answer is 3.

The infant described in the vignette has a number of features of DiGeorge syndrome. DiGeorge syndrome results from abnormal cervical neural crest migration into the derivatives of the third and fourth pharyngeal arches and pouches during early embryogenesis. The pattern of malformations includes hypoplasia or aplasia of the thymus and parathyroid glands and structural abnormalities of the great vessels. The defects lead to the classic clinical manifestations of deficient cellular immunity due to T-cell dysfunction, causing increased susceptibility to infection; hypocalcemia due to absent parathyroid hormone, resulting in hypocalcemic seizures; and aortic arch abnormalities. Some affected infants also have facial dysmorphic features, which can include hypertelorism, short palpebral fissures, short philtrum, micrognathia, and ear abnormalities.

Most patients who have DiGeorge syndrome are found to have partial monosomy for the proximal long arm of chromosome 22 due to microdeletion of 22q11.2. This microdeletion can be detected by fluorescent in situ hybridization (FISH) using a molecular probe specific for the region. Although the deletion occasionally is evident on routine chromosome analysis, the FISH study is much more sensitive. Most cases represent de novo deletion events, although familial cases have been described.

The 22q11.2 deletion is associated with a variety of other phenotypes, including the Shprintzen syndrome (velocardiofacial syndrome), Takao syndrome, and isolated outflow tract defects of the heart (eg, tetralogy of Fallot, truncus arteriosus, interrupted aortic arch). In general, Takao syndrome is diagnosed when the patient primarily has cardiac disease, with normal T-cell and parathyroid function. Shprintzen syndrome denotes those patients who have the features of DiGeorge syndrome plus craniofacial and palatal abnormalities. Of interest, all three phenotypes can be evident in a single family in which a heritable chromosome 22 deletion is present. It has been suggested that this constellation of related syndromes that have the common etiologic factor of a chromosome 22 deletion should be termed CATCH22 for Cardiac abnormality, Abnormal facies, T-cell deficit, Cleft palate, and Hypocalcemia resulting from 22q11 deletion. In general, the diagnosis of DiGeorge syndrome requires a neonatal presentation of thymic hypoplasia and hypocalcemia; Shprintzen syndrome requires the presence of nasal speech due to palatal insufficiency.

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Please remember that you must answer all 10 of the questions in order to claim CME credit for this month.

Of the following, the disorder associated with the GREATEST risk for a similarly affected child in a future pregnancy is:

1	atrial septal defect
2	hypothyroidism
3	open neural tube defect
4	phenylketonuria
5	unilateral club foot

You selected 4, the correct answer is 4.

In general, single gene disorders, such as phenylketonuria (PKU), which are inherited as mendelian traits, have the highest recurrence for future pregnancies. The inheritance of PKU, which results from the deficiency of specific enzymatic activities, is autosomal recessive. Therefore, there is a 25% risk in each future pregnancy for a similarly affected child. All families who have a child affected by a single gene disorder should be referred for genetic evaluations and counseling to apprise them of their risks and to discuss options for future pregnancies. These include prenatal or preimplantation diagnosis, adoption, and the use of donor sperm or ova.

Atrial septal defects, clubfoot, and open neural tube defects each are inherited as multifactorial traits in which a combination of genetic and environmental factors contribute to the development of the defect. In general, multifactorial traits have a recurrence risk of 2% to 4% in future children. The risk is greater if one of the parents also has the defect, but it usually does not approach the risk conferred by a single gene defect (ie, 25% for recessive traits and 50% for dominant traits). Although rare autosomal recessive forms of hypothyroidism have been reported, this generally is considered a sporadic condition that has a low recurrence risk.

References:
Bennett RL. The Practical Guide to the Genetic Family History. New York, NY: Wiley-Liss; 1999:71-83
Robinson A, Linden MG, eds. Clinical Genetics Handbook. 2nd ed. Boston, Mass: Blackwell Scientific Publications; 1993
Vogel F, Motulsky AG. Human Genetics: Problems and Approaches. 3rd ed. New York, NY: Springer-Verlag; 1997

Content specification(s):
Recognize specific patterns of Mendelian inheritance
Know the incidence of various single-gene disorders

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The neonatologist is called by a pediatrician regarding a 2-week old boy being seen for a health supervision visit. This mother expresses concern about her son's poor feeding and small penis. On physical examination the pediatrician notes micropenis and hypotonia.

Of the following, the MOST likely diagnosis is:

1	Kallman syndrome
2 ✗	Klinefelter syndrome
3	Noonan syndrome
4	Prader-Willi syndrome
5	septo-optic dysplasia

You selected 2, the correct answer is 4.

The clinical presentation of hypotonia, poor feeding, and micropenis is most consistent with Prader-Willi syndrome (Figure 98A), which is associated with hypogonadotropic hypogonadism. Although affected infants are hypotonic and poor feeders, they develop morbid obesity during childhood. Short stature, small hands and feet, and hypogonadism are common. The diagnosis is confirmed by demonstration of a 15q11 deletion.

A penile length of less than 2 standard deviations below the mean for age is considered micropenis (Figure 98B). The mean penile length for a term infant is 3.5 cm. The etiologies of micropenis in the newborn period include decreased gonadotropin-releasing hormone and growth hormone stimulation of the testes and penis, primary gonadal failure in which lack of testosterone secretion results in poor penile growth, partial androgen insensitivity, and idiopathic or undiagnosed etiology.

Most newborns who have isolated micropenis have a hypothalamic-pituitary defect that results in hypogonadism. Many syndromes that present with micropenis can be difficult to diagnose in the neonate. They may present with hypoglycemia due to the associated deficiency of counterregulatory hormones or they may have a midline central nervous system defect (eg, Kallman syndrome, septo-optic dysplasia). Kallman syndrome is associated with anosmia, and septo-optic dysplasia is characterized by optic nerve hypoplasia and absence of the septum pellucidum. Abnormal hypothalamic-pituitary gonadal axis activity results in low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in Kallman syndrome, in contrast to the typical neonatal elevation.

In primary gonadal failure, the baseline FSH and LH levels may be elevated and accompanied by a poor testosterone response to human chorionic gonadotropin stimulation. Patients who have partial androgen insensitivity demonstrate poor penile growth response to testosterone stimulation.

The infant described in the vignette has hypotonia and poor feeding, which are not features of Kallman syndrome or septo-optic dysplasia. Klinefelter syndrome rarely is diagnosed before puberty and is characterized by increased height, behavior problems (such as immaturity, poor judgement), and small testes and penis. Typical symptoms of Noonan syndrome (Figure 98C) include short stature, webbing of the

neck, congenital heart disease, and cubitus valgus, but generally not micropenis.

References:
Danish RK, Lee PA, Mazur T, Amrhein JA, Migeon CJ. Micropenis. II. Hypogonadotropic hypogonadism. Johns Hopkins Med J. 1980; 146:177-184
Lee PA, Mazur T, Danish R, et al. Micropenis. I. Criteria, etiologies and classification. Johns Hopkins Med J. 1980;146:156-163
Lee PA, O'Dea LS. Primary and secondary testicular insufficiency. Pediatr Clin North Am. 1990;37:1359-1387

Content specification(s)
Know how to evaluate and manage an infant with micropenis

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Because deafness is not a major feature of DiGeorge syndrome, obtaining brainstem auditory evoked potentials is not indicated. The etiology of the seizure in the infant described in the vignette is hypocalcemia, and electroencephalography would not provide additional useful information for management, which should include administration of calcium. Hypothyroidism usually is not evident in the newborn period, and thyroid function is preserved in DiGeorge syndrome.

References:

Burn J. Closing time for CATCH22. J Med Genet. 1999;36:737-738

Burn J, Wilson DI, Cross I, et al. The clinical significance of 22q11 deletion. In: Clark EB, Markwald RR, Takao A, eds. Developmental Mechanisms of Heart Disease. Armonk, NY: Futura Publishing Co; 1995:559-567

DeSilva D, Duffty P, Booth P, Auchterlonie I, Morrison N, Dean JC. Family studies in chromosome 22q11 deletion: further demonstration of phenotypic heterogeneity. Clin Dysmorphol. 1995;4:294-303

Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet. 1997;34:798-804

Stevens CA, Carey JC, Shigeoka AO. DiGeorge anomaly and velocardiofacial syndrome. Pediatrics. 1990;85:526-530

Content Specification(s):

Understand the indications and limitations of molecular cytogenetic studies (eg FISH), specifically in the diagnosis of aneuploidy and microdeletion

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A female newborn, delivered by emergent cesarean section to a primiparous woman, has hydrops, respiratory distress, and a large umbilical cord. The estimated gestational age at birth is 32 weeks, based on maternal dates and early ultrasonographic confirmation. The size of the infant is consistent with a 37-weeks' gestation infant. The pregnancy was complicated by polyhydramnios and fetal hydrops during the last 4 weeks prior to delivery. Maternal testing, including amniotic fluid analysis for viral infection and karyotype, failed to reveal a cause for the fetal hydrops. Prenatal screening for diabetes had normal results. At birth, the infant requires high-frequency ventilatory support and supplemental oxygen. Physical examination reveals anasarca with a disproportionately large abdomen and an umbilical cord that is 2 cm in diameter. Other physical findings include a prominent tongue, disparity in the length and circumference between the right and left extremities, and generalized hypotonia, but no neck masses or creases on ear lobes. The hematocrit is 68% (0.68), and blood glucose concentrations are normal. Chest radiography reveals large pleural effusions. During placement of an umbilical arterial catheter, leakage of approximately 30 mL of clear yellow fluid prompts cessation of the procedure. The umbilical defect is closed surgically. Findings on head ultrasonography, echocardiography, and electrocardiography are normal. Abdominal ultrasonography reveals a moderate amount of ascites, a 2 × 4-cm gallbladder, normal liver anatomy, a 4.5-cm right kidney that has normal anatomy, a 6.1-cm left kidney that has a duplex collecting system, and normal pelvic structures.

Of the following, the complication MOST associated with the syndrome affecting this infant that requires frequent evaluations through early childhood is

1	hypoglycemia
2	polycythemia
3	premature menarche
4	short stature
5	Wilms tumor

You selected 1, the correct answer is 5.

The infant described in the vignette has clinical features characteristic of Beckwith-Wiedemann syndrome. The typical features of Beckwith-Wiedemann syndrome include macroglossia, omphalocele, macrosomia, and ear creases. Additional features that are present in the infant in the vignette are macroglossia, large kidneys, prematurity, hypotonia, polycythemia, hemihypertrophy, renal anomalies, and nonimmune hydrops. Linear fissures in the ear lobes are a unique feature of this syndrome, but they were not present in this case. Adrenomegaly, hepatomegaly, nevus flammeus of the middle forehead, and hypoglycemia, which occur in more than 50% of affected neonates, also are absent in this infant.

The incidence of Beckwith-Wiedmann syndrome is estimated at 1 in 15,000 live births. Most cases are sporadic, but the mode of inheritance is complex. Possible patterns of inheritance include autosomal dominant inheritance with variable expressivity, contiguous gene duplication at 11p15, and genomic imprinting resulting from a defective or absent copy of the maternally derived gene.

Children who have Beckwith-Wiedemann syndrome have a 5% to 7% risk of

developing cancer, primarily Wilms tumors. These tumors generally develop before the age of 4 years, although ultrasonographic screening is recommended through age 7 years and may be recommended as frequently as every 3 months. Ultrasonographic screening may detect nonmalignant renal abnormalities in 25% of patients, including medullary renal cysts, caliceal diverticula, hydronephrosis, and nephrolithiasis. It is important to distinguish these nonmalignant abnormalities to avoid unnecessary nephrectomy.

Other tumors, including neuroblastoma and hepatoblastoma, also occur with increased frequency in children who have Beckwith-Wiedemann syndrome. Periodic chest radiographs for thoracic neuroblastoma and alpha-fetoprotein measurements at 6-week intervals for hepatoblastoma are recommended. Alpha-fetoprotein concentrations normally are high at birth, declining gradually during the next 10 to 11 months. If concentrations do not decline, further diagnostic testing (liver ultrasonography, computed tomography, magnetic resonance imaging) should be considered. Alpha-fetoprotein concentrations may remain elevated in patients who have Beckwith-Wiedemann syndrome without tumor development, leading some authors to recommend use of values specific for this population to determine cancer risk. Tumor risk appears to be higher in patients who have hemihypertrophy and large kidneys.

Although severe hypoglycemia affects about 33% of neonates who have Beckwith-Wiedemann syndrome, this metabolic abnormality usually resolves during the first postnatal days. Because untreated hypoglycemia may have neurologic consequences, serial screening is recommended. Some patients who have Beckwith-Wiedemann syndrome may require frequent feedings or diazoxide to avoid hypoglycemia. Therefore, some authors recommend that patients demonstrate the ability to maintain euglycemia during an age-appropriate fast.

Polycythemia is reported during the immediate neonatal period in infants who have Beckwith-Wiedemann syndrome, but this is not a persistent finding that warrants extended screening.

Neither premature menarche nor any other abnormality in pubertal development occurs with Beckwith-Wiedemann syndrome. Growth and bone maturation is accelerated in affected children until age 4 to 6 years and normalizes thereafter. At puberty, many children have a height that is greater than the 90th percentile for age. Short stature is not a characteristic of this disorder.

References:

Beckwith-Wiedemann syndrome. *Online Mendelian Inheritance in Man*. #130650.

Ferry RJ, DeBaun MR. Beckwith-Wiedemann syndrome.

Jones KL. Beckwith-Wiedemann syndrome. In: ***Smith's Recognizable Patterns of Human Malformation***. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997:164-167

Content Specification(s):

2368. Recognize the clinical features of Beckwith-Wiedemann Syndrome

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An infant born at 37 weeks' gestation is referred to you for evaluation of severe hypotonia. He was born to a 19-year-old primigravida following a pregnancy that was complicated by breech presentation. No concern about fetal movement was voiced. Cesarean delivery was required because of failure to progress. At birth, the infant was floppy but had no cardiopulmonary distress. During an attempt to feed from a bottle, the formula rolled out the side of infant's mouth, and he failed to swallow. On physical examination, you note severe hypotonia, silver blond hair, narrow bifrontal diameter, almond-shaped palpebral fissures, thin upper lip, small hands and feet, micropenis, and bilateral cryptorchidism. No omphalocele, high forehead, downslanting palpebral fissues, flat facies or occiput, single transverse palmer crease, contractures, seizures, or skin lesions are present, although the skin is fair and the right hip is dislocated. Both parents are healthy and participate actively in a variety of athletic activities.

Of the following, the evaluation that is MOST likely to determine the diagnosis in this infant is

1	electromyography
2	fluorescent in situ hybridization probe
3	magnetic resonance imaging of the brain
4	muscle biopsy
✗ 5	routine karyotype

You selected 5, the correct answer is 2.

The infant described in the vignette has clinical findings characteristic of Prader-Willi syndrome, including severe hypotonia. Among the diagnostic clues are silver or blond hair, relatively small hands and feet, small penis, and cryptorchidism. Narrow bifrontal diameter, almond-shaped palpebral fissures, and thin upper lip with hypotonia also are suggestive of Prader-Willi syndrome. The natural history for this disorder is failure to thrive that transitions to overeating and obesity during early childhood. Hypotonia and poor feeding improve with age. Mild-to-moderate mental retardation; behavioral problems with stubbornness, rage, perseverance; and hypogonadism may accompany the disorder. A reduced life expectancy because of morbid obesity also complicates Prader-Willi syndrome. The condition is diagnosed with fluorescence in situ hybridization probes or high-resolution chromosome analysis to detect the absence of the paternally contributed Prader-Willi Syndrome/Angelman Syndrome (PWS/AS) region on chromosome 15 q11.2-q13. Such testing detects more than 99% of patients.

Uniparental disomy is the inheritance of two chromosomes from the same parent. This pattern explains the basis for syndromes demonstrating "genomic imprinting" or differential contribution of maternal and paternal alleles to an offspring. Hydatidiform moles are placental tumors derived from two paternal sets of chromosomes. Prader-Willi syndrome is due to genomic imprinting. Most cases have a paternally derived cytogenetic deletion of chromosome 15 {del (15) (q11-q13)}. Approximately 25% of affected patients have both copies of chromosome 15 containing a small deletion (15 q11-13) derived from their fathers. Uniparental disomy also has been implicated in some cases of Beckwith-Wiedemann syndrome, Russell-Silver syndrome, neonatal diabetes, and unexplained developmental delay.

Muscle biopsy, electromyography, magnetic resonance imaging of the brain, and karyotype may be indicated to evaluate for the numerous causes of neonatal hypotonia (eg, myopathies, spinal muscular atrophy, congenital myotonic dystrophy, myasthenia syndromes, central nervous system structural abnormalities, chromosomal disorders). However, the combination of hypotonia, blond hair, small genitalia, and small hands and feet reported for the infant in the vignette suggests Prader-Willi syndrome as the possible diagnosis.

References:

Baraitser M, Winter RM.: ***Color Atlas of Congenital Malformation Syndromes***. London, England: Mosby-Wolfe; 1997:160

Cassady SB, Schwartz S. Prader-Willi Syndrome. In Gene Tests @ **www.geneclinics.org/profiles/pws**. (9/15/2004)

Jones KL. Genetics, genetic counseling, and prevention. In: ***Smith's Recognizable Patterns of Human Malformation***. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997:706-726

Sarnat HB. Neuromuscular disorders. In: Behrman RE, Kliegman RM, Jenson HB, eds. ***Nelson Textbook of Pediatrics***. 17th ed. Philadelphia, Pa: Saunders; 2004:2060-2076

Schwartz S, Dickerman LH. Genetic aspects of perinatal disease and prenatal diagnosis. In: Fanaroff AA, Martin RJ, eds. ***Neonatal-Perinatal Medicine, Diseases of the Fetus and Newborn***. 7th ed. St. Louis, Mo: Mosby; 2002:80-108

Content Specification:

Understand the differential diagnosis, management and outcomes of neonatal hypotonia

Understand the etiology, molecular phenotype, and clinical manifestations of disorders associated with genomic imprinting, such as Prader-Willi syndrome

Understand the etiology, molecular phenotype, and clinical manifestations of disorders associated with uniparental disomy

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You are called to the delivery room for emergency management of a term infant who suffered intrauterine growth restriction and is experiencing severe respiratory distress. After stabilizing the infant with mechanical ventilation, oxygen, and thoracostomy tube placement for bilateral pneumothoraces, you notice multiple abnormal physical features. These include a 3x4 cm occipital encephalocele, flattened nose, cleft palate, microphthalmia, small thorax, large bilateral flank masses (5x9 cm), single umbilical artery, polydactyly, and bilateral club feet. Facial symmetry, ears, genitalia, and lips appear normal, as are the results of cardiac examination.

Of the following, the MOST likely diagnosis is:

1	amniotic rupture sequence
2	Meckel-Gruber syndrome
3	oculo-auriculo-vertebral anomalad
4	Potter syndrome
5	trisomy 13

You selected 4, the correct answer is 2.

Meckel-Gruber syndrome is distinguished classically by the triad of encephalocele, polydactyly, and cystic dysplasia of the kidneys. In addition, there are frequently associated anomalies of growth, central nervous system, face, neck, limbs , kidney, liver , and genitalia (Table 1). There is marked heterogeneity of the clinical presentation, as seen with the infant described in the vignette. The condition appears to be inherited via an autosomal recessive pattern, with no expression in carriers. The genetic locus for Meckel-Gruber syndrome is found at 17q21-q24. Death within days to weeks is expected due to abnormalities of the central nervous system and kidneys or occasionally to pulmonary hypoplasia.

Amnion rupture sequence is a disruption sequence in which structural defects are caused by strands of amnion attaching to or encircling body structures, especially limbs. This sequence results in an inconsistent variety of annular constrictions, amputations, pseudosyndactyly, edema, hemorrhage, and resorption necrosis of tissues. Oligohydramnios may occur due to constriction of the umbilical cord and result in deformational defects caused by limited movement, as found in Potter syndrome. Encephalocele, polydactyly, and cystic renal disease are not present in the amnion rupture sequence. Although unknown, the cause of amnion rupture sequence is speculated to be a vascular disruption that affects the embryonic blood supply or intrauterine constraint that impairs ventral folding of the embryo at 4 to 6 weeks' gestation. Adhesion of amnion to necrotic tissues results in adhesive bands that may appear similar to amniotic bands. The recurrence risk probably is negligible.

Similar limb defects to those seen with the amnion rupture sequence are found in the limb-body wall complex, which also is characterized by thoraco- or abdominoschisis, exencephaly, anterior encephalocele, and facial clefts of the mouth and nares. There are additional congenital anomalies of most internal organs and limbs. Occipital encephalocele, polydactyly, and cystic renal disease are not present.

Oculo-auriculo-vertebral sequence (Goldenhar syndrome, hemifacial microsomia, first and second branchial arch syndrome, facio-auriculo-vertebral spectrum) is a nonrandom association of anomalies due to abnormal morphogenesis of the structures developing from the first and second branchial arches. Occasionally it is associated with vertebral or ocular abnormalities. The most common findings include abnormalities of the face , ear , mouth, eye, and vertebra (**Table 2**). Occipital encephalocele, multicystic dysplastic kidneys, cleft palate, prenatal growth deficiency, and other anomalies are seen occasionally. Polydactyly is not found. Most affected patients have normal intelligence. The occurrence is sporadic and the cause is unknown. The recurrence rate in first-degree relatives is about 2%.

Potter syndrome (oligohydramnios sequence) presents most frequently with physical signs of deformation and compression due to oligohydramnios (abnormal position of hands and feet, compressed nasal bridge, downslanting crease below the eyes, low-set ears) and respiratory failure due to pulmonary hypoplasia. Encephalocele and polydactyly are unusual in Potter syndrome.. The underlying cause is reduced volume of amniotic fluid due to diminished fetal urine production; this is often associated with renal agenesis. Renal agenesis may be a primary defect or associated with more extensive anomalies of the caudal axis. Other causes of severe oligohydramnios, such as urinary tract obstruction, polycystic kidneys, and chronic leakage of amniotic fluid beginning in mid-gestation, may present with similar findings. Unknown renal lesions may be found in first-degree relatives if the oligohydramnios is due to renal agenesis or dysgenesis of both kidneys.

Trisomy 13 frequently involves defects of the eye, nose, lip, and forebrain (holoprosencephaly); polydactyly; narrow, hyperconvex fingernails; and cutis aplasia of the scalp in the parieto-occipital area. These defects typically manifest as cleft lip and palate, microcephaly, scalp defects, microphthalmia, hypotelorism, postaxial polydactyly, rocker-bottom feet, forehead hemangiomata, and genital abnormalities. Frequently associated anomalies affect the central nervous system, hearing, cranium, eyes, mouth, ears, skin, extremities, cardiac system, genitalia, and blood system (**Table 3**). Encephalocele is not typical, although polydactyly and cystic kidney disease are relatively common. Death usually occurs by 1 month after birth, with most infants dying within days of birth and only occasionally not until several years of age.

The most common genetic finding in trisomy 13 is the presence of three copies of the chromosome 13. Some cases of trisomy 13 result from balanced translocations present in one of the parents. The risk of recurrence after the birth of one affected child who has classic trisomy 13 is about 1%. Trisomy 13 mosaicism and partial trisomy for the proximal segment (13pter->q14) present with less severe physical and developmental disabilities. Partial trisomy for the distal segment (13q14->qter), however, is associated with severe mental deficiency and characteristic facies.

References:

Baraitser M, Winter RM. ***Color Atlas of Congenital Malformation Syndromes***. London, England: Mosby-Wolfe; 1996

Jones KL. ***Smith's Recognizable Patterns of Human Malformation***. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997

Content Specification(s):

Recognize the clinical features associated with autosomal recessive disorders.

Recognize the clinical findings and chromosomal pattern in trisomy 13.

Recognize the consequences of the amniotic band syndrome.

Recognize dysmorphic syndromes associated with hearing loss such as Waardenburg and Goldenhar syndromes.

Recognize the clinical manifestations of anatomic abnormalities of the urinary tract in infants.

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Table 1

Table 1. Associated Anomalies With Meckel-Gruber Syndrome

Affected Parameter	Findings
Growth	Variable prenatal growth deficiency
Central nervous system	Occipital encephalocele Microcephaly Cerebral and cerebellar hypoplasia Anencephaly Hydrocephaly Arnold-Chiari malformation Absence of olfactory lobes and tract Absence of corpus callosum and septum pellucidum
Face	Microphthalmia Cleft palate Micrognathia Ear anomalies
Neck	Short
Limbs	Polydactyly Club feet
Kidney	Dysplasia with variable cyst formation
Liver	Bile duct proliferation Fibrosis Cysts
Genitalia	Cryptorchidism Incomplete development of external and/or internal genitalia

Close

Table 2. Common Abnormalities Associated With Oculo-auriculo-vertebral Sequence

Affected System	Anomaly
Face	Malar, maxillary, or mandibular hypoplasia Macrostomia Facial muscle hypoplasia
Ear	Microtia Preauricular tags and pits Middle ear anomaly Deafness
Mouth	Parotid gland hypoplasia Tongue anomalies Malfunction of soft palate
Eye	Microphthalmia Epibulbar dermoid Notch in upper lid
Vertebra	Hemivertebrae, especially cervical

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Table 3. Common Associated Anomalies With Potter Syndrome

Affected System	Anomaly
Central nervous system	Holoprosencephaly Variable development of the forebrain and olfactory and optic tissues Hypsarrhythmia Apnea Severe mental deficiency)
Hearing	Deafness
Cranium	Microcephaly Split sagittal suture Large fontanelles
Eyes	Microphthalmia Colobamata Retinal dysplasia
Mouth	Cleft lip Cleft palate
Ears	Abnormal, low-set
Skin	Capillary hemangiomata, especially on the forehead Cutis aplasia of scalp Loose nuchal skin
Extremities	Distal palmar axial triradii Simian crease Hyperconvex narrow fingernails Flexion of fingers with or without overlapping and camptodactyly Polydactyly of hands and sometimes feet Rocker-bottom feet Thin ribs Pelvis hypoplasia
Cardiac system	Ventricular septal defect Patent ductus arteriosus Auricular septal defect Dextroposition
Genitalia	Cryptorchidism Bicornuate uterus
Blood system	Increased number of nuclear projections in neutrophils

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A newborn female has an open neural tube defect, low-set ears, ventricular septal defect, and rib and vertebral column malformations.

Of the following, the MOST likely maternal condition that was present during this pregnancy is:

1	alcoholism
2	diabetes mellitus
3	hypothyroidism
4	iodine deficiency
5	syphilis

You selected 1, the correct answer is 2.

Maternal diabetes mellitus can have profound effects on the development and health of the fetus. The severity of the maternal disease and the subsequent fetal effects can vary considerably. Because the maternal diabetic state can be present from the time of conception, early prenatal effects can result in malformations, growth deficiency, and stillbirth. There is a threefold increase in malformations among offspring of diabetic mothers; the incidence is correlated with the severity and level of control of the maternal illness. The most common defects involve the heart, central nervous system, kidneys, and skeleton, as described for the infant in the vignette. Of the cardiac defects, ventricular septal defect, transposition of the great vessels, and dextrocardia are most common. Central nervous system defects can range from **anencephaly** or **holoprosencephaly** to **spina bifida** and hydrocephalus. Malformations of the lower spine also occur and are termed the caudal regression syndrome. The spine may be segmented defectively or terminate in the sacral or lumbar region, resulting in abnormal neurologic function below the level of the defect. Rib defects also may be seen. Although many types of malformations can occur in infants of diabetic mothers, holoprosencephaly and the caudal regression syndrome are characteristic.

Infants of diabetic mothers also may present in the newborn period with macrosomia due to hyperinsulinemia and excessive glucose availability. The macrosomia affects both linear growth and weight. Alternatively, if the diabetic mother has substantial vascular disease, fetal growth can be impaired, resulting in growth retardation. Other complications in infants of diabetic mothers can include hyperbilirubinemia, hypoglycemia, vascular thromboses, respiratory distress, and birth injury due to macrosomia.

Fetal alcohol syndrome is characterized by prenatal growth deficiency, microcephaly, and cardiac defects. Neural tube and vertebral column defects are not common features. Maternal hypothyroidism has little effect on the fetus, which produces its own thyroid hormone; women who have untreated hypothyroidism have been reported to give birth to normal offspring. Maternal iodine deficiency can cause fetal deficiency of the mineral, which results in **goiter**, signs of cretinism, retarded bone growth, constipation, umbilical hernia, and mottling in the newborn. Prompt treatment with iodine is necessary to prevent mental retardation. Maternal syphilis can affect the fetal skin, mucous membranes, liver, central nervous system, and bones. Cardiac anomalies and open neural tube defects are not common features.

References:

Schwartz R, Teramo KA. Effects of diabetic pregnancy on the fetus and newborn. Semin Perinatol. 2000;24:120-135

Stevenson RE, Hall JG, Goodman RM. Human Malformations and Related Anomalies. New York, NY: Oxford University Press; 1993:137-162. New York, NY: Oxford University Press; 1993:137-162

Content Specification(s):

Know the effect of diabetes mellitus and its treatment on the fetus.

Know the effects on the fetus of maternal substance abuse, including alcohol, smoking, and drugs of abuse.

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A newborn has multiple congenital anomalies, including coloboma of the iris, tetralogy of Fallot, choanal atresia, and dysplastic ears. The pregnancy history is unremarkable. Results of chromosome analysis are normal, and fluorescence in situ hybridization (FISH) evaluation results are negative for a 22q11 deletion.

Of the following, the MOST plausible diagnosis for this infant is:

1	CHARGE association
2	Cornelia de Lange syndrome
3	Noonan syndrome
4	VATER association
5	Williams syndrome

You selected 2, the correct answer is 1.

Recognizable patterns of malformation may be classified broadly into syndromes, sequences, and associations. Syndromes typically have a common cause, whereas associations have multiple potential causes. Sequences represent a cascade of effects stemming from a single abnormality. Associations may be more appropriately designated as descriptors rather than as diagnoses. For any given association, it is important to know what criteria must be met to assign a particular label.

The newborn described in the vignette is most likely to have **CHARGE association**. In this acronym, C = coloboma, H = heart defect, A = atresia choanae, R = retardation of growth (postnatal) and development, G = genital anomalies, and E = ear anomalies. Affected individuals must have at least four of the six features, with at least one being coloboma or atresia choanae, which this newborn does. Because there are many possible causes of this association, prenatal exposures, chromosome anomalies, and appropriate submicroscopic deletion syndromes must be investigated.

Cornelia de Lange syndrome, **Noonan syndrome**, VATER association, and **Williams syndrome** are not associated with iris coloboma or choanal atresia.

References:
Gorlin RJ, Cohen MM Jr, Hennekam RCM, et al. CHARGE association and Hall-Hittner syndrome. In: ***Syndromes of the Head and Neck***. 4th ed. New York, NY: Oxford University Press; 2001:1135-1137
Jones KL. Introduction. In: ***Smith's Recognizable Patterns of Human Malformation***. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997:1-7

Content Specification(s):
Recognize the clinical features of syndromes, such as Waardenburg, Treacher Collins, Cornelia de Lange, Mobius, Vater, Rubenstein-Taybi, Beckwith, etc

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A 4-day-old infant had an uncomplicated delivery by elective cesarean section. Tachypnea and mild cyanosis are noted on discharge examination. The second heart sound is single, and precordial activity is increased. There is no murmur. Pulse oximetry documents a saturation of 85% in room air.

Of the following, the MOST likely diagnosis is:

1	hypoplastic left heart syndrome
2	pulmonary atresia with intact ventricular septum
3	tetralogy of Fallot
4	total anomalous pulmonary venous connection
5	transposition of the great arteries

You selected 5, the correct answer is 1.

The **hypoplastic left heart** syndrome often presents with tachypnea in the first few days of life. Pulmonary overcirculation at the expense of systemic circulation is present even while the ductus arteriosus is still patent. As pulmonary vascular resistance decreases in the first days and weeks of life, more of the output of the right ventricle is diverted to the pulmonary arteries rather than to the systemic circulation via the patent ductus. Excessive pulmonary blood flow not only contributes to symptomatic pulmonary edema, but it results in far more pulmonary venous return to the heart than systemic venous blood return. This large pulmonary venous blood return crosses the normal patent foramen ovale and is received by the right ventricle.

Consequently, the right ventricle can deliver a high saturation of blood to both the aorta (via the open ductus) and to the pulmonary arteries. In fact, many infants who have hypoplastic left heart syndrome do not have visible cyanosis. A single loud second heart sound and increased right ventricular precordial activity, as noted for the infant in the vignette, reflect the high pressure in the right ventricle and main pulmonary artery, which supply both systemic and pulmonary circulations. The relatively high room air oxygen saturation for cyanotic congenital heart disease coupled with the findings of tachypnea and a single second heart sound reported for the infant are most consistent with the diagnosis of hypoplastic left heart syndrome.

In infants who have **pulmonary atresia** with intact ventricular septum, there is a single second heart sound because the aortic valve is the only semilunar valve that is patent. Blood flow to the pulmonary arteries is sustained by the ductus arteriosus, which often does not produce any cardiac murmur in the neonate because of a low pressure difference between the aorta and pulmonary arteries. Although the pulmonary vascular resistance remains relatively elevated, it is unlikely that pulmonary blood flow will be so high as to cause serious tachypnea due to pulmonary overcirculation. For the same reason, it is unlikely for the room air saturation to be as high as reported in the vignette if the diagnosis is pulmonary atresia. In some cases of an extremely large patent ductus and rapidly decreasing pulmonary vascular resistance, excessive pulmonary blood flow is possible with this lesion, but that is exceptional.

In newborns who have **tetralogy of Fallot**, cyanosis can be minimal or absent if the degree of pulmonary stenosis is not critical. Therefore, room air oximetry readings above 85% are not unusual. In fact, normal oxygen saturations are common. However, this finding is accompanied by a prominent systolic ejection murmur within the first few hours of life due to the normal pulmonary blood flow across the moderate or even moderately severe pulmonic stenosis. The clinical signs of tetralogy of Fallot with pulmonary atresia are similar to those seen with pulmonic atresia with intact ventricular septum. In some cases, there is excessive pulmonary blood flow due to large collateral vessels arising from the aorta and supplying the pulmonary circulation. However, when oxygen saturation is normal or near-normal, continuous murmurs of flow through the multiple aortopulmonary collateral vessels usually can be appreciated.

Total anomalous pulmonary venous connection results in return of the pulmonary circulation to the right side of the heart. A patent foramen ovale must be present to allow some shunting of mixed oxygenated and desaturated blood to the left side of the heart and supply the systemic circulation. If the pulmonary venous return is not obstructed (commonly supracardial return to the innominate vein), the oxygen saturation can be high and cyanosis may not be apparent or may be mild. However, the volume overload of the right ventricle produced by the return of the systemic and pulmonary circulations results in delayed closure of the pulmonary valve and, therefore, a widely split or fixedly split second heart sound.

Transposition of the great arteries is associated with a single second heart sound on clinical examination because the pulmonic closure sound is obscured by the loud aortic closure sound from the systemic pressure aorta arising from the right ventricle and overlying the pulmonary artery arising from the left ventricle. The systemic pressure right ventricle also is responsible for increased precordial activity in affected newborns. However, unless patency of a very large ductus arteriosus persists in the presence of a very large atrial septal defect, severe and obvious cyanosis generally presents in the first hours of life.

References:

Bernstein D. Hypoplastic left heart syndrome. In: Behrman RE, Kliegman RM, Jenson HB, eds. ***Nelson Textbook of Pediatrics***. 16th ed. Philadelphia, Pa: WB Saunders Co; 2000:1402-1403

Rosenthal A. Hypoplastic left heart syndrome. In: Moller JH, Hoffman JIE, eds. ***Pediatric Cardiovascular Medicine***. Philadelphia, Pa: Churchill Livingstone; 2000:594-598

Content Specification(s):

Understand the pathophysiology, recognize the clinical, laboratory, and radiographic features, and formulate a differential diagnosis of a cyanotic neonate

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On physical examination of a female infant, you note that she has a short neck, low hairline, limited movement of the head, and facial asymmetry. Neck radiographs reveal fusion of the cervical vertebrae.

Of the following, the MOST likely etiology of the infant's abnormalities is:

1	CHARGE association
2	Klippel-Feil sequence
3	Noonan syndrome
4	trisomy 13
5	Turner syndrome

You selected 5, the correct answer is 2.

Klippel-Feil is a malformation sequence characterized by fusion of cervical vertebrae that also may be accompanied by hemivertebrae. The vertebral fusion may result in webbed neck, torticollis, and facial asymmetry. In some instances, Klippel-Feil occurs as part of a more serious abnormality in neural tube development, such as cervical myelomeningocele. In these cases, associated neurologic deficits also will be evident, including paraplegia or hemiplegia and cranial or cerebral nerve palsies. The disorder occurs more commonly in females, but can affect both genders. Other associated abnormalities can include deafness in up to 30% of affected individuals, congenital heart defects, mental deficiency, cleft palate, posterior fossa dermoid cysts, scoliosis, and renal abnormalities. Therefore, affected infants must be evaluated carefully for these associated defects via audiologic evaluation, echocardiography, and renal ultrasonography. In addition, lateral flexion-extension radiographs must be obtained to identify patients who have hypermobility of the upper cervical segment and are at risk for developing neurologic impairment. If hypermobility is present, the child should be evaluated annually and avoid contact sports. Usually Klippel-Feil is a sporadic occurrence, although rare families have been described in which there was an autosomal dominant form with variable expression.

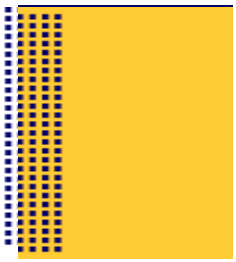
CHARGE association is characterized by Coloboma, Heart defects, Atresia choanae, Retarded growth, central nervous system anomalies, Genital anomalies, and Ear abnormalities. Although features of both Noonan syndrome and Turner syndrome can include a low hairline and short neck, neither is associated with fused vertebrae or facial asymmetry. Infants who have trisomy 13 present in the newborn period with defects of the forebrain, which can include holoprosencephaly, microcephaly, polydactyly, and clefting.

References:

Gunderson CH, Greenspan RH, Glaser GH, Lubs HA. The Klippel-Feil syndrome: genetic and clinical reevaluation of cervical fusion. Medicine. 1967;46:491-512

Jones KL. Smith's Recognizable Patterns of Human Malformation. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997:618

McGaughran JM, Kuna P, Das V. Audiological abnormalities in the Klippel-Feil syndrome. Arch Dis Child. 1998;79:352-355



Content Specification(s):
Recognize the clinical features and know how to manage craniofacial anomalies

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Please remember that you must answer all 10 of the questions in order to claim CME credit for this month.

A newborn male has multiple congenital anomalies, including bilateral clubfeet, amputation of the fourth and fifth digits on the right hand, and distal syndactyly of the third and fourth digits on the left hand.

Of the following, the MOST likely etiology of these birth defects is:

1	amniotic bands
2	fetal hydantoin syndrome
3	fetal varicella effects
4	maternal hyperthermia
5	trisomy 13

You selected 5, the correct answer is 1.

Rupture of the amnion is associated with a number of structural defects that result from mechanical compression of the developing fetus. Specifically, strands of ruptured amnion can entrap developing limbs, leading to intrauterine amputations and syndactyly, which typically are asymmetric. The amniotic bands also can act as tethers that restrict fetal movement and result in lower limb deformities, such as clubfoot. Accordingly, the anomalies described for the infant in the vignette, including bilateral clubfeet, amputation of the digits, and syndactyly, are most likely due to amniotic bands. The diagnosis can be confirmed by examination of the placenta.

Most infants who have amnion rupture sequence have no internal anomalies. In a small number of affected infants, chronic leakage of amniotic fluid may lead to oligohydramnios and failure of the lungs to develop normally. For most of these infants, the prognosis for postnatal lung development is good, and aggressive therapy should be pursued to provide adequate oxygenation.

In the past, the amnion rupture sequence was believed to be associated with encephaloceles, facial clefting, gastroschisis, and thoracic defects. However, this pattern of defects now is referred to as the limb-body wall complex, which results from persistence of the extraembryonic coelom during fetal life. Limb defects similar to the amnion rupture sequence may be seen, but they usually are accompanied by more severe structural defects of the chest and abdomen and by anomalies of the internal organs.

Fetal hydantoin syndrome is characterized by moderate growth deficiency, mental deficiency, and a typical facies. Limb abnormalities also have been reported, but they usually involve hypoplasia of the distal phalanges, a digitalized thumb, and hip dislocation, rather than amputations and syndactyly. Maternal varicella infection in the first trimester can result in limb hypoplasia and severe skin changes, including scarring, but amputation and syndactyly are not characteristic. Maternal hyperthermia (>40°C [>104°F]) has been reported to be associated with a variety of structural abnormalities in the fetus, including neural tube defects, microcephaly, and clefting, but not with syndactyly or amputations. Trisomy 13 is characterized by

severe central nervous system abnormalities, clefting, cardiac defects, and polydactyly.

References:
Jones KL. Smith's Recognizable Patterns of Human Malformation. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997

Moerman P, Fryns JP, Vandenberghe K, Lauweryns JM. Constrictive amniotic bands, amniotic adhesions, and limb-body wall complex: discrete disruption sequences with pathogenetic overlap. Am J Med Genet. 1992;42:470-479

Content Specification(s):
Recognize the consequences of the amniotic band syndrome
Know the effect of maternal nervous system diseases, including seizures, and their treatment on the fetus

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A female infant is born with unilateral cleft lip and palate. Findings on the remainder of the physical examination are normal, and you inform the parents that this apparently is an isolated birth defect.

During counseling of the family about their risk for having another similarly affected child, the statement that you are MOST likely to include is that

1	because the defect is isolated, their risk is no greater than that of any other couple
2	cleft lip and palate is a multifactorial trait that has a 4% risk of recurrence
3	the recurrence risk can be estimated only after a chromosome analysis has been obtained
4	the risk is increased for future females, but not males
5	the risk would be increased only if one of the parents had cleft lip and palate

You selected 1, the correct answer is 2.

Isolated cleft lip and palate is inherited as a multifactorial trait that is due to the interaction of genetic and environmental factors. Multifactorial inheritance commonly refers to traits that occur with greater frequency among individuals in a particular family than they do in the general population, but at a lower rate than would be expected for single gene traits. Recurrence risk for multifactorial traits have been derived by analysis of many families that express the trait. For cleft lip and palate, the recurrence risks for a family in which neither parent is affected and there is one affected child is approximately 4% in the next pregnancy.

In general, disorders that are inherited as multifactorial traits include most of the common **birth defects** as well as many adult-onset diseases. For most multifactorial birth defects, the recurrence risks for parents who have had one affected child ranges from 2% to 5%, although some traits are associated with higher risks (eg, 10% for hypospadias). Risks may be modified based on other characteristics, such as the severity of the defect, the gender of the affected individual, and the number of affected individuals in the family. For example, unilateral cleft lip has a recurrence risk of 4%, while bilateral cleft lip has a risk of 6%. Similarly, it has been noted that some defects have a gender predilection, including Hirschsprung disease and pyloric stenosis, which appear more commonly in males, and hip dislocation, which is more common among females. In families in which one of these defects has occurred, the risk to future offspring is greater if the original affected child is of the less commonly affected gender. Estimation of recurrence risks also requires that information be obtained about the extended family to determine if there are other similarly affected individuals, particularly first-degree relatives. The risk will be lowest in families in whom a single individual is affected, whereas families that include multiple affected individuals will have a higher risk. For example, the recurrence risk for subsequent siblings of a child who has clubfoot is 3%. However, if one parent also had clubfoot, the risk increases to 10%.

To provide the most accurate information about recurrence risk to families, all children who have birth defects should be examined carefully for the presence of other abnormalities. The possibility that the most obvious defect actually is part of a genetic syndrome, which may carry a higher risk, must be considered in all cases.

For example, cleft lip is the most obvious feature of van der Woude syndrome, which also includes lip pits and the possible absence of central incisors. This disorder is transmitted as an autosomal dominant trait, with a 50% recurrence risk. Thus, families who have this genetic syndrome would be at much higher risk for recurrence, and the parents should be examined if this disorder is suspected.

Alternatively, some birth defects can occur following exposure to a teratogen, in which case the recurrence risk in future pregnancies would not be increased if the teratogen is avoided (eg, cleft lip and palate in fetuses exposed to phenytoin).

In general, chromosome analysis should be obtained in infants and children who have two or more major abnormalities (eg, clefting, congenital heart disease) or one major anomaly and two or three minor defects (eg, epicanthal folds, simian line). Accordingly, chromosome analysis would not be indicated for the infant described in the vignette, who has an isolated cleft lip and palate.

References:

Rimoin DL, Connor JM, Pyeritz RE, eds. Emery and Rimoin's Principles and Practice of Medical Genetics. 3rd ed. New York, NY: Churchill Livingstone; 1997

Seashore MR, Wappner RS. Genetics in Primary Care & Clinical Medicine. Stamford, Conn: Appleton & Lange; 1996

Toomey KE. Medical genetics for the practitioner. Pediatr Rev. 1996;17:163-174

Content Specification(s):

Understand the incidence, genetics, recognition, and treatment of cleft lip and palate

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A 3,550-g male infant is born at term. The mother is thin and expressionless and has had one miscarriage. This pregnancy was complicated by polyhydramnios, decreased fetal movements, and prolonged labor. The delivery was vaginal. The infant's respiratory efforts are weak and periodic, and he exhibits marked hypotonia, expressionless facies, tent-shaped triangular upper lip, absent deep tendon reflexes, and bilateral talipes equinovarus. He requires resuscitation with bag/mask ventilation and subsequent mechanical ventilation. Chest radiography shows an elevated diaphragm on the right and a bell-shaped thoracic cage. The mother is unable to release her grip after squeezing your hand.

Of the following, the inheritance pattern MOST frequently found in this infant's condition is

1	autosomal dominant
2	autosomal recessive
3	mitochondrial
4	uniparental disomy
5	X-linked recessive

You selected 3, the correct answer is 1.

Congenital myotonic dystrophy, the condition characterized by the symptoms reported for the mother-infant dyad in the vignette, most often is inherited as an autosomal dominant multisystem disorder with variable expression. Therefore, 50% of the offspring of affected parents have the gene. The disorder is one of the most frequent causes for neonatal hypotonia, with an incidence of 1 in 3,500 live births. The gene mutation is in the myotonin protein kinase gene on chromosome 19q13.3 and is characterized by an unstable CTG repeat in the 3 prime untranslated region. Progressively more severe disease occurs with successive generations due to increasing size of the genetic expansion. Amplification of the trinucleotide repeat of greater than 45 generally is associated with disease expression. The mother almost always is the source of the mutation. Infants who survive the perinatal period may show improved but delayed motor function; mental retardation and learning disabilities are frequent.

Autosomal recessive inheritance is associated with the following congenital muscular dystrophies: Merosin-positive, or classic, myopathy, Merosin-deficient congenital muscuar dystrophy with white matter abnormality, Fukuyama congenital muscular dystrophy, muscle-eye-brain disease and Walker-Warburg syndrome. The risk for two parents who carry the recessive gene of having an affected infant is 25%. As with congenital myotonic dystrophy, the symptoms of severe hypotonia, lack of facial expression, and respiratory insufficiency often are present; although arthrogryposis is common, central nervous system involvement may be significant.

Mitochondrial inheritance affects the processes of oxidative phosphorylation and is unique because mitochondrial genes do not follow mendelian patterns of inheritance as found in cell nuclei. Mitochondrial DNA is circular, found in the cytoplasm of the cell, and produces some, but not all, of the proteins important for mitochondrial function and oxidative phosphorylation. Mitochondrial DNA also contains a genetic code different from nuclear DNA, and there are no introns. Two ribosomal RNA

genes and 22 transfer RNA genes are present. The inheritance pattern is "matrilineal" because all affected women pass the trait to all of their children; affected men never pass the trait to their children. This pattern is due to all functional mitochondria being derived from the maternal oocyte. At fertilization, mitochondria within the sperm are not transferred to the ovum. This inheritance pattern is complicated further by significant tissue and organ variability due to a concept called "heteroplasmy." Heteroplasmy results from the presence of both mutant and normal mitochondrial DNA within the cytoplasm of cells that are passed into the ovum from the mother. Depending on the replication and distribution patterns of the mutant mitochondria in tissues, the clinical phenotype may be highly variable and change over time, which results in marked heterogeneity in severity of illnesses within the same family. Mitochondrial disorders affect tissues that require high amounts of energy, such as muscle (myopathies), heart (hypertrophic cardiomyopathy), and brain (myoclonic epilepsy). Diagnosis requires special DNA testing. Treatment of these disorders is limited to cofactor replacement to maximize energy production.

Uniparental disomy is the inheritance of two chromosomes from the same parent. This pattern explains the basis for syndromes demonstrating "genomic imprinting" or differential contribution of maternal and paternal alleles to an offspring. Hydatidiform moles are placental tumors derived from two paternal sets of chromosomes. Prader-Willi syndrome is due to genomic imprinting. Prader-Willi syndrome is characterized by neonatal hypotonia, feeding problems, hypogonadism, and silver hair. Although failure to thrive may occur during the first year, overeating and obesity begin during the toddler years. Additional problems with short stature, mild-to-moderate mental retardation, small hands and feet, and skin "picking" behaviors occur with time. Most cases have a paternally derived cytogenetic deletion of chromosome 15 {del (15) (q11-q13)}. Approximately 25% of affected patients have both copies of chromosome 15 containing a small deletion (15 q11-13) derived from their fathers. Uniparental disomy also has been implicated in some cases of Beckwith-Wiedemann syndrome, Russell-Silver syndrome, neonatal diabetes, and unexplained developmental delay. No primary congenital muscular diseases are known to have this inheritance pattern.

X-linked recessive inheritance is associated with Duchenne type muscular dystrophy (Xp21-linked dystrophin-deficient muscular dystrophy). Duchenne type muscular dystrophy rarely presents in a neonate.

Muscular dystrophies are characterized by being a primary myopathy, genetic in origin, progressive, and resulting in muscle fiber degeneration and death. The distinctive clinical features of Duchenne type muscular dystrophy include hypertrophy of the calves, progressive weakness, intellectual impairment, and proliferation of connective tissue in muscle. X-linked recessive inheritance is associated with Duchenne type muscular dystrophy, but approximately 30% of cases are new mutations. With X-linked recessive inheritance, the risk for affected sons and carrier daughters each is 50%. Therefore, males are predominantly affected. However, symptomatic girls have been reported due to the expression of some of the abnormal muscular dystrophy genes, which is caused by inactivation of some normal X chromosomes and activation of some chromosomes that have the gene deletion (Lyon hypothesis).

References:

Baraitser M, Winter RM. In: Color Atlas of Congenital Malformation Syndromes. London, England: Mosby-Wolfe; 1997:160

Jones KL. Genetics, genetic counseling, and prevention. In: Smith's Recognizable Patterns of Human Malformation. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997:706-726

Sarnat HB. Neuromuscular disorders. In: Behrman RE, Kliegman RM, Jenson HB, eds.

Nelson Textbook of Pediatrics. 17th ed. Philadelphia, Pa: Saunders; 2004:2060-2070

Schwartz S, Dickerman LH. Genetic aspects of perinatal disease and prenatal diagnosis. In: Fanaroff AA, Martin RJ, eds. Neonatal-Perinatal Medicine, Diseases of the Fetus and Newborn. 7th ed. St. Louis, Mo: Mosby; 2002:80-108

Content Specifications:

Understand the differential diagnosis, management and outcomes of neonatal hypotonia

Recognize clinical features associated with autosomal dominant disorders

Demonstrate understanding of inheritance patterns and recurrence risk of autosomal dominant disorders

Demonstrate understanding of inheritance patterns and recurrence risks for autosomal recessive disorders

Demonstrate understanding of inheritance patterns and recurrence risks for x-linked recessive disorders

Demonstrate understanding of maternal inheritance of mitochondrial disorders

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You are called to evaluate a term male infant in the delivery room for cyanosis. His mother's prenatal course, labor, and vertex vaginal delivery were uncomplicated. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Upon your arrival 15 minutes after birth, the baby is crying and pink, has normal findings on physical examination, and has a transcutaneous oxygen saturation of 98%. After calming, he exhibits good skin perfusion, but he has cyanosis and intercostal retractions, and the transcutaneous oxygen saturation is 84%. As the infant resumes crying, his color becomes pink, and the transcutaneous oxygen saturation returns to 98%.

Of the following, the MOST likely diagnosis in this infant is

1	Apert syndrome
2	CHARGE association
3	choanal atresia
4	DiGeorge sequence
5	trisomy 18

You selected 1, the correct answer is 3.

Choanal atresia is a potentially life-threatening emergency in the delivery room due to airway obstruction. Neonates breathe oronasally, with nearly 70% of tidal volume inspired nasally and 30% inspired orally. This partitioning is controlled by the tone of the soft palate and may vary among individual infants. When nasal obstruction occurs, increased negative pressure during inspiration is transmitted to the soft palate and tends to pull the tongue against the soft palate, resulting in obstruction of the oropharynx. Variation in partitioning the tidal volume through the nose and mouth and variable tone of the soft palate and nasal pharynx may explain the variation in age at presentation and severity of symptoms in neonates who have choanal atresia. Some infants do not have manifestations for months or even years. Symptoms that characterize bilateral choanal atresia include cyclic cyanosis and respiratory distress that worsens during feeding and improves with crying or mouth breathing, as reported for the infant in the vignette. However, if nasal obstruction leads to oropharyngeal obstruction in the delivery room, severe respiratory distress and cyanosis occur. Risk factors for this occurrence include maternal medications that depress pharyngeal and soft palate tone; neck flexion and an anatomically small, narrow nasopharynx; a widened vomer; and a medialized lateral nasal wall or high-arched palate. All of these conditions are found in many patients who have choanal atresia. Treatment with an oropharyngeal tube, oral airway, intubation, or laryngeal mask airway may be lifesaving.

The incidence of choanal atresia is estimated at 1 in 12,000 births, with more females than males affected. Bilateral atresia occurs in about one third of affected infants, and 90% of cases are bony. The cause is believed to be failure of rupture of the buccopharyngeal membrane that separates the nasal cavities from the oral cavity until the 38th day of fetal life. Other theories include medial outgrowth of the palatine bone, abnormal mesodermal adhesions, and misdirection of mesodermal development due to local factors.

Choanal atresia is detected in the delivery room based on symptoms and an inability to detect air movement through the nares by auscultation, sound of air movement, or

movement of cotton placed before each nares. An inability to pass a nasogastric tube followed by endoscopy or computed tomography confirm the diagnosis (Figure). Surgical intervention and preventive treatment for gastroesophageal reflux until postoperative healing occurs often is recommended. Surgical techniques include transnasal puncture, transseptal window, transpalatal repair, endoscopic repair, and laser excision. The use of stents has variable support because the benefit of preventing stenosis must be balanced by the risk of infection and foreign body reaction.

The outcome for idiopathic choanal atresia not complicated by other anomalies is excellent. Additional anomalies primarily affecting the palate, pharynx, and the nose and genetic syndromes and associations may accompany choanal atresia. Nonspecific malformations occur in 47% of infants who do not have chromosomal anomalies. Chromosomal abnormalities occur in 6% of affected infants, and syndromes or associations occur in 5% of infants. Outcomes in the latter cases usually reflect anomalies other than the choanal atresia.

Apert syndrome, or acrocephalosyndactyly, occurs in 1 in 160,000 births and infrequently is associated with choanal atresia. However, upper airway obstruction due to mid-face hypoplasia, small nose, narrow palate, maxillary hypoplasia, adenoid and tonsillar hypertrophy, and laryngeal anomalies (anomalous tracheal cartilage) occurs in about one third of infants. Irregular craniosynostosis, mid-face hypoplasia, syndactyly, broad distal phalanx of thumb and big toe, and numerous other anomalies also characterize Apert syndrome. Although most of the cases are sporadic, autosomal dominant inheritance can occur. The recurrence risk in unaffected parents is negligible. Mutations in the fibroblast growth factor receptor 2 gene, which maps on chromosome 10q25-10q26, are associated with this syndrome.

CHARGE association is a spectrum of disorders that includes ***c***oloboma, ***h***eart disease, ***a***tresia choanae, ***r***etarded ***g***rowth and development and/or central nervous system anomalies, ***g***enital anomalies and/or hypogonadism, and ***e***ar anomalies and/or deafness. Numerous other anomalies have been reported. Choanal atresia occurs in about 60% of patients. The cause of this disorder is unknown, and the recurrence risk for infants of unaffected parents is low.

DiGeorge sequence occurs in about 1 in 5,000 births and occasionally includes choanal atresia. Among the characteristic features are conotruncal defects, thymus hypoplasia with a deficit in cellular immunity, and parathyroid hypoplasia and hypoparathyroidism with a predisposition for hypocalcemia and seizures. The cause in most cases is related to partial monosomy of the proximal long arm of chromosome 22 due to microdeletion of 22q11.2, which is detectable using fluorescent in situ hybridization analysis. Shprintzen syndrome, or velo-cardio-facial syndrome, is associated with the same microdeletion.

Trisomy 18 is associated with choanal atresia in fewer than 10% of patients. This trisomy is the second most common multiple malformation syndrome, with a prevalence of 1 in 330 births. Anomalies occur in multiple systems, and the syndrome is characterized by clenched hands, short sternum, low-arch dermal ridge patterning on fingertips, and early mortality. Most cases of trisomy 18 include three full chromosomes 18, although translocation, mosaic, and partial trisomy 18 cases have been reported. The recurrence risk is less than 1%.

The absence of other physical anomalies in the infant described in the vignette supports the diagnosis of isolated choanal atresia and precludes the diagnoses of Apert syndrome, CHARGE association, DiGeorge sequence, and trisomy 18.

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Tewfik TL. Choanal atresia.

Content Specifications:

Recognize the diagnostic implications of single vs. multiple anomalies

Recognize the clinical features and know how to manage craniofacial anomalies

Understand the clinical features of an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Plan appropriate management for an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

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One month after moving into her newly built house that has all the modern amenities, including a sauna adjacent to the exercise room, a woman presents with a positive pregnancy test. She relates that she has used the sauna regularly and that she exercises daily. She estimates that she is 7 weeks pregnant.

Of the following, the fetal condition that has the STRONGEST relationship to maternal hyperthermia is

1	absence of corpus callosum
2	neural tube defect
3	paroxysmal supraventricular tachycardia
4	trisomy 21
5	Turner syndrome

You selected 2, the correct answer is 2.

Maternal hyperthermia in early gestation due either to maternal infection-related fever or to exogenous thermal stress of sauna baths is associated with an increased risk of neural tube defects. However, the timing, intensity, and duration of hyperthermia sufficient to yield this outcome are unknown. The specific neural tube defect may range from anencephaly to spina bifida. Data regarding the relationship between characteristics of the hyperthermia and specific types of the neural tube defect are lacking. Maternal screening for serum alpha-fetoprotein and early ultrasonography can be used to assess the fetus.

Absence of the corpus callosum results from abnormalities of number or migration of callosal axons in early fetal brain development. One type of absent corpus callosum involves only the abnormalities of related neural structures and may be associated with no or little neurologic impairment. The second type of absent corpus callosum is seen in conjunction with a variety of chromosomal and inherited metabolic disorders and usually is symptomatic. In neither case is hyperthermia a postulated causal event.

Maternal fever in early gestation has not been reported to be associated with abnormalities of heart rhythm. However, maternal fever during labor may result in fetal tachycardia, with an increase in fetal heart rate of 10 beats/min with each degree centigrade rise in maternal body temperature. In a cohort of term newborns who had no congenital anomalies, chromosomal aberrations, or central nervous system abnormalities, the infants whose mothers experienced fever during labor with or without chorioamnionitis had a ninefold increase in the risk of cerebral palsy compared with infants whose mothers had no fever during labor. No persistent or paroxysmal neonatal tachycardia has been described with hyperthermia in early gestation.

Maternal hyperthermia has not been implicated in increasing the risk for nondisjunction or other genetic mechanisms for chromosomal abnormalities. Therefore, trisomy 21 and Turner syndrome would not be expected risks for the infant of the mother described in the vignette.

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Milunsky A. ***Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment***. 3rd ed. Baltimore, Md: Johns Hopkins University Press; 1992

Content Specification(s):

2129. Know the effects on the fetus of maternal hyperthermia

PREVIOUS NEXT

Overview

Assessment 04

1 January 04
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A newborn female has loose neck skin and nonpitting edema of the lower extremities.

Of the following, the MOST appropriate evaluation for this infant is:

1	blood chromosome analysis
2	magnetic resonance imaging of the brain
3	slitlamp ophthalmologic examination
4	ultrasonography of the liver
5	voiding cystourethrography

You selected 2, the correct answer is 1.

The finding of loose neck skin, which is suggestive of the presence of a **cystic hygroma** in fetal life, and nonpitting edema of the lower extremities in a newborn female should raise the suspicion of **Turner syndrome**. Congenital lymphedema, which occurs in up to 80% of affected females, typically disappears during infancy, leaving only a puffy appearance to the hands and feet, although in some patients it reappears when estrogen therapy is initiated. The posterior neck skin can persist as the pterygium colli, or webbed neck. The clinical diagnosis of **Turner syndrome** should be confirmed by peripheral blood chromosome analysis, which will reveal monosomy X, mosaic monosomy X, or the presence of an abnormal X chromosome that contains a deletion.

Affected girls also have short stature, ovarian dysgenesis, broad chest with wide-spaced nipples, ear anomalies, cubitus valgus, and renal and cardiac defects. Intelligence is normal. Estrogen replacement therapy at the expected time of puberty is required in most cases, and treatment with growth hormone also should be offered.

Magnetic resonance imaging of the brain, slitlamp ophthalmologic examination, and ultrasonography of the liver are not indicated because central nervous system and ophthalmologic findings are not features of **Turner syndrome**, and liver size and function is normal. Although renal defects may be present, the most common abnormality is horseshoe kidney, which can be detected by ultrasonography and usually has no clinical effects that would prompt the need for voiding cystourethrography.

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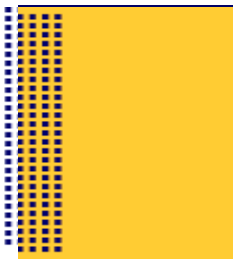
Rosenfeld RG, Tesch LG, Rodriguez-Rigua LJ, et al. Recommendations for diagnosis, treatment, and management of individuals with Turner syndrome. Endocrinologist. 1994;4:351-358

Content Specification(s):

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy.



You are called to the nursery to evaluate a 1-hour-old baby who has respiratory distress and intermittent cyanosis that is relieved by crying. The nurse has been unable to pass an 8-French catheter through the right naris and has difficulty passing the catheter on the left. On physical examination, the baby is normally grown. You note right central facial nerve palsy and a lop ear malformation on the right. The genitalia are hypoplastic.

Of the following, the studies that will be MOST helpful in immediate management and diagnosis for this baby are

1	chromosome analysis, ophthalmology consultation, echocardiography
2	chromosome analysis, renal ultrasonography, ophthalmology evaluation
3	echocardiography,head computed tomography, ophthalmology evaluation
4	head ultrasonography, chromosome analysis, renal ultrasonography
5	head ultrasonography, echocardiography, ophthalmology evaluation

You selected 1, the correct answer is 3.

The infant described in the vignette has intermittent cyanosis that is relieved by crying, which is the classic presentation of choanal atresia or severe choanal stenosis. The inability to pass a catheter through the right naris of the infant confirms atresia on that side, and the difficulty passing the catheter on the left suggests stenosis on that side.

Choanal atresia occurs in about 1:8,000 infants. It is due to failure of the buccal pharyngeal membrane in the posterior nasal cavity to dissolve in the seventh week of embryogenesis, thereby preventing communication between the posterior nasal cavity and the posterior pharynx. Although crying relieves the problem, eventually the babies tire, and they become hypercarbic and can die without intervention. Evaluation using computed tomography (CT) is recommended. While awaiting CT, an oral airway should be placed. Once the diagnosis of choanal atresia is suspected, an otolaryngologist should be consulted. Sometimes it is possible to dilate the stenotic choanal passage, although this also may be accomplished surgically.

Although choanal atresia/stenosis can be an isolated condition, as many as 50% of affected children have associated abnormalities. The infant presented in the vignette has features of the CHARGE association in which C=coloboma of the eye, H=heart defect, A=atresia choanae, R=postnatal retardation of growth or development, G=genital anomalies, and E=ear abnormalities. Classically, affected individuals must have at least four of the features listed, with at least one being either choanal atresia or coloboma (Figure 6.1). It is not unusual for the children to have seventh nerve palsies (Figure 6.2), and the most common ear malformation is a lop ear (Figure 6.3). In addition to choanal abnormalities, the infant in the vignette has genital and ear anomalies.

Echocardiography is an important aspect of the immediate management of children who have CHARGE association because they are likely to have cardiac birth defects. Head CT is required to evaluate the infant for choanal abnormalities; these cannot be detected on head ultrasonography. Finally, an ophthalmology consultation is necessary even if no coloboma is seen on direct ophthalmoscopic examination because it is possible that a coloboma involves the posterior aspect of the eye, which could have significant impact on the child?s prognosis for vision. At a later point in time, chromosome analysis will be helpful because 2% of individuals who have CHARGE association have chromosome abnormalities, but this is not

useful in immediate management. Renal ultrasonography is recommended for later evaluation because children who have CHARGE association may have renal anomalies.

References:
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Moore KL, Persaud TVN. Human birth defects. In: *The Developing Human: Clinically Oriented Embryology*. 7th ed. Philadelphia, Pa: WB Saunders Co; 2003:157-186

Content specifications:
Recognize the incidence, clinical manifestations, and management of bilateral and unilateral choanal atresia
Know the syndromes associated with abnormalities of the eye including cranio-facial abnormalities, abnormalities of the orbit, the eyebrows, the eyelids, the eyelashes, the cornea, the iris, and the retina
Know the causes and risk factors for congenital hearing loss in the neonate
Recognize the clinical features and know how to manage craniofacial anomalies

PREVIOUS NEXT

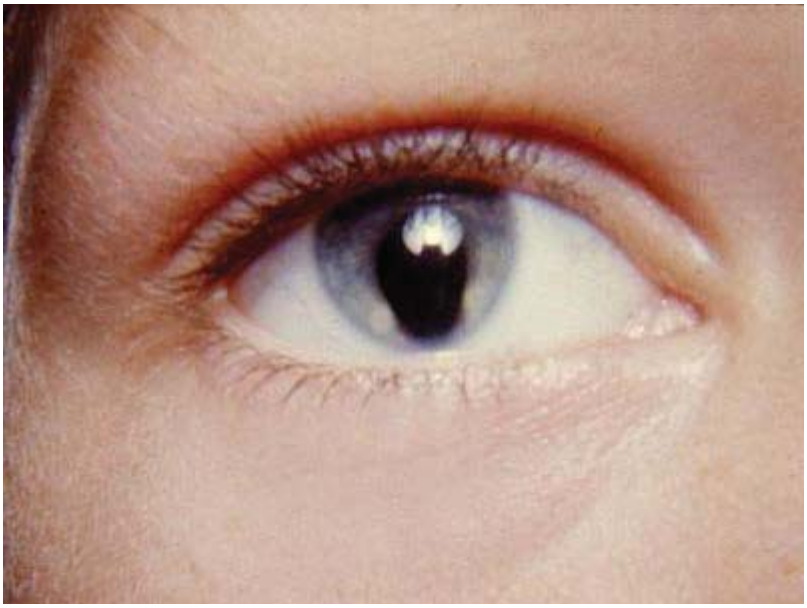
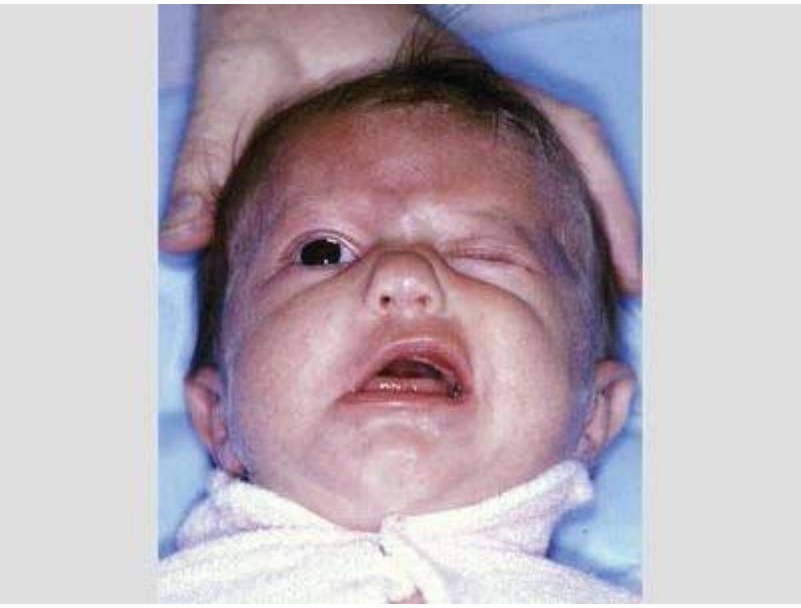


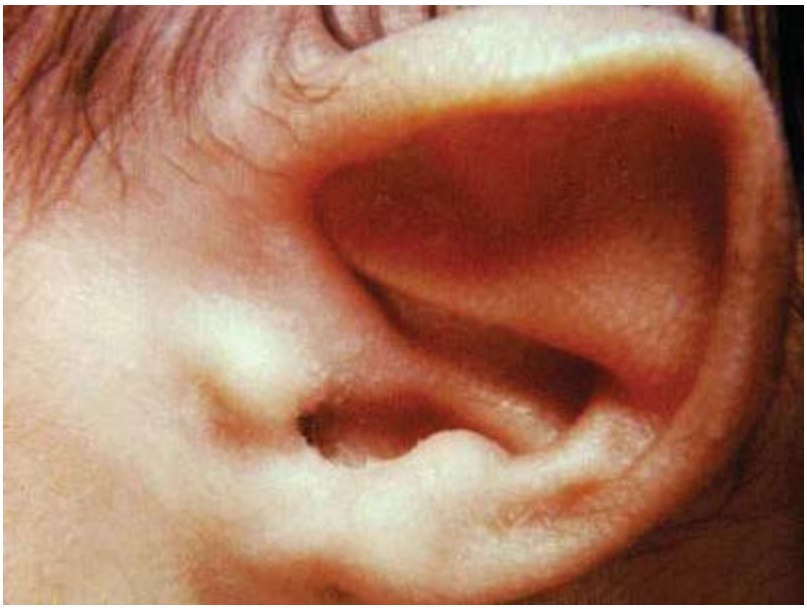
Fig 6.2



Right peripheral seventh nerve palsy: note the inability of the infant to close the eye or open the right side of the mouth. Seventh nerve palsy often accompanies choanal atresia.(Courtesy of M Rimsza)

Close

Fig 6.3



A lop ear anomaly may be associated with choanal atresia. (Courtesy of M Rimsza)

Close

A term male newborn was delivered vaginally and immediately developed severe cyanosis and respiratory distress. Physical examination revealed a large-for-gestational age infant who had coarse facies, cloudy corneas, anteverted nares, cleft lip and palate, digital hypoplasia, absent nails, single transverse palmar crease, and heart sounds best heard to the right of the sternum. Breath sounds were heard only at the apex of the right lung. Despite resuscitation in the delivery room with positive pressure ventilation, oxygen, volume expansion, chest compressions, and epinephrine, the infant died. His mother had undergone amniocentesis because of advanced maternal age, and results showed a 46,XY karyotype. Four siblings are alive and well, but a fifth sibling died from severe respiratory failure following a home delivery. No autopsy or other records were available. Both parents are from a small town and are believed to be distant cousins. Fetal ultrasonography performed at 18 weeks showed a left-sided cleft lip and cleft palate. The postmortem examination is shown in Figure 1. Hirschsprung disease was evident on microscopic examination.

Of the following, the MOST likely diagnosis for this infant is

1	Beckwith-Wiedemann syndrome
2	Cornelia de Lange syndrome
3	DiGeorge sequence
4	Fryns syndrome
5	Smith-Lemli-Opitz syndrome

You selected 4, the correct answer is 4.

Congenital diaphragmatic hernia affects 1 to 5 in 10,000 live births. Males account for about two thirds of affected infants, most of whom are born at term. The left diaphragm is affected in 90% of cases, as seen for the infant in the vignette (Figure 1). Isolated congenital diaphragmatic hernia occurs in approximately 60% of cases; the remainder is complicated by other congenital anomalies. Cardiac anomalies predominate, although other body systems, including the brain, kidneys, bowel, or skeleton, may be involved, especially in infants who have chromosomal or multiple malformation syndromes. Such syndromes include trisomies 13 and 18, Fryns syndrome, Beckwith-Wiedemann syndrome, Cornelia de Lang syndrome, DiGeorge sequence, Ehlers-Danlos syndrome, and Marfan syndrome. The mortality associated with diaphragmatic hernia in conjunction with other congenital anomalies is about 2.4 times that for infants who have isolated diaphragmatic hernia.

The infant described in the vignette has the classic features of Fryns syndrome, a rare, autosomal recessive disorder that often presents with respiratory failure due to diaphragmatic hernia. In addition to the diaphragmatic defect, cardinal features of Fryns syndrome include digital and nail hypoplasia and coarse facies. Among the other frequent findings are brain malformations such as agenesis of the corpus callosum, Dandy-Walker malformation, hypoplasia of optic or olfactory tracts; eye abnormalities such as cloudy cornea and microphthalmia; anteverted nares; and cleft lip or palate. Other distinctive malformations of Fryns syndrome include ventricular dilatation or hydrocephalus, neuronal or cerebellar heterotopias, abnormalities of the aorta, renal cysts, dilatation of the ureters, bicornuate uterus, renal dysplasia, proximal thumbs, and broad clavicles. Some infants are large for gestational age and have a variety of gastrointestinal malformations, such as duodenal atresia, Hirschsprung disease, and imperforate anus.Polyhydramnios is a frequent feature of pregnancies when Fryns syndrome is present. Most infants who have Fryns syndrome are stillborn or die shortly after birth; those who survive have significant mental impairments.

Beckwith-Wiedemann syndrome affects about 1 in 14,000 live births. Most cases are sporadic, although familial inheritance occurs in 15% of cases. In familial cases, autosomal dominant inheritance with variable penetrance is characteristic. However, imprinting of the maternal allele at 11p15 or paternal uniparental disomy can result in an imbalance of expression of the paternal allele or underexpression of the maternal allele that leads to overgrowth and tumor formation. Characteristic findings of Beckwith-Wiedemann syndrome include macrosomia, omphalocele, macroglossia, and ear creases. Diaphragmatic hernia occasionally is a presenting feature, although eventration of the diaphragm is more frequent. Other distinctive features include organomegaly (especially adrenocortical cytomegaly), hypoglycemia, advanced bone age, and hemihypertrophy. Close follow-up for malignancy, especially Wilms tumor and hepatoblastoma, is important. Normal development often is possible if complications are avoided through interventions. The only features of Beckwith-Wiedemann syndrome exhibited by the infant in the vignette are being large for gestational age and having a diaphragmatic hernia, but the other features are more characteristic of Fryns syndrome.

Cornelia de Lange syndrome, or Brachmann-de Lange syndrome, often presents with synophrys, a thin downturning upper lip, and micromelia. Most affected infants have pre- and postnatal growth restriction, microcephaly, severe mental retardation, speech delay, feeding problems, major malformations that can include limb defects, and characteristic facial features. The facial features include arched eyebrows, synophrys, short nose with anteverted nares, long philtrum, thin upper lip, and micrognathia. Most cases of Cornelia de Lange syndrome are sporadic; nearly 50% are associated with mutations of the NIPBL gene located on chromosome 5p13. Inheritance following an autosomal dominant pattern or due to balanced chromosomal translocations has been identified. Diaphragmatic hernia only occasionally is present in this syndrome. The infant described in the vignette has a diaphragmatic defect and anteverted nares, but he is large for gestational age rather than growth-impaired, has digital nail hypoplasia rather than micromelia, and has a cleft lip/palate rather than a high-arched palate.

DiGeorge sequence is one of three disorders that involve sporadic de novo deletion of genes on chromosome 22q11.2. The other disorders are velocardiofacial syndrome and conotruncal anomaly face syndrome; collectively, they are referred to as the 22q11 deletion syndrome. Karyotyping with fluorescent in situ hybridization can identify the 22q11 deletion. This chromosomal deletion syndrome occurs in 1 in 3,000 live births, making the disorder one of the most common microdeletion syndromes. Characteristic features of the DiGeorge sequence evolve from defects in development of the thymus, parathyroids, and great vessels. The most common presentation is with symptoms associated with conotruncal congenital heart defects, hypocalcemia, or immune deficiency. Facial features include hooded eyelids, hypertelorism, overfolded ears, bulbous nasal tip, small mouth, and micrognathia. Diaphragmatic hernia, cleft palate, choanal atresia, renal agenesis, neural tube defects, imperforate anus, and hypospadias are seen occasionally. A wide range of neurodevelopmental delays, learning disabilities, and hypotonia are reported in children, but severe mental and physical impairments are unusual. The infant in the vignette has a diaphragmatic hernia, cleft palate, and coarse facial features, but none of the other features of DiGeorge sequence.

Smith-Lemli-Opitz syndrome is an autosomal recessive malformation syndrome caused by a defect in cholesterol biosynthesis. The incidence is estimated at 1 in 10,000 to 100,000 live births. The gene defect in cholesterol biosynthesis is located on chromosome 11 and results in reduced activity of 7-dehydrocholesterol (7DHC) reductase, the enzyme responsible for converting 7DHC to cholesterol. Low serum cholesterol and elevated serum 7DHC concentrations establish the diagnosis in symptomatic infants. Treatment with cholesterol supplementation has been shown to cause improvements in behavior, growth, hypotonia, developmental skills, and irritability. The distinctive features of Smith-Lemli-Opitz syndrome include anteverted nares, ptosis of the eyelids, syndactyly of second and third toes, hypospadias, and cryptorchidism. Other findings often include intrauterine growth deficiency, microcephaly, hypotonia, micrognathia, simian crease, and other renal anomalies. Occasionally, cleft palate, asymmetrically short fingers, polydactyly, flexed fingers, abnormal pulmonary lobation, and Hirschsprung disease are present. Diaphragmatic hernia is not associated with this syndrome.

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Content Specifications:

Recognize the diagnostic implications of single versus multiple anomalies

Recognize the clinical features of extrapulmonary causes of respiratory distress including diaphragmatic hernia, diaphragmatic paralysis and cord transection

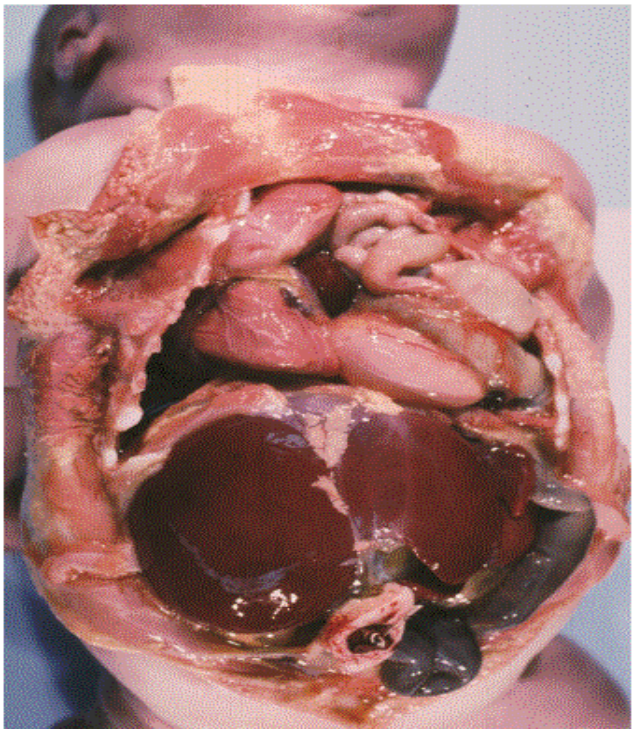
Recognize the karyotype and clinical manifestations associated with common deletion syndromes

Recognize clinical features of Smith-Lemli-Opitz syndrome

Recognize clinical features of Beckwith-Wiedemann syndrome

Recognize the clinical features of and how to manage craniofacial anomalies

Recognize the clinical features of and how to manage congenital anomalies of the upper extremities such as syndactyly, polydactyly, absent clavicles, absent radius, Sprengel deformity and limb reduction



You are caring for a 2-month-old infant who was born at 30 weeks' gestation and weighed 1,000 g at birth. At 2 weeks after birth, the infant developed severe necrotizing enterocolitis and underwent a resection of the ileum and ileocecal valve. She is estimated to have approximately 70 cm of remaining jejunum connected to a stoma. Most of the colon remains, but it is not in continuity with the small intestine. The infant has been maintained exclusively on parenteral nutrition, but you are planning to transition her to enteral feedings.

Of the following, a TRUE statement about feeding this child who has short bowel syndrome is that

1	a stool-reducing substance of 1% or greater suggests good tolerance of enteral feedings
2	bolus feedings are preferred over continuous feedings
3	cow milk protein formulas are preferred because of their decreased osmolarity
4	rectal bleeding in this patient suggests intolerance of enteral feeding
5	small bowel bacterial overgrowth is a frequent cause of feeding intolerance

You selected 5, the correct answer is 5.

Infants may undergo bowel resection in the neonatal period for a variety of conditions, including necrotizing enterocolitis, Hirschsprung disease, omphalocele, gastroschisis, and intestinal atresias. Ideally, infants undergoing bowel resection should receive calories enterally. However, in some cases, short- or long-term parenteral nutrition is necessary to promote health and bowel growth. Infants who have large amounts of bowel resected are at risk for developing short bowel syndrome, which is characterized by chronic diarrhea, micronutrient deficiency, and feeding intolerance. The primary determinants of the risk of short bowel syndrome are the amount of remaining bowel and whether the ileocecal valve has been resected. If the ileocecal valve has been resected, 30 to 50 cm of bowel must be present for the infant to grow enough intestine to allow weaning off parenteral nutrition. Resection of the ileum (as opposed to jejunum) leads to malabsorption of vitamin B_{12} and bile acids.

Initially, patients who undergo extensive bowel resections may have a high-output secretory diarrhea, with stool sodium levels of 80 to 100 mEq/L (80 to 100 mmol/L), and require aggressive fluid and electrolyte repletion. Once stool output and serum electrolyte concentrations are stable, enteral feeding may be attempted. Patients who have short bowel syndrome and are fed enterally may have a limited tolerance for fat and carbohydrate. Protein hydrolysates and modular formulas (in which the proportion of carbohydrate is increased gradually) often are beneficial and are preferred over intact cow milk protein formulas. Slow continuous feedings delivered by gastrostomy tube frequently are tolerated better than bolus feedings. Ostomy output may be used to determine carbohydrate tolerance. An ostomy output that equals or exceeds the amount of formula delivered implies malabsorption. In addition, a stool reducing substance of 0.25% or less suggests good tolerance of the carbohydrate, and a stool reducing substance of 1% implies malabsorption. Patients who have short bowel syndrome are at risk for bacterial overgrowth in stagnant, hypomotile loops of bowel. Bacterial overgrowth has been shown to increase feeding intolerance and decrease survival in affected infants. Therefore, periodic courses of antibiotic therapy should be considered for all infants who have short bowel syndrome.

Patients who have bowel resections often have a portion of colon that is not in continuity with the remainder of the bowel. Because this colon is not in continuity with the fecal stream, the patient may develop a condition termed diversion colitis. Diversion colitis presents with rectal

bleeding, but it does not imply feeding intolerance. The preferred treatment for diversion colitis is restoration of bowel continuity; if this is not possible, corticosteroid or short-chain fatty acid enemas may be helpful.

References:

Garcia-Careaga M, Kerner JA. Malabsorptive disorders: short bowel syndrome. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, Pa: WB Saunders Co; 2004;1262-1264

Utter SL, Duggan C. Short bowel syndrome. In: Hendricks KM, Walker WA, Duggan C, eds. *Manual of Pediatric Nutrition*. 3rd ed. Hamilton, Ontario, Canada: BC Decker Inc; 2000:529-541

Vanderhoof JA, Langnas AN. Short-bowel syndrome in children and adults. *Gastroenterology*. 1997;113:1767-1778.
Abstract available online

Content Specifications:
Understand the factors that may improve intestinal motility
Know the clinical manifestations, diagnosis, and treatment of acquired malabsorption syndrome
Understand the diagnostic procedures and approach to therapy of infectious enteritis and colitis in the neonate

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A 37-year-old woman with three normal children opts for chorionic villus sampling due to advanced maternal age. An abnormal chromosomal pattern is noted.

Of the following, the chromosomal pattern MOST likely to result in early fetal loss is:

1	monosomy X (45, X)
2	triploidy (69)
3	trisomy 16 (47, +16)
4	trisomy 18 (47, +18)
5	trisomy 21 (47, +21)

You selected 5, the correct answer is 3.

Although never seen among live newborns, trisomy 16 is the most prevalent of the autosomal trisomies noted among abortuses. Of the 50% of spontaneous abortuses found to have chromosomal abnormality, about one-half have an autosomal trisomy. Autosomal trisomy is a major contributor to increased pregnancy loss associated with advanced maternal age. Most trisomies result from errors in maternal meiosis (stage 1). Trisomies involving every autosome except chromosome 1 have been documented in abortuses. Prognosis depends on the specific chromosome involved, with uniform early loss with trisomy 16.

Monosomy X is noted in 19% of chromosomally abnormal abortuses. Some 99% of 45, X embryos will succumb in the first or early second trimester; 1% of embryos survive and present with the Turner syndrome phenotype (short stature, shield chest, webbed neck, hypoplastic nails, short 4th metacarpal, cubitus valgus, lymphedema, ovarian dysgenesis, and congential heart abnormalities). This pattern is not associated with advanced maternal age and is thought to result from anaphase lag during meiosis or mitosis.

Triploidy results from the embryo receiving a full set of extra chromosomes. Diandric triploidy is the more common variant (90%), resulting from fertilization of a single egg by two sperm or by a diploid sperm. In this variant, fetal size is mildly restricted, fetal head size is normal or slightly microcephalic, and the placenta is large with partial hydatidiform mole. Digynic triploidyresults from fertilization of a diploid ovum. This variant is less common (10%), results in a severely growth restricted macrocephalic fetus, and is associated with a small, noncystic placenta. Although most triploid fetuses die in utero, occasional live births occur (mostly digynic) with death coming in early infancy. Long-term survival has not been reported. No data support an increased recurrence risk in subsequent pregnancies.

Trisomy 18 occurs in 1 in 5,500 live births, making it the second most common autosomal trisomy detected in live births. Three quarters of affected infants are female. As with the other autosomal trisomies, it is associated with advanced maternal age, and 90% are due to meiotic nondisjunction. Translocation trisomy 18 is rare. Neonatal mortality is high and infant mortality is 90% to 95%. Survivors have severe developmental retardation. Recurrence risk for subsequent fetuses is estimated at 1%, but less than 1% of subsequent live-born siblings will be affected due to early fetal loss of many trisomy 18 embryos.

Trisomy 21 is the most commonly detected autosomal trisomy among midtrimester amniocenteses and live-born infants, occurring in 1 in 730 live births. Of trisomy 21 fetuses detected early in gestation, one-third survive to term. Nondisjunction during maternal meiosis underlies 95% of cases, and 5% result from abnormal spermatogenesis.

References:

Down syndrome (Trisomy 21). In: *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:8-13

Hsu LY. Cytogenetic abnormalities in the embryo, fetus and infant. Available at http://www.uptodate.com (subscription required). Accessed March 28, 2005

Petrozza JC, O'Brien B. eMedicine: early pregnancy loss. Available at http://www.emedicine.com/med/topic3241.htm. Accessed April 15, 2005

Singh D, Singh JR. eMedicine: prenatal diagnosis for congenital malformations and genetic disorders. Available at http://www.emedicine.com/oph/topic485.htm. Accessed April 15, 2005

Triploidy syndrome and Diploid/Triploid Mixoploidy syndrome. In: Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:30-31

Trisomy 18 syndrome. In: Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:14-15

XO syndrome. In: Jones KL. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia, Pa: Saunders; 1997:81-83

Content Specifications:

Understand the implications of a prenatal diagnosis of sex chromosome aneuploidy for the long-term developmental outcome of an infant

Know fetal and placental manifestations of triploidy

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You are called to see a 3.5-kg child born 20 minutes ago. The child has cyanosis, despite receiving 100% oxygen, and is in shock. Clinical examination reveals poor pulses, mottled appearance, oxygen saturation (SpO_2) 40%, and blood pressure 35/25 mmHg. The mother, whose prenatal care was not provided locally, tells you that some sort of congenital heart disease was suspected several months ago, but she cannot remember any specifics. You immediately start prostaglandin E_1 (PGE_1) at 0.1 mcg/kg per minute by intravenous route and call for an emergency echocardiogram. Over the next 20 minutes, the child worsens, with SpO_2 of 30% and blood pressure of 30/20 mmHg.

Of the following, the MOST likely explanation for this child's deterioration is

1	hypoplastic left heart syndrome with restricted atrial septum
2	interrupted aortic arch
3	total anomalous pulmonary venous return with obstruction of the common pulmonary vein
4	transposition of the great arteries with ventricular septal defect
✗ 5	viral myocarditis

You selected 5, the correct answer is 1.

Prostaglandin E_1 (PGE_1) often is used in infants suspected to have ductus-dependent congenital heart disease. PGE_1 is believed to exert its actions by two mechanisms: by activating adenylate cyclase in the vascular smooth muscle cells of the ductus arteriosus, thereby inhibiting the sensitivity of the contractile proteins to calcium; and by opening potassium channels to hyperpolarize the muscle cells, thereby reducing muscle tone. Due to its half-life of minutes, PGE_1 is given by constant infusion at doses of 0.01 to 0.4 mcg/kg per minute. Acute adverse effects include fever, apnea, hypotension, hypertonia, and irritability. Long-term adverse effects may include renal insufficiency, hypoglycemia, hypocalcemia, hyperostosis, obstructive gastropathy, thrombocytopenia, and seizures. Maternal inhibition of prostaglandin synthesis by chronic nonsteroidal anti-inflammatory drugs is associated with premature ductal closure and persistent pulmonary hypertension of the newborn.

Clinical deterioration once PGE_1 is started can be a useful sign of conditions in which there is obstruction to the pulmonary veins or to left atrial outflow. These conditions include total anomalous pulmonary venous return with pulmonary vein obstruction (TAPVR-PVO), hypoplastic left heart syndrome with restrictive atrial septum (HLV-RAS), mitral atresia with restrictive foramen ovale, and transposition of great arteries (TGA) with intact ventricular septum. Without the "pop-off" through the foramen ovale or atrial septal defect, pressure builds up in the left atrium and pulmonary veins to quickly cause pulmonary congestion, and markedly decreased pulmonary flow. The fully opened ductus would worsen the pulmonary overload.

Interrupted aortic arch usually presents as shock or congestive heart failure in the first fortnight. More than half the time, it is associated with a microdeletion of chromosome 22 and the DiGeorge syndrome. These children are dependent on a patent ductus arteriosus for blood flow to the descending aorta. Such a case would be expected to benefit from PGE_1 infusion.

TAPVR-PVO usually presents with cyanosis and tachypnea, often initially diagnosed as a primarily pulmonary problem. Delayed presentation until after age 12 hours helps differentiate it from respiratory distress syndrome. Physical findings, including murmurs, thrills or hyperactive pulses, seldom are found. Drainage often is below the diaphragm into the inferior vena cava.

TAPVR-PVO is difficult to find by echocardiogram, especially in the prenatal period; it is unlikely that the mother would have been warned about it.

HLV-IAS could present as in the vignette and fail to respond to PGE_1. The small size of the left ventricle would have been seen on prenatal echocardiogram and mentioned to the mother, as in the vignette. The severe obstruction to left-atrial outflow requires rapid palliation (atrial septostomy) or surgical intervention. Most other causes of left-sided obstruction should improve with PGE_1, including critical aortic stenosis, coarctation of the aorta, interrupted aortic arch, and HLV with atrial septal defect.

TGA with ventricular septal defect is likely to present with a higher SpO_2 than in the vignette. Improvement rather than deterioration is expected with PGE_1; the better mixing between the two parallel circulations would give even higher saturations.

Viral myocarditis might present with shock but would be unlikely to produce such low SpO_2 levels. The peripheral vasodilatation caused by PGE_1 might even help cardiac function by reducing afterload. Most cases should resolve over two months into either adequate cardiac function, or failure and death. It is unlikely that this was the problem the mother was told about prenatally.

References:

Clyman RI, Mechanisms regulating closure of the ductus arteriosus. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: Elsevier Saunders; 2004:743-748.

Fulton DR, Frees MD. Pathology, pathophysiology, recognition, and treatment of congenital heart disease. In Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart.* 11th ed. New York, NY: McGraw-Hill; 2004:1785-1850.

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Wernovsky G, Gruber PG. Common congenital heart disease: presentation, management, and outcomes. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:827-871.

Content Specifications:

For therapeutic drugs commonly used in the neonate, know the indications for their use, clinical effects, pharmacokinetics, adverse effects, and toxicity

Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion

Formulate a differential diagnosis of a neonate with a left-sided cardiac obstructive lesion

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A term male infant evaluated in your nursery has a large anterior fontanel (5 cm x 4 cm), occipito-frontal circumference 37 cm, deep-set eyes, flat nasal bridge, cleft lip and palate, midface hypoplasia, pointed chin, bilateral transverse palmar creases, hypotonia, sacral dimple, cyanosis, and systolic heart murmur. Family history is not contributory, and both parents are healthy. This is the first infant for these parents. Chest radiograph shows cardiomegaly, and echocardiogram shows Ebstein anomaly and large patent ductus arteriosus. Karyotype is normal. Fluorescence in situ hybridization (FISH) analysis for subtelomeric microdeletions demonstrates a terminal deletion at chromosome 1p36.

Of the following, the outcome MOST likely to develop in this infant is

1	asthma
2	diabetes mellitus
3	leukemia
4	mental retardation
5	renal failure

You selected 2, the correct answer is 4.

Telomeres are the "protective" caps at the ends of each chromosome and are highly conserved in all vertebrate species (Figure 1). These protective caps are composed of a repeating DNA sequence (TTAGGG) and can reach a length of 15,000 base pairs. Telomeres function to protect chromosomes from losing base pairs (genes and other genetic material) during cell replication. They also prevent chromosomes from adhering to one another during mitosis. During each cell division, 25 to 200 base pairs are lost from the telomere. The chromosome is shortened, or eroded, with each cell division until a "critical length" is reached, at which additional cell division is no longer possible. In other words, the cells in which the telomeres have reached this critical length have aged and prepared for programmed cell death, or apoptosis. Telomerase, or telomere terminal transferase, is an enzyme that adds TTAGGG sequences to the end of existing chromosomes. Telomerase activity is low in most of the body's somatic cells but is active in fetal tissues, adult germ cells, and tumor cells. Telomere and telomerase research are important to understand the biology of aging and cancer.

The base pair sequences adjacent to the telomeric repeats are called subtelomeres (Figure 2). This area of each chromosome is highly polymorphic and rich in repetitive DNA elements (subtelomeric repeats) and genes. Base pair rearrangements, duplications, and deletions in the subtelomeric region have been associated with microscopically visible chromosome abnormalities (4p-, Wolf-Hirschorn; 5p-, cri du chat; 22q11.2-, DiGeorge/Velocardiofacial; 7q-, Williams; 17p-, Miller-Diecker; 15q-, Prader-Willi/Angelman; 9p-, 13q- and 18p- syndromes). In addition, submicroscopic subtelomeric abnormalities (<2 to 3 Mb) found only with newer cytogenetic and molecular techniques, such as subtelomeric fluorescence in situ hybridization (FISH), spectral karyotyping, multiplex FISH telomere integrity assays, automated fluorescent genotyping, and comparative genomic hybridization, also have been associated with multiple malformation syndromes and mental retardation. The incidence of subtelomeric abnormalities is not well established. However, in as many as 5% of infants who have multiple malformations and 5% of children who have mental retardation, the clinical outcome may be related to subtelomeric chromosomal abnormalities.

In nearly half of neonates who have multiple anomalies, the abnormalities are not explained using routine chromosome analysis, amino and organic acid analysis, physical examination by

an experienced geneticist, and history. It is estimated that subtelomeric testing will establish a diagnosis in approximately 5% of these infants. Subtelomeric testing currently is considered as a second tier of tests for neonates who have multiple congenital anomalies, dysmorphic facial features, and intrauterine growth restriction in which a diagnosis is not otherwise explained.

The infant in this vignette has a contiguous gene deletion of chromosome 1p36 (ie, monosomy 1p36 -- see figures 3, 4, 5, and 6). The incidence of de novo monosomy for 1p36 has been estimated at 1 in 10,000 newborns. Parental chromosomal translocation is estimated to account for 1 in 30 of these patients; therefore, parental testing is indicated. This infant likely will have moderate to severe mental retardation and severe developmental delay, both commonly found in many of the syndromes caused by submicroscopic subtelomeric abnormalities. Hypotonia, large anterior fontanel, prominent forehead, deep-set eyes, depressed nasal bridge, midface hypoplasia, pointed chin, cleft lip and palate, ear asymmetry, and facial dysmorphism characterize this syndrome. Hydrocephalus occurs occasionally. Ebstein anomaly, a rare congenital heart malformation, appears to be represented disproportionately in this syndrome, although other congenital heart defects, especially patent ductus arteriosus, also are found. Ebstein anomaly, large anterior fontanel/hydrocephalus, cleft lip/cleft palate and facial dysmorphism should raise suspicion for this subtelomeric disorder. Later complications include growth failure, seizures, sensorineural hearing loss, visual abnormalities, and a variety of musculoskeletal, genitourinary, and miscellaneous features. Asthma, diabetes mellitus, leukemia, and renal failure are not reported in this syndrome.

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Rosenberg MD, Killoran C, Dziadzio L, et al. Scanning for telomeric deletions and duplications and uniparental disomy using genetic markers in 120 children with malformations. *Hum Genet.* 2001;109:311-318.

Slavotinek A, Shaffer LG, Shapira SK. Monosomy 1p36. *J Med Genet.* 1999;36:657-663.

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What are telomeres and telomerase? Available at: http://www.swmed.edu/home_pages/cellbio/shay-wright/research/sw_research.html. Accessed April 18, 2005.

Content Specifications:

Recognize the karyotype and clinical manifestations associated with the contiguous gene disorders

Recognize the karyotype and clinical manifestations associated with the microdeletion syndromes

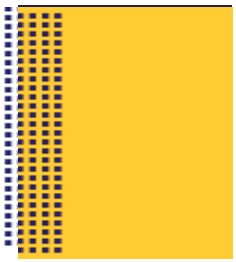

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Figure 1. Telomere and Subtelomeric Region of Chromosome 1

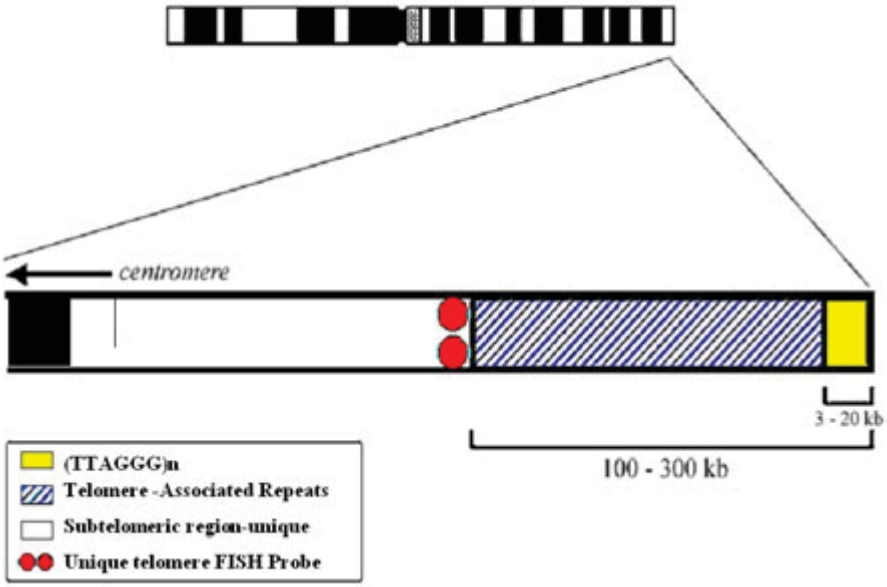


Figure 2. Subtelomeric Microdeletion of Chromosome 1

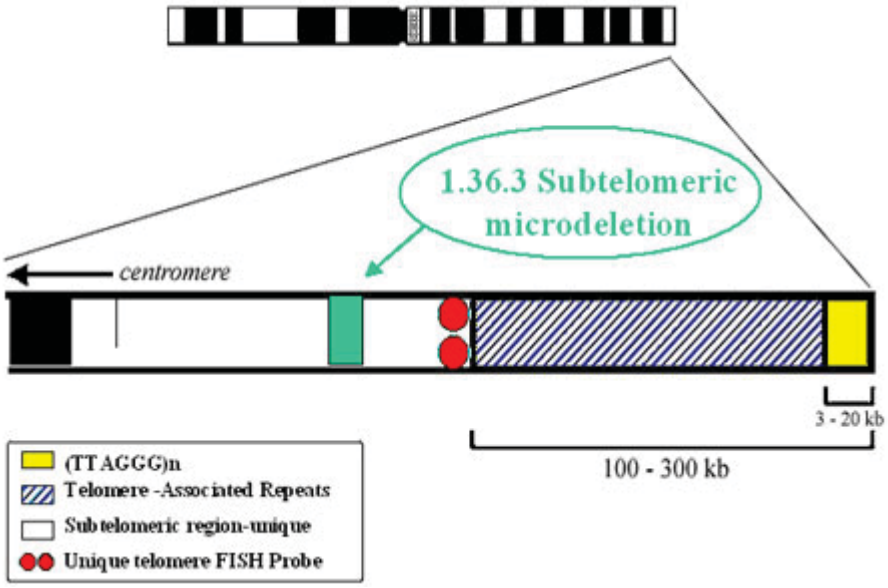


Figure 3. Newborn with 1p36.3 microdeletion

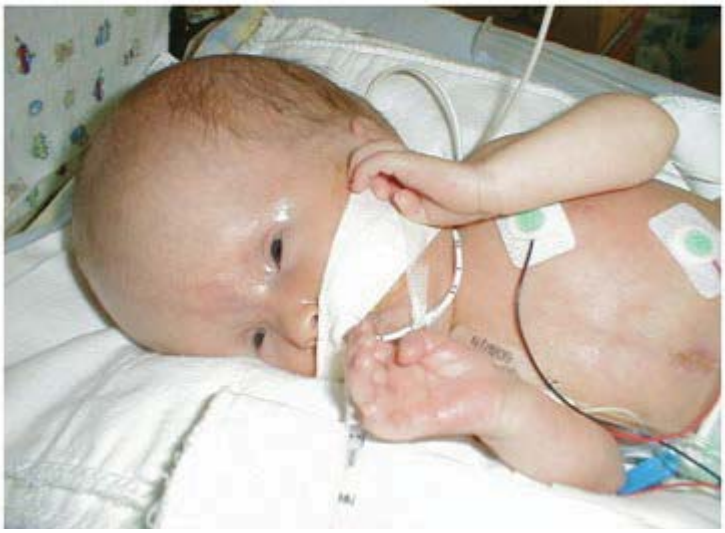


Figure 4. Newborn with 1p36.3 microdeletion

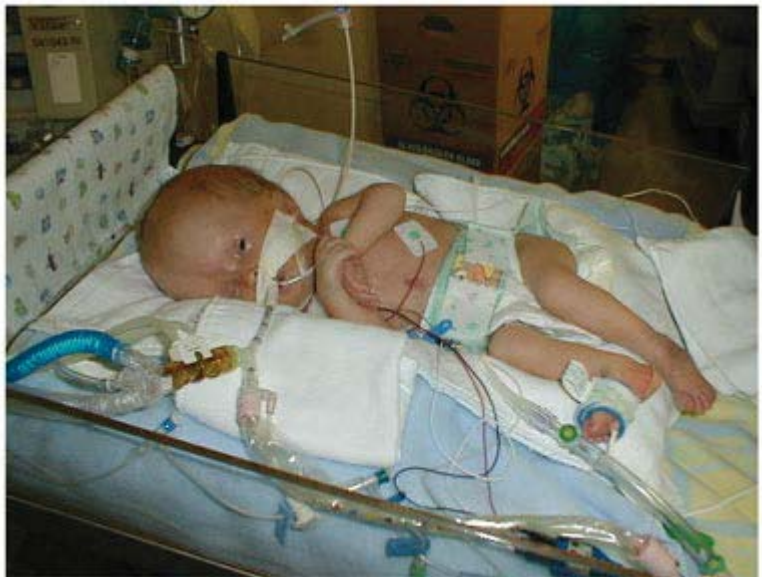
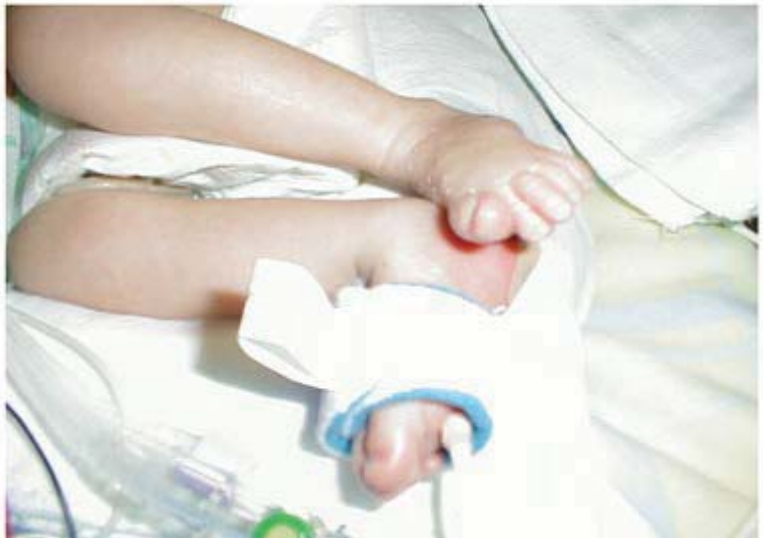


Figure 5

Figure 5. Newborn with 1p36.3 microdeletion



Close

Figure 6

Figure 6. Newborn with 1p36.3 microdeletion

Close

A 32-year-old woman received a single embryo by in vitro fertilization. Ultrasonographic examination confirmed twin females with a single placenta, a two-layered dividing membrane between the fetal sacs, and no projection of placental tissue into the dividing membrane. Genetic amniocentesis in the second trimester confirmed both fetuses to be 46,XX. At 25 weeks' gestation, ultrasonographic examination showed discordant fetal growth, oligohydramnios associated with the smaller twin, and polyhydramnios with the larger twin.

Of the following, the treatment that MOST directly addresses the underlying cause of this condition is

1	amnioreduction
2	cord occlusion by bipolar diathermy
3	laser coagulation of placental vascular anastomoses
4	microseptostomy
5	termination of pregnancy

You selected 3, the correct answer is 3.

Because the twin gestation described in the vignette resulted from implantation of a single embryo, it is nearly certain that the twins are identical. Twinning occurs in 0.8% of single embryo implantations. Approximately 70% of identical twins are monochorionic. In multiple-gestation pregnancy, prematurity, monochorionicity, and growth restriction contribute most to fetal and neonatal health risks. Monochorionic twins have a perinatal mortality rate of 26%.

Although all monochorionic (and rarely dichorionic) twins have vascular anastomoses and some degree of twin-twin transfusion, about 15% have sufficient blood transfer from arteriovenous anastomoses to result in the clinical syndrome of mid-trimester discordance in fetal size and amnionic fluid volumes known as the twin-twin transfusion syndrome. The exact incidence of this syndrome is not known because twin-twin transfusion may result in the death and subsequent resorption of one twin in the first trimester, an entity called "vanishing twin syndrome." In 70% of monochorionic twin pregnancies, arteries from one twin enter placental cotyledons drained by veins going to the other twin. In most situations, bidirectional arterioarterial anastomoses compensate for the arteriovenous shunting. Studies have demonstrated that a paucity of arterioarterial connections combined with a number of deep arteriovenous connections is associated with twin-twin transfusion syndrome. The donor twin develops uteroplacental insufficiency and hypovolemia; the recipient twin develops hypervolemia, with resultant cardiac dysfunction from right ventricular dilatation and tricuspid regurgitation, as well as a 9% risk for right ventricular outflow obstruction due to hypertrophy. Twin-twin transfusion noted before 26 weeks' gestation and left untreated is associated with up to 90% perinatal mortality and a significant risk of developmental abnormalities among the surviving infants. The severity of the syndrome is assessed by a scoring system developed by Quintero and associates:

Stage 1	**Abnormal amnionic fluid levels only, urinary bladder of donor twin filled**
Stage 2	**Collapsed urinary bladder in oliguric donor twin**
Stage 3	**Abnormal Doppler flow in umbilical artery or ductus venosus in either twin**
Stage 4	**Hydrops in either twin**
Stage 5	**Intrauterine death of either twin**

Among the therapeutic options presented, laser coagulation of aberrant blood vessels on the placental surface most directly influences the arteriovenous anastomoses that are the underlying cause of the syndrome. Because selective fetoscopic laser coagulation involves the combination of fetoscopy, laser therapy, and experience with placental vascular anatomy, its use requires experience in appropriate patient selection as well as in the technique itself. In one study by Senat and associates, 142 women who had twin-twin transfusion presenting between 16 and 26 weeks' gestation with polyuric polyhydramnios in the recipient twin and oliguric oligohydramnios in the donor twin were randomized to either amnioreduction or laser vascular occlusion performed percutaneously. Greater survival and a reduced incidence of neurologic impairment were noted among the infants of mothers treated with laser compared with those treated with amnioreduction. Survival to 28 days after birth was 76% for infants in the laser group and 56% for infants in the serial amnioreduction group. The relative risk (RR) of death of both fetuses was 0.63 (95% confidence interval [CI], 0.25 to 0.93) with laser treatment, and survival without neurologic complications was 52% in the laser cohort compared with 31% in the amnioreduction group. Even with laser therapy, only 36% of the pregnancies resulted in two surviving infants. Factors still needing elucidation in this procedure include identification of clinically relevant anastomoses using vascular tracers, identification of deeper anastomoses that cannot be seen with the fetoscope, and underlying poor placentation in the donor fetuses. In situations associated with the death of one twin in utero, the relative risk for cerebral lesions in the surviving twin was reduced (RR 0.2; 95% CI, 0.05 to 0.85) among fetuses in the laser group.

Amnioreduction is directed at effects of the twin-twin transfusion syndrome rather than at its cause. The therapeutic goals are to reduce polyhydramnios, thereby decreasing the risk of preterm delivery, and to reduce pressure on the fetal surface of the placenta, thereby improving fetal hemodynamics. Amnioreduction is more readily available, simpler, and safer than fetoscopy and laser coagulation, and an initial trial of amnioreduction may prevent disease progression in 20% of cases. In one investigation, Quintero stage 1 or 2 disease treated with laser was associated with greater fetal mortality (odds ratio [OR], 2.7), but in Quintero stage 3 or 4 disease, the affected fetuses had reduced mortality (OR, 0.4) with laser treatment. In two large registries of twin-twin transfusion syndrome, amnioreduction has been associated with 60% fetal survival, although the data from these registries are not directly comparable to the data from the population presenting at 15 to 26 weeks' gestation in the laser coagulation study.

In cases in which fetal death is likely, cord occlusion by bipolar diathermy may protect the surviving fetus from the complications of hypotension associated with agonal intertwin transfusion. However, this treatment does not affect the placental vascular anastomoses underlying the twin-twin transfusion syndrome.

Connecting the two amniotic sacs by microseptostomy attempts to balance the amnionic fluid volumes between the two fetuses. Similar to amnioreduction, microseptostomy may reduce the impact of polyhydramnios and may increase the intravascular volume of the donor twin by promoting fetal swallowing, but it does not improve the circulatory imbalance between the fetuses.

Termination of pregnancy may be presented as an option when the fetus develops signs of a worsening condition, such as hydrops, critical pulmonary outflow obstruction, grade 3 or 4 intracranial hemorrhage, porencephaly, or hydrocephaly, in spite of therapy. In the laser/amnioreduction comparison study, 11 of 70 women randomized to the amnioreduction group eventually elected termination of pregnancy for one or more of the above reasons. None of the 72 women in the laser group electively terminated the pregnancy.

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Content Specification:

Understand the implications and complications of multiple gestation, such as cord problems, twin-twin transfusion, "stuck twin," conjoined twins, etc.

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A 32-hour-old term female infant develops respiratory distress. On physical examination, she has midfacial hypoplasia, short philtrum, low-set ears, and retrognathia. Her respiratory rate is 76 breaths/min, she has a grade 2/6 systolic heart murmur, and she is jittery. Her 3-year-old sister has recurrent viral infections and persistent oral thrush. A complete blood cell count reveals: hemoglobin, 20 g/dL (200 g/L); hematocrit, 60% (0.60); platelet count, $160x10^3$/mcL ($160x10^9$/L); and total leukocyte count, $7.6x10^3$/mcL ($7.6x10^9$/L), with a differential count of 70% neutrophils, 3% band forms, 8% lymphocytes, 8% monocytes, and 11% eosinophils. Ionized calcium is 2.8 mg/dL (0.70 mmol/L). Echocardiography reveals an interrupted aortic arch.

Of the following, the MOST likely diagnosis for the infant and her sister is

1	Bruton agammaglobulinemia
2	Chédiak-Higachi disease
3	chronic granulomatous disease
4	DiGeorge syndrome
5	Wiskott-Aldrich syndrome

You selected 3, the correct answer is 4.

The infant described in the vignette has clinical features and laboratory findings consistent with the diagnosis of DiGeorge syndrome (DGS). DGS occurs when the third and fourth pharyngeal pouches fail to differentiate into the thymus and parathyroid glands by the sixth week of gestation. The facial anomalies are due to abnormal development of the first arch. The syndrome is the result of a deletion on the long arm of chromosome 22. The deletion, known as the DGS critical region, is located on band 22q11.2 and can be transmitted in an autosomal dominant inheritance pattern or from an unbalanced translocation from an unaffected parent. DGS is diagnosed by high-resolution chromosomal analysis with fluorescent in situ hybridization probe for the 22q11 deletion.

Cardiac defects occur in 50% to 90% of patients who have DGS. The most common defects are conotruncal anomalies such as the type B interrupted aortic arch [coarctation of aorta figure from Neopix], right aortic arch, bicuspid aortic valve, truncus arteriosis, and tetralogy of Fallot. Other potential cardiac anomalies include membranous ventricular septal defects, atrial septal defects, aberrant right subclavian artery, and the absent pulmonary vein syndrome.

Characteristic facies of DGS may not be apparent at birth but become more pronounced with aging. The classic phenotype includes midface hypoplasia, velopharyngeal insufficiency (such as cleft soft palate), narrow palpebral fissures with hypertelorism, long face, shortened philtrum (fish-mouth), low-set posteriorly rotated ears, and retrognathia.

Approximately 25% of affected patients have clinically significant immune deficiency because of thymic hypoplasia. The degree of immune deficiency depends on the amount of thymic tissue present. Thymic aplasia is rare; most patients have "partial DGS" with thymic hypoplasia. Patients who have DGS usually exhibit mild lymphopenia. Low numbers of T cells can be quantified by flow cytometry, and generally there are decreased numbers of $CD3^+$, $CD4^+$, and $CD8^+$ T cells. The numbers of B cells and natural killer cells usually are normal. Patients who have complete DGS are susceptible to opportunistic infections with organisms such as *Pneumocystis carinii* as well as viral and fungal infections. Graft versus host disease can develop from nonirradiated blood transfusions.

Parathyroid gland hypoplasia in DGS results in hypoparathyroidism and hypocalcemia. Because approximately 10% to 20% of patients develop seizures due to hypocalcemia, calcium supplementation may be required.

Bruton agammaglobulinemia (BA), also known as X-linked agammaglobulinemia, is associated with the development of recurrent infections because of absent circulating B cells and low levels of all immunoglobulin isotypes. The infections, caused by pyogenic bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* develop after maternal immunoglobulin (Ig) G concentrations wane at 6 to 9 months of age. BA only occurs in males and is not associated with cardiac defects, hypocalcemia, or facial abnormalities.

Chédiak-Higashi syndrome (CHS) is characterized by oculocutaneous albinism and recurrent infections. The immunodeficiency is due to abnormal lysosomal granule function. Giant lysosomal granules, seen in neutrophils, cannot fuse with phagosomes, and ingested bacteria are not killed. CHS is an autosomal recessive disorder. The genetic defect has been localized to chromosome 1q42-43. CHS usually is fatal by 30 months of age. The lack of oculocutaneous albinism or abnormal neutrophils in the infant in the vignette, and the viral and fungal rather than bacterial recurrent infections in her sister rule out this diagnosis.

Chronic granulomatous disease (CGD) is an inherited disorder in which phagocytic cells (neutrophils and macrophages) can ingest but cannot kill certain microorganisms. Phagocytes of affected patients have an impaired ability to assemble the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The incidence of CGD is 1 per 200,000 individuals. Most affected patients present in early childhood with recurrent skin infections, suppurative lymphadenitis, or pneumonia. They also may develop granulomas of the skin or gastrointestinal tract; osteomyelitis; and perianal, hepatic, or splenic abscesses. Affected patients do not have cardiac abnormalities, facial dysmorphology, or hypocalcemia.

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by recurrent bacterial sinopulmonary infections, eczema, and thrombocytopenia. Recurrent infections are due to low IgM and IgG concentrations and a lack of antibody production against polysaccharides. Decreased numbers of $CD8^+$ T cells result in elevated CD4/CD8 ratios. WAS may present with recurrent bleeding from thrombocytopenia before the development of recurrent infections. Episodes of recurrent otitis media begin at 3 to 8 months of age, as maternal IgG levels diminish. Pneumonia and meninigitis caused by encapsulated bacteria such as *S pneumoniae* and *H influenzae* and life-threatening varicella and herpes simplex infections may develop. Eczema may be mild or severe and may be associated with milk or food allergies.

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Nowicki R, Szarmach H. eMedicine: Chediak-Higashi syndrome. Available at: http://www.emedicine.com/derm/topic704.htm. Accessed January 2005.

Shigeoka AO. eMedicine: Wiskott-Aldrich syndrome. Available at: http://www.emedicine.com/ped/topic2443.htm. Accessed January 2005.

Content Specifications:

Understand the DiGeorge anomaly.

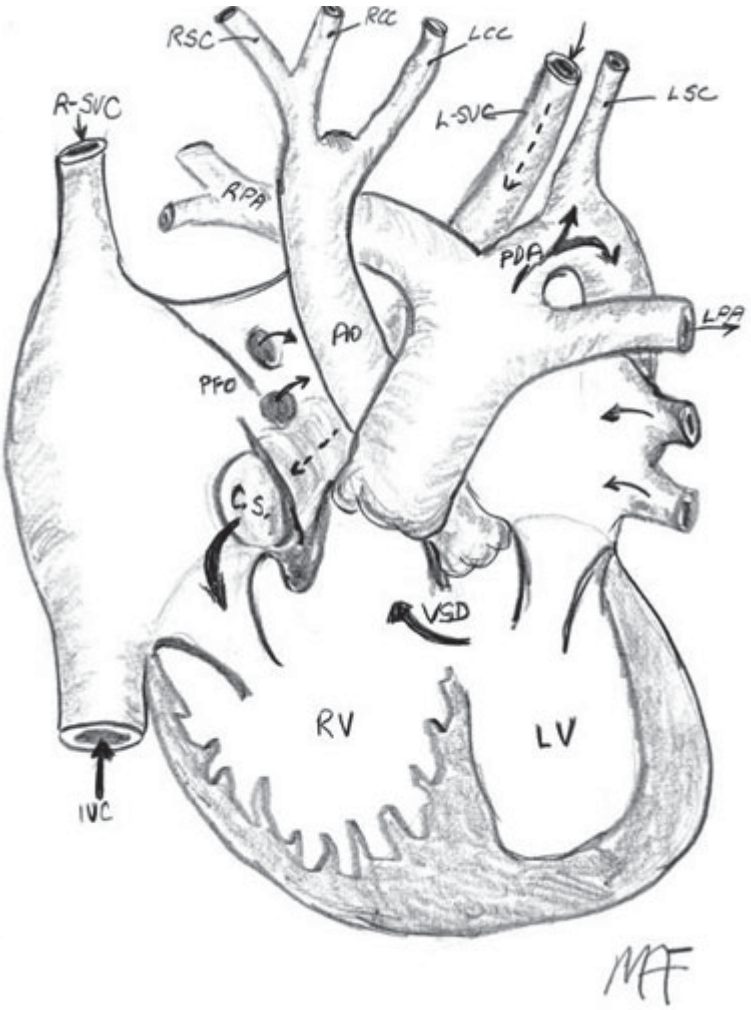
Be aware of the clinical features and differential diagnosis of neonates with immune deficiency.

Understand the pathophysiology, including genetics, of a neonate with a left sided cardiac obstructive lesion.

Recognize the karyotype and clinical manifestations associated with the common deletion syndromes.

Understand the etiology and clinical manifestations of neonatal hypocalcemia.

PREVIOUS NEXT


RSC
RCC
LCC
L-SVC
LSC
R-SVC
RPA
PDA
LPA
AO
PFO
CS
VSD
RV
LV
IVC
MF

You care for a boy who has severe hemophilia A (factor VIII deficiency). His mother tells you that she is 6 weeks pregnant and is interested in prenatal testing for this condition. Family history reveals that the mother has a brother who also is affected.

Of the following, the MOST reasonable next step is to suggest

1	amniocentesis at 14 to 18 weeks' gestation
2	chorionic villus sampling at 10 to 12 weeks' gestation
3	DNA testing on her son or brother
4	fetoscopy with fetal blood sampling at 18 weeks' gestation
5	linkage analysis for her family

You selected 3, the correct answer is 3.

Before pursuing prenatal genetic testing for any condition, it is critical to know what information must be gathered. The mother of the boy described in the vignette is an obligate hemophilia carrier because both her brother and her son are affected. However, it is important to know which, if any, factor VIII gene mutation is detectable in the family. Therefore, the most appropriate next step is to send blood from an affected family member for mutational analysis.

The factor VIII gene, located at the tip of the long arm of the X chromosome at Xq28, is very large. Many changes within the gene can cause hemophilia A. Hemophilia occurs in 1 of 5,000 males born, 85% of which are Hemophilia A. One of the most common, a gene inversion, occurs in approximately 45% of individuals who have severe disease; 50% to 90% of remaining individuals have a detectable mutation. If there is no detectable mutation, linkage analysis is available, but this typically requires multiple affected and unaffected family members.

Once a gene mutation or linkage is established, a woman can choose the method of prenatal testing she prefers. Chorionic villus sampling has the advantage of providing results earlier in the pregnancy than amniocentesis, but it may confer a higher risk to the fetus (depending on the experience of the practitioner).

Fetoscopy is not the test of choice because it confers too great a risk to the fetus, and it overlaps with amniocentesis with respect to time of sampling.

Of note, molecular genetic testing also is available for factor IX deficiency (hemophilia B) and identifies disease-causing mutations in more than 95% of affected individuals.

References:

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Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoin's Principles and Practice of Medical Genetics*. 4th ed. New York, NY: Churchill Livingstone; 2002

Sawaf H, Lorenzana A. Hemophilia A and B. Emedicine.com. Available at: http://www.emedicine.com/ped/topic962.htm. Accessed February 26, 2005.

Content specifications:

Understand the inheritance pattern of the common factor deficiencies

PREVIOUS NEXT

You work in a perinatal center that has active services in genetics and maternal-fetal medicine. Infants delivered by these services usually are referred to you for delivery room care and neonatal care. Prenatal diagnosis of the fetal condition is usual.

Of the following, the fetal condition MOST likely to predispose to fetal heart rate (FHR) abnormalities during labor is

1	Down syndrome
2	meningomyelocele
3	Potter syndrome
4	prematurity
5	trisomy 18

You selected 4, the correct answer is 3.

Potter syndrome occurs in about 1 in 4,000 births and is associated with renal agenesis and resultant oligohydramnios. In contrast, Potter sequence refers to conditions characterized by diminished amniotic fluid in the presence of kidneys. The oligohydramnios associated with these conditions may result from amniotic fluid loss or decreased fetal urinary output from renal or urinary tract abnormalities. Fetal compression due to the lack of amniotic fluid results in chest compression, limb contractures, distinctive "compressed" facial features, pulmonary hypoplasia, and respiratory failure after birth. The oligohydramnios predisposes the infant during labor to cord compression and resultant FHR abnormalities, which are more likely due to the direct effect on the cord than to fetal effects of hypoxia. Because variable decelerations reflect abnormal umbilical cord blood flow, frequent variable decelerations may occur early in labor when the cord is not protected in Potter syndrome or sequence. Prolonged labor may compromise umbilical cord blood flow to the fetus that progresses to fetal acidosis with delayed recovery of the FHR.

Down syndrome may be associated with fetal anomalies, most of which do not affect the infant's tolerance for labor and vaginal delivery. FHR monitoring in labor can be interpreted using the same criteria as for infants who do not have Down syndrome.

Meningomyelocele often is diagnosed prenatally. The criteria for interpreting FHR patterns during labor in fetuses that have meningomyelocele are unchanged from those used in monitoring of normal fetuses.

Prematurity affects the median baseline FHR. At 28 weeks' gestation, the baseline heart rate is 150±20 beats/min. There is variability in FHR, albeit at lower amplitude (eg, 5 beats/min) than seen near term. A flat baseline reading should not be attributed solely to prematurity. Vibroacoustic stimulation results in a reactive (normal) response to nonstress testing in 90% of preterm fetuses that are at least at 26 weeks' gestation. FHR monitoring during labor of the preterm fetus can be useful as long as the gestational age-specific norms are considered.

Fetuses that have trisomy 18 have basal FHR rates and responses to hypoxia similar to those seen in normal fetuses, unless specific renal anomalies result in oligohydramnios.

References:

Intrapartum assessment. In: Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC,

Wenstrom KD, eds. *Williams Obstetrics*. 21st ed. New York, NY: McGraw-Hill; 2004:331-360

Parer JT, Nageotte MP. Intrapartum fetal surveillance. In: Creasy RK, Resnik R, eds. *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia, Pa: WB Saunders; 2004:403-427

Parilla BV. Evaluation of the intrapartum fetus. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 7th ed. St. Louis, Mo: Mosby; 2002:131-138.

Content Specification(s):

Know how to assess fetal well-being during labor
Understand the significance, interpretation, and management of variable fetal heart rate decelerations in labor

PREVIOUS NEXT

A term infant has rhizomelic shortening of the arms and legs, a disproportionately long trunk, trident hands, midfacial hypoplasia, and a prominent forehead (frontal bossing) (Figure). Radiographic examination shows caudal narrowing of the interpedicular spaces. Parents have average-stature.

Of the following, the MOST appropriate recurrence risks for the parents and for the son when he becomes a father are:

1	25% for the parents; less than 1% for the son
2	50% for the parents; less than 1% for the son
3	less than 1% for the parents; 25% for the son
4	less than 1% for the parents, 50% for the son
5	50% for the parents; 50% for the son

You selected 4, the correct answer is 4.

The infant has the cardinal features of achondroplasia, a non-lethal form of chondrodysplasia. Achondroplasia is an autosomal dominant condition in which approximately 80% of affected individuals have a de novo gene mutation. Frequency is estimated at 1 case per 15,000-40,000 births. Since the condition shows complete penetrance, the average-stature parents of children who have achondroplasia have a low recurrence risk, estimated to be less than 1%, although parental germline mosaicism has been reported rarely. Of interest, de novo gene mutations are associated with advanced paternal age (>35 to 40 y). Even in the absence of advanced paternal age, de novo mutations are inherited exclusively from the father, apparently due to a gene change during spermatogenesis.

More than 99% of individuals who have achondroplasia have one of two point mutations (G1138A or G1138C) in the fibroblast growth factor receptor 3 ($FGFR_3$) gene at chromosome 4p16.3. The genetic dysfunction results in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy, and decreased cartilage matrix production. The likelihood that the child of a person who has achondroplasia will be affected is 50% if his or her partner is not affected. However, when counseling the couple described in the vignette, it is important to point out that little people often choose to marry other little people. Should their son choose to marry a woman who has achondroplasia, their risk for having a child who has homozygous achondroplasia (inheriting two copies of the unusual gene) is 25%, and this is a lethal condition. Of the remaining three possible outcomes, two children would be affected with achondroplasia, and one would not inherit the unusual gene.

References:

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Park JG, Wallerstein R. Achondroplasia. Emedicine.com. Available at: http://www.emedicine.com/ped/topic12.htm.

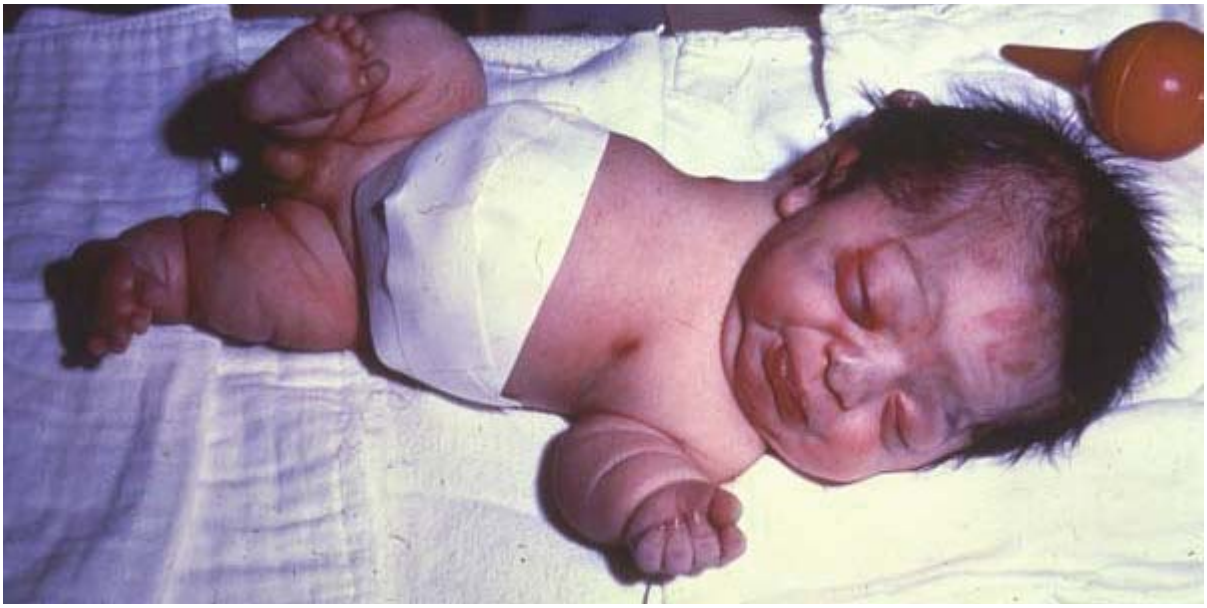
Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoin's Principles and Practice of Medical Genetics*. 4th ed. New York, NY: Churchill Livingstone; 2002

Content specifications:

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

Demonstrate understanding of inheritance patterns and recurrence risks for autosomal dominant disorders

Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoinís Principles and Practice of Medical Genetics*. 4th ed. New York, NY: Churchill Livingstone; 2002



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A newborn female at term has excess nuchal skin and a shield-like chest. You suspect Turner syndrome. The mother, a registered nurse, asks you what cardiac problems to expect.

Of the following, the MOST common cardiac abnormality in Turner syndrome is:

1	aortic dissection
2	bicuspid aortic valve
3	coarctation of the aorta
4	partial anomalous pulmonary venous drainage
5	ventricular septal defect

You selected 5, the correct answer is 2.

Turner syndrome is a heterogeneous collection of disorders related to the X chromosome. The syndrome represents approximately 3% of conceptuses but only about 1 in 2,500 female births. Half of all patients have a single X chromosome, with approximately 80% missing the paternally derived X chromosome. Mosaics with a normal cell line make up 15%, and the rest have structural isochromosomes of the X chromosome. Recurrence risk is no higher than for the general population.

Congenital heart abnormalities are seen in up to 50% of patients with Turner syndrome, with monosomy-X patients having the higher rate. Reproductive, renal, and thyroid problems can occur.

Bicuspid aortic valve incidence in the general population is approximately 2%, making it second only to mitral valve prolapse. It is present in 30% to 50% of patients with Turner syndrome. Physical findings, when present, include an early systolic ejection click heard best at the apex, with a soft murmur at the upper right sternal border. Bicuspid aortic valves hold the risks in later life of valvular fibrosis, calcification, stenosis, regurgitation and infective endocarditis.

Coarctation of the aorta occurs in 7% to10% of patients with Turner syndrome. A webbed neck at birth increases the risk for finding coarctation. Symptoms seen when the ductus closes include shock from myocardial dysfunction, abdominal and lower limb hypoperfusion, and respiratory failure from pulmonary edema. Heart sounds may be normal unless the frequently seen bicuspid aortic valve or ventricular septal defect (VSD) also is present.

Valvular aortic stenosis affects 3% of patients with Turner syndrome. Patent ductus and patent foramen ovale lessen the severity at birth. Congestive heart failure can develop within two weeks of birth, but most patients present with a murmur within the first four months after birth.

Partial anomalous pulmonary venous return is seen in 2% of patients with Turner syndrome. In the general population, it is found in 0.6% of autopsy series and in 15% of cases of atrial septal defect. The partial flow back to the right side of the heart increases pulmonary overcirculation and increases the long-term risk for pulmonary artery hypertension and congestive heart failure.

VSD in isolation occurs in 1 in 244 patients with Turner syndrome and in 1 in 280 live births of the general population.

Other cardiovascular abnormalities in Turner syndrome include hypertension, lipid

abnormalities, and aortic dilatation and dissection.

References:

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Saitta SC, Zackai EH. Specific chromosome disorders in the newborn. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:204-215

Sybert VP. Cardiovascular malformations and complications in Turner syndrome. *Pediatrics.* 1998;101:E11

Content specifications:

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

Understand the pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion

PREVIOUS NEXT

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You are asked to consult on a term female infant with a strong family history of recurrent infections that develop in childhood due to an inherited primary immunodeficiency syndrome. There are equal numbers of affected males and females in the family.

Of the following, the primary immunodeficiency disorder MOST likely to occur in both males and females is

1	Bruton agammaglobulinemia
2	Chédiak-Higashi syndrome
3	Duncan disease
4	Hyperimmunoglobulin M syndrome
5	Wiskott-Aldrich syndrome

You selected 3, the correct answer is 2.

Immunodeficiency disorders can be classified as primary or secondary. Primary immunodeficiency disorders are genetically determined conditions that result in increased susceptibility to infections. Secondary immunodeficiency disorders are the result of aging, infections, malnutrition, or medications.

More than 100 primary immunodeficiency disorders have been described. There is a 5-to-1 male-to-female sex predominance for primary immunodeficiency disorders that present in childhood, because many are due to X-linked recessive mutations (Figure). Among the primary immunodeficiency disorders in this vignette, only Chédiak-Higashi syndrome (CHS) affects both males and females, whereas the rest of the syndromes are X-linked and affect only males.

CHS is characterized by recurrent infections, excessive bleeding, and partial oculocutaneous albinism. The hallmark of CHS is giant lysosomal granules seen in neutrophils, melanocytes, neural Schwann cells, hepatocytes, renal tubular cells, and gastric mucosa. Defective melanization of melanosomes causes partial oculocutaneous albinism. Children with CHS have light skin and silvery hair. Photophobia is caused by loss of iris pigmentation. Progressive neurologic deterioration, characterized by weakness, ataxia, neuropathies, and seizures, develops if the infant survives until late childhood.

The immunodeficiency is due to abnormal lysosomal granule function. The giant lysosomal granules in neutrophils cannot fuse with phagosomes, and ingested bacteria are not killed. Recurrent skin infections, pyoderma, and subcutaneous abscesses caused by *Staphylococcus aureus* are common. CHS usually is fatal by 30 months of age due to infection, bleeding or secondary lymphoma.

CHS is an autosomal recessive disorder with equal numbers of affected males and females. The genetic defect has been localized to chromosome 1q42-43. The CHS protein is important in the synthesis and maintenance of storage and secretory lysosomal granules.

Bruton agammaglobulinemia (BA), also known as X-linked agammaglobulinemia, is associated with the development of recurrent infections because of absent circulating B cells and low levels of all immunoglobulin isotypes. The infections, caused by pyogenic bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* develop after maternal immunoglobulin (Ig)G concentrations wane at 6 to 9 months of age. BA is due to a mutation in

B-cell tyrosine kinase gene mapped to position Xq22. This kinase is necessary for pro-B-cell maturation into pre-B cells. The bone marrow of males with BA has normal numbers of pro-B cells but severely decreased numbers of pre-B cells. Patients with BA have no B cells in their blood or lymphoid tissue, and their sera contain only small amounts of IgG and no IgA, IgM, IgE or IgD.

Duncan disease, also referred to as X-linked lymphoproliferative disease (XLP), is due to abnormal B-cell polyclonal expansion triggered by Epstein Barr virus (EBV). Affected males are healthy until an EBV infection triggers fulminant, frequently fatal infectious mononucleosis, B-cell lymphomas, hepatitis, aplastic anemia, or hypogammaglobulinemia. The median age of onset is 5 years, and 70% die by age 10 years. XLP is caused by a mutation in the SH2D1A gene at Xq26-27. This gene encodes the signaling lymphocyte activation molecule-associated protein (SAP). In patients with XLP, the lack of SAP leads to uncontrolled cytotoxic T-cell response to EBV and polyclonal B-cell expansion.

HyperIgM syndrome (HIgM) is a life-threatening, X-linked, inherited disorder that results in extremely elevated IgM concentrations and low concentrations of other Ig isotypes (IgG, IgA, and IgE). Males with HIgM develop recurrent sinopulmonary infections and chronic diarrhea between 6 months and 12 months of age as maternally derived IgG wanes. Frequent sinopulmonary infections with *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* result in chronic cough and bronchiectasis. The gastrointestinal tract becomes infiltrated with IgM-producing B cells. Intractable diarrhea caused by *Cryptosporidium*, rotavirus, *Giardia*, or *Campylobacter* results in malnutrition and cachexia. Patients with HIgM have high rates of malignancies, particularly lymphomas and gastrointestinal adenomas. The mean age at death from HIgM is 11.7 years; only 20% survive to 25 years of age.

In HIgM, B cells can initiate the immune response by producing IgM but cannot make the isotype switch from IgM to synthesis of IgG, IgA, or IgE. HIgM is due to a mutation in the gene for the CD40 ligand on T cells. T-cell CD40 ligand must bind to CD40 receptors on B cells for Ig heavy chain class isotype switch to occur. The absence of CD40 ligand on T cells interrupts B-cell activation. The abnormal gene for HIgM is localized to Xq26.

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by recurrent bacterial sinopulmonary infections, eczema, and thrombocytopenia. Recurrent infections are due to low IgM and IgG concentrations and a lack of antibody production against polysaccharides. Decreased numbers of $CD8^+$ T cells result in elevated CD4/CD8 ratios. WAS may present with recurrent bleeding from thrombocytopenia before the development of recurrent infections. Episodes of recurrent otitis media begin at age 3 months to 8 months as maternal IgG levels diminish. Pneumonia and meningitis caused by encapsulated bacteria such as *S pneumoniae* and *H influenzae* and life-threatening varicella and herpes simplex infections may develop. Eczema may be mild or severe and may be associated with milk or food allergies. The WAS gene is localized on Xp11.23, and it encodes the WAS protein (WASP). *WASP* appears to regulate actin polymerization in hematopoietic cells, but its exact function has not been elucidated.

References:

Buckley RH. Primary immunodeficiency. In: Paul WE, ed. *Fundamental Immunology*. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:1593-1620

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Nowicki R, Szarmach H. eMedicine: Chediak-Higashi syndrome. Available at: http://www.emedicine.com/derm/topic704.htm. Accessed April 2005

Shigeoka AO. eMedicine: Wiskott-Aldrich syndrome. Available at: http://www.emedicine.com/ped/topic2443.htm. Accessed April 2005

Shigeoka AO. eMedicine: X-linked immunodeficiency with hyper IgM. Available at http://www.emedicine.com/ped/topic2457.htm. Accessed April 2005

Content Specifications:

Know how to diagnose hypopigmentation, including albinism, phenylketonuria, Chédiak-Higashi syndrome, tuberous sclerosis, partial albinism, and Waardenburg syndrome

Recognize the clinical features associated with X-linked disorders

Demonstrate understanding of inheritance patterns and recurrence risks for X-linked recessive disorders

Understand the consequences of immunoglobulin deficiencies

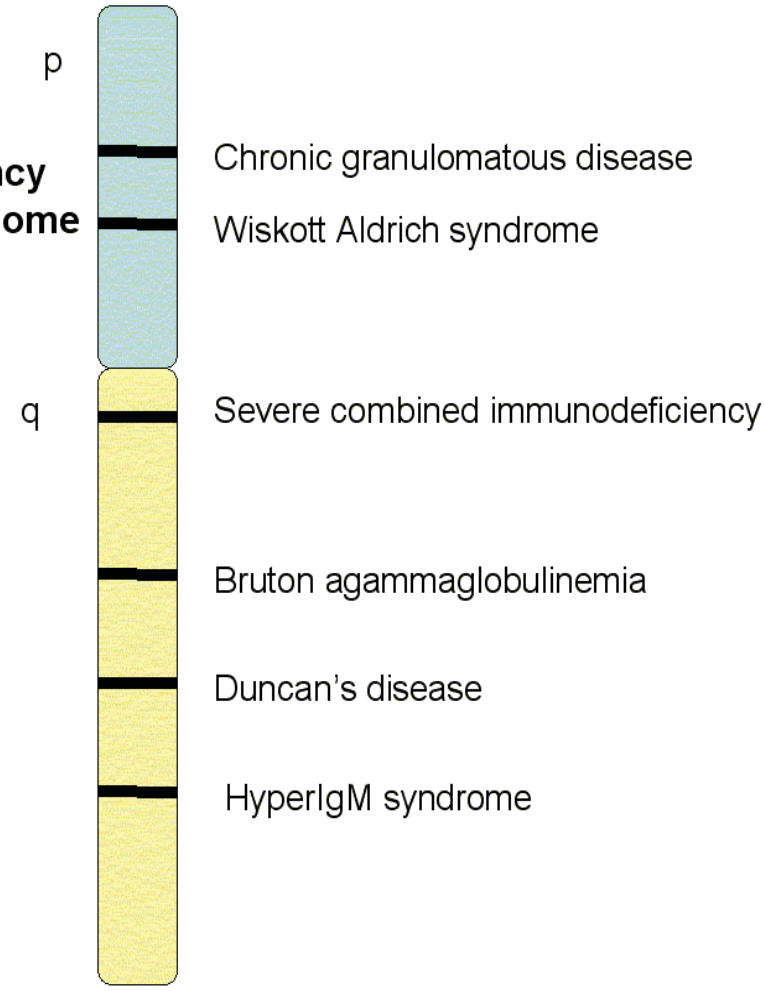
Be aware of the clinical features and differential diagnosis of neonates with immune deficiency

Be aware of the prognosis for neonates with common immune deficiencies

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

PREVIOUS NEXT

Gene location of primary immunodeficiency disorders on X chromosome



April: Question 10

A 1-week-old term infant is transferred to your care for evaluation and treatment of seizures. Physical examination reveals a normally grown, nondysmorphic, and well-appearing infant. A Wood's lamp examination of his skin reveals six small, macular, hypopigmented lesions, and an ash-leaf-shaped hypopigmented lesion on the trunk. A cranial ultrasonogram demonstrates multiple subependymal echogenic foci. Medical history and physical examination of both parents are unrevealing. This is the first child for this couple, who ask you about the risk of this same disorder in future children.

Of the following, the recurrence risk for future offspring is CLOSEST to:

1	less than 1%
2	3%
3	25%
4	50%
5	100%

You selected 4, the correct answer is 2.

The infant in the vignette has phenotypic findings consistent with the neurocutaneous disorder tuberous sclerosis complex (TSC). With an estimated incidence of 1 in 6,000 live births, TSC is a dominantly inherited genetic disease with variable expression but 100% penetrance. However, the spontaneous new mutation rate is estimated as high as 60% to 80%. TSC demonstrates genetic heterogeneity, with one of two gene deletions causing the clinical phenotype, and each deletion representing about 50% of cases. TSC1 is on the long arm of chromosome 9 (9q34; protein product hamartin), and TSC2 is on the short arm of chromosome 16 (16p13.3; protein product tuberin, and only 48 base pairs of DNA from the gene for adult onset polycystic kidney disease, PKD1). Both genes are tumor suppressor genes whose function is to regulate cell growth and differentiation. No differences in phenotype occur with the deletion of TSC1 or TSC2, except when a contiguous deletion occurs affecting both TSC2 and PKD1.

For the infant in the vignette, neither parent is affected with TSC. The infant could represent a new mutation or be affected due to germ-line mosaicism. If the abnormal cell line is confined to the gonad, then a phenotypically normal parent has a high risk of producing affected offspring. With unaffected parents, the risk of a second affected child is 1% to 4% due to this possibility of germ-line mosaicism. In the vignette, had either parent been affected, the risk would have been 50% for subsequent children due to autosomal dominant inheritance. Currently, mutational analysis of DNA extracted from fetal cells is available on a limited basis and may be useful in prenatal testing.

Characterized by the formation of multiple hamartomas, TSC may involve multiple organ systems. In 1998, revised diagnostic criteria for TSC eliminated nonspecific features, such as infantile spasms, and classified signs into major and minor features (Table). No single sign is present in all affected individuals, and the diagnosis relies upon two or more distinct types of lesions, rather than on multiple lesions in the same organ system.

Table. Revised Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features

1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungula or periungual fibroma
3. Hypomelanotic macules (three or more)
4. shagreen patch (connective tissue nevus)

5. multiple retinal nodular hamartomas
6. cortical tuber*
7. subependymal nodule
8. subependymal giant cell astrocytoma
9. cardiac rhabdomyoma, single or multiple
10. lymphangiomyomatosis**
11. renal angiomyolipoma**

Minor Features

1. multiple, randomly distributed pits in dental enamel
2. hamartomatous rectal polyps
3. bone cysts
4. cerebral white matter radial migration lines
5. gingival fibromas
6. nonrenal hamartoma
7. retinal achromic patch
8. "confetti" skin lesions
9. multiple renal cysts

Definite Tuberous Sclerosis Complex:

Either two major features or one major feature plus two minor features

Probable Tuberous Sclerosis Complex:

One major plus one minor feature

Possible Tuberous Sclerosis Complex:

Either one major feature or two or more minor features

*When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.

**When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definitive diagnosis is assigned.

From Roach ES, et al. Tuberous Sclerosis Complex Consensus Conference: revised clinical diagnostic criteria. *J Child Neurol.* 1998;13:624-628.

The skin is affected in nearly all individuals with TSC. Ash-leaf-shaped, hypopigmented macules are present in 90% of those affected and may be present at birth or may develop during the first two years. One or two hypopigmented macules are common in the general population, but three or more raindrop or guttate hypomelanotic macules distributed in confetti-like configurations suggest TSC. Shagreen patches or collagenomas which are raised, firm plaques located on the forehead or sacrum, also may be present in the newborn. Other major skin features of TSC, not present at birth, include facial angiofibromas and periungual fibromas.

The brain lesions of TSC include cortical or subcortical white matter tubers composed of abnormal giant astrocytes (found in 70% of affected individuals) and subependymal glial nodules (90%). Seizures, reflecting underlying cortical dysplasia, occur in up to 80% of cases and often begin in infancy with a pattern of hypsarrhythmia and infantile spasms. Up to 50% of affected individuals will have normal intellect, with the risk of mental retardation associated with the number of cerebral tubers and the presence of seizures.

Cardiac rhabdomyomas represent the earliest detectable hamartomas in TSC, diagnosed in fetal life as early as 22 weeks' gestation. Up to 60% of infants with TSC have diagnosed cardiac rhabdomyomas, which may be single or multiple. Renal involvement includes angiomyolipomas (75% of cases) and, more rarely, features of autosomal dominant polycystic kidney disease.

Asymptomatic retinal hamartomas and achromic patches (75% of cases) and lymphangiomyomatoses of the lung (1% to 6%) may develop as well.

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Content specification(s):

Understand the management and outcome of neurocutaneous disorders, including neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, etc.

Understand the diagnosis of neurocutaneous disorders, including neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, etc.

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April: Question 6

A 1450-g, 35-weeks'-gestation male newborn has multiple dysmorphic features (Figure 1),

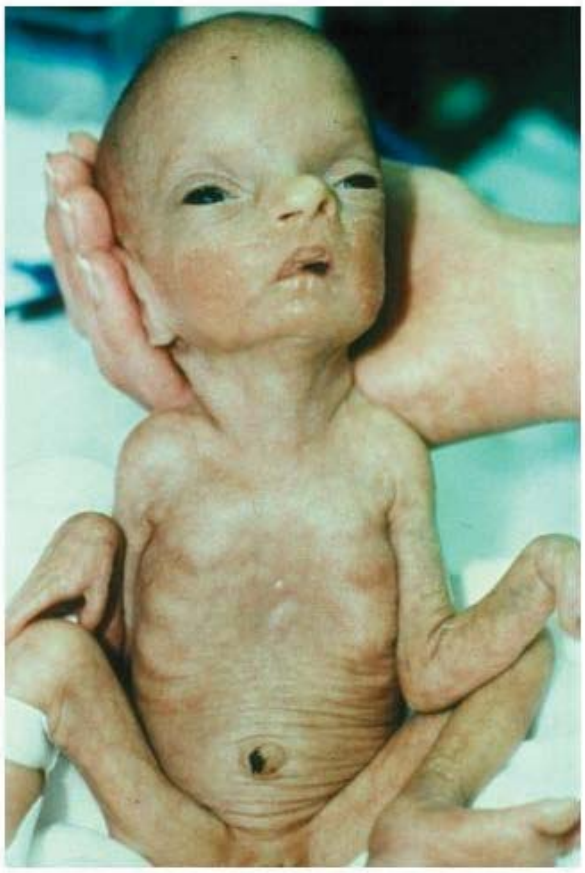

Figure 1.

including a large posterior fontanel, low-set malformed ears, micrognathia, a large bulbous nose, hypertelorism (Figure 2),

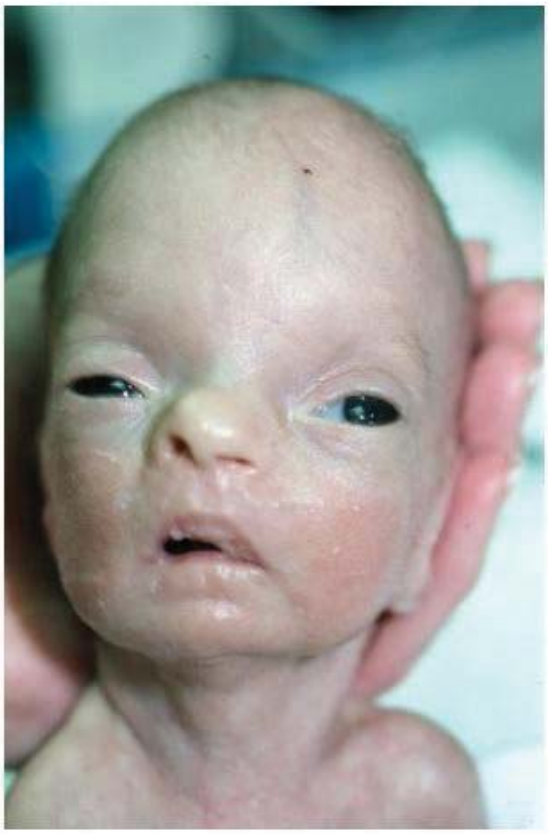

Figure 2.

talipes equinovarus, camptodactyly (Figure 3),

Figure 3.

and syndactyly involving the second and third toes. A chest radiograph demonstrates thin ribs and cardiomegaly (Figure 4).

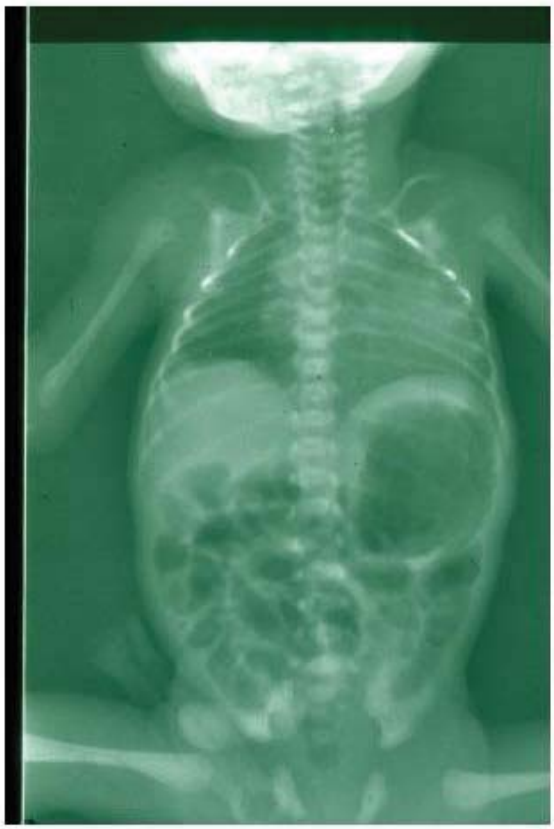

Figure 4.

A sonogram of the head demonstrates hydrocephalus. The pregnancy was complicated by midtrimester preeclampsia. The placenta was enlarged and cystic, and the pathologist informs you that it is a partial hydatiform mole.

Of the following, the MOST likely mechanism of the polyploidy in this infant and placenta is fertilization of a:

1	diploid ovum by a diploid sperm
2	diploid ovum by a haploid sperm
3	haploid ovum by a diploid sperm
4	haploid ovum by two haploid sperm
5	haploid ovum fused with a haploid polar body by a haploid sperm

You selected 3, the correct answer is 4.

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The infant and placenta described in the vignette have triploidy, a complete extra set of chromosomes (69) in the nucleus of each cell. It is estimated that 2% of all conceptuses are triploid, yet triploidy occurs in only 1 in 10,000 live births. Thus, most triploid conceptions are spontaneously aborted. Triploid pregnancies are associated with maternal hypertension, proteinuria, edema, and polyhydramnios.

The additional set of chromosomes encodes a large number of surplus gene products that cause

multiple anomalies. Infants with triploidy have intrauterine growth restriction (Figure 1), dysplastic calvaria with a large posterior fontanel, low-set malformed ears, micrognathia, a large bulbous nose, hypertelorism (Figure 2), camptodactyly (Figure 3), syndactyly involving the third and fourth fingers or the second and third toes, talipes equinovarus, and brain anomalies, such as holoprosencephaly or hydrocephalus. Cardiac lesions occur in approximately two-thirds of cases and include endocardial cushion defects, atrial and ventricular septal defects, and valvular anomalies. Chest radiography may demonstrate thin ribs and cardiomegaly (Figure 4). Associated abnormalities include myelomeningoceles, genitourinary anomalies, intestinal malrotation, adrenal gland hypoplasia, and cleft lip and palate.

The type of placenta that develops with triploidy depends upon the source of the extra set of chromosomes. If triploidy is the result of an extra set of paternal chromosomes, an abnormally enlarged and swollen placenta, classified as a partial hydatiform mole, occurs. If triploidy is the result of an extra set of maternal chromosomes, a small fibrotic placenta occurs. The large cystic placenta described in the vignette implies an extra set of paternal chromosomes.

Triploidy can occur because of abnormal fertilization or because of abnormalities during gametogenesis. The most common cause of triploidy (66% of cases) is abnormal fertilization by two sperm (dispermy). The resulting zygote receives 23 chromosomes from each sperm and 23 chromosomes from the ovum. The chromosomal complement is described as 69XYY, 69XXY, or 69XXX.

Fertilization is a complex sequence of coordinated events that begins with contact between sperm and the oocyte. The oocyte is surrounded by an acellular glycoprotein called the zona pellucida. Several sperm participate in the penetration of the zona pellucida, but usually only one sperm enters the oocyte and fertilizes it. Dispermy is when two sperm penetrate the zona pellucida and both fertilize the oocyte.

Abnormal gametogenesis is a less common cause of triploidy. Failure of meiosis during gametogenesis can result in a diploid egg or sperm. Fertilization of a diploid egg by a haploid sperm (10% of cases) or a haploid egg by a diploid sperm (24% of cases) will result in a triploid zygote.

Fusion of a haploid ovum and a haploid polar body each containing 23 chromosomes with subsequent fertilization by a haploid sperm is rare (less than 1% of cases). Because the extra set of chromosomes is maternal, the placenta is usually small and fibrotic rather than large and cystic as described in the vignette.

Fertilization of a diploid ovum by a diploid sperm would result in tetraploidy (92 chromosomes in each cell nucleus). Tetraploidy also can occur because of a mitotic failure in an early embryo in which all of the duplicated chromosomes migrate to one of the two daughter cells, or tetraploidy can result from the fusion of two diploid zygotes. A few live-born infants with tetraploidy have been reported, but they are exceedingly rare.

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Content Specification(s):

Know the fetal and placental manifestations of triploidy

PREVIOUS NEXT

February: Question 5

You are asked to evaluate a 2400-g term newborn with multiple anomalies (Figure 1, Figure 2, Figure 3, and Figure 4).

Ophthalmologic examination reveals coloboma of iris and retinal dysplasia. Echocardiography reveals a large ventricular septal defect. Cranial ultrasonography reveals holoprosencephaly. The placenta is grossly normal in size and appearance.

Of the following, the MOST likely karyotype of this infant is shown in:

1	karyotype A (Figure 5)
2	karyotype B (Figure 6)
3	karyotype C (Figure 7)
4	karyotype D (Figure 8)
5	karyotype E (Figure 9)

You selected 5, the correct answer is 1.

Critique:

Making the diagnosis of a syndrome in an infant with multiple birth defects requires recognition of overall patterns of anomalies. The diagnosis of a syndrome is rarely possible upon identification of a single birth defect. Even unusual defects, such as coloboma of iris or cutis aplasia, may be present in several different syndromes. Moreover, individuals with the same syndrome vary in the expression of anomalies. Most clinical features are found in fewer than 80% of individuals with any given syndrome. Obtaining a karyotype is of central importance in confirming the clinical diagnosis of an infant with multiple anomalies.

The infant described in the vignette has the pattern of anomalies consistent with trisomy 13 (karyotype A). The pattern of anomalies associated with trisomy 13 first was described by Bartholin in 1657, and the chromosomal pattern was discovered by Patau in 1960. The incidence of trisomy 13 is approximately 1 in 5000 live births. Approximately 60% to 80% of patients with trisomy 13 have a cleft lip and cleft palate, frequently midline (Figure 1). Localized scalp defects in the parieto-occipital area (Figure 2), abnormal helices with low-set ears (Figure 3), holoprosencephaly, polydactyly (Figure 4), colobomata of iris, and retinal dysplasia occur in more than 50% of patients. Congenital heart disease occurs in 80%, with ventricular septal defect (VSD) the most common. The defects of the

forebrain, eye, and midface are due to abnormal development of the prechordal mesoderm in the first three weeks of development. The size and gross appearance of the placenta in trisomy 13 usually is normal.

Karyotype B is trisomy 18. Its clinical features include clenched hands with overlapping fingers, prominent occiput, short palpebral fissures and skin redundancy. Trisomy 18 is more common than trisomy 13. The incidence of trisomy 18 is approximately 3 in 1000 live births. Some features occur with approximately equal frequency in trisomy 13 and trisomy 18, including low-set malformed ears and cardiac anomalies, such as VSD. Polydactyly and coloboma of iris occur in fewer than 10% of individuals with trisomy 18. Cleft lip and palate and cutis aplasia are rare.

Karyotype C is trisomy 21. Its clinical features include flat facies with a tendency to keep the mouth open and tongue protruding, a small nose with low nasal bridge, inner epicanthal folds and upward slant of eyes, cardiac anomalies, and a single palmar crease. Cleft lip and palate, cutis aplasia, coloboma of iris, and retinal dysplasia are unusual in trisomy 21.

Karyotype D is 45X or Turner syndrome. Its clinical features include congenital lymphedema, broad chest with wide-spaced nipples, prominent auricles, and webbed posterior neck. Bicuspid aortic valve or coarctation of the aorta occur in approximately 40% of Turner syndrome patients. The clinical features described in the infant in the vignette would be unusual for Turner syndrome.

Karyotype E is triploidy, a complete extra set of chromosomes (69) in the nucleus of each cell. Its clinical features include dysplastic calvaria with a large posterior fontanel, a large bulbous nose, and hypertelorism. Many anomalies occur with approximately equal frequency in triploidy and trisomy 13, including cleft lip and palate, low-set malformed ears, coloboma of iris, camptodactyly, talipes equinovarus, cardiac lesions, and holoprosencephaly. Cutis aplasia and retinal dysplasia, as described in the infant in the vignette, are rare in triploidy. Unlike trisomy 13, most cases of triploidy have grossly abnormal placentas. If the extra set of chromosomes is maternal in origin, the placenta is small and fibrotic. If the extra set of chromosomes is paternal, the placenta is enlarged, swollen, and classified as a partial hydatiform mole.

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Content Specification(s):

Recognize the physical findings and chromosomal pattern in trisomy 13

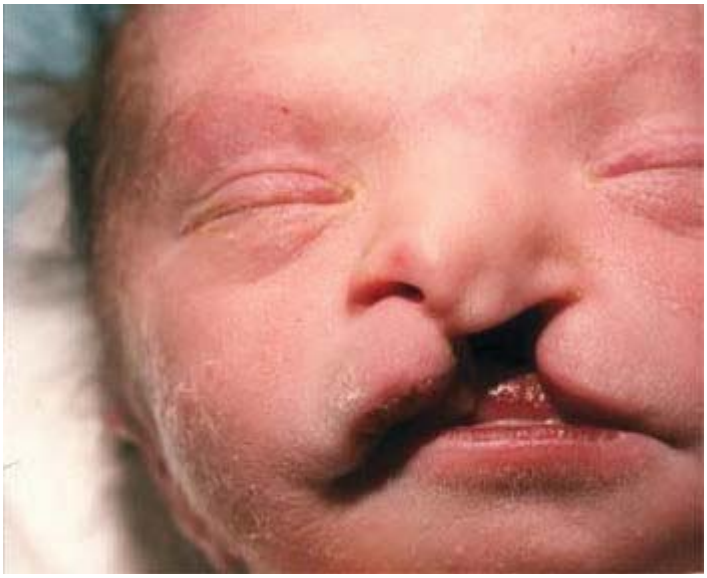
Identify the physical characteristics and chromosomal pattern in trisomy 18

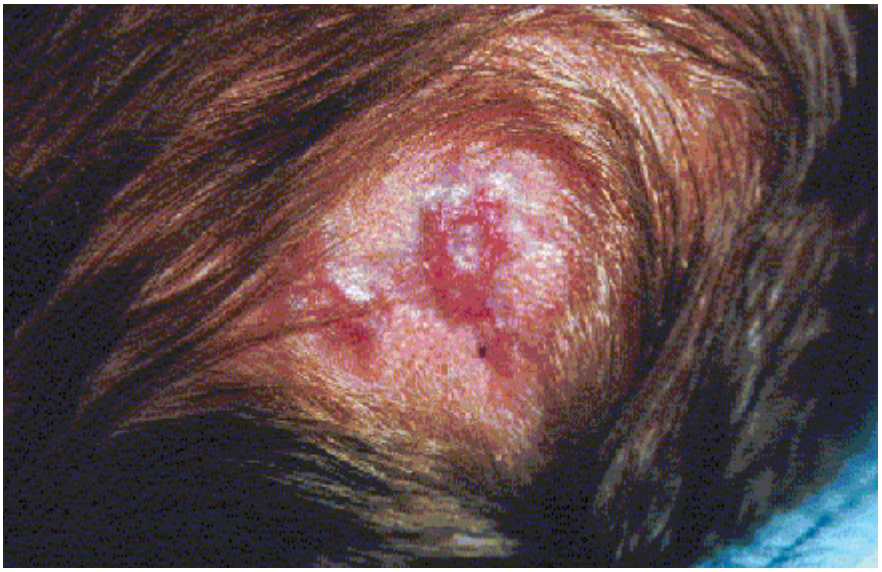
Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

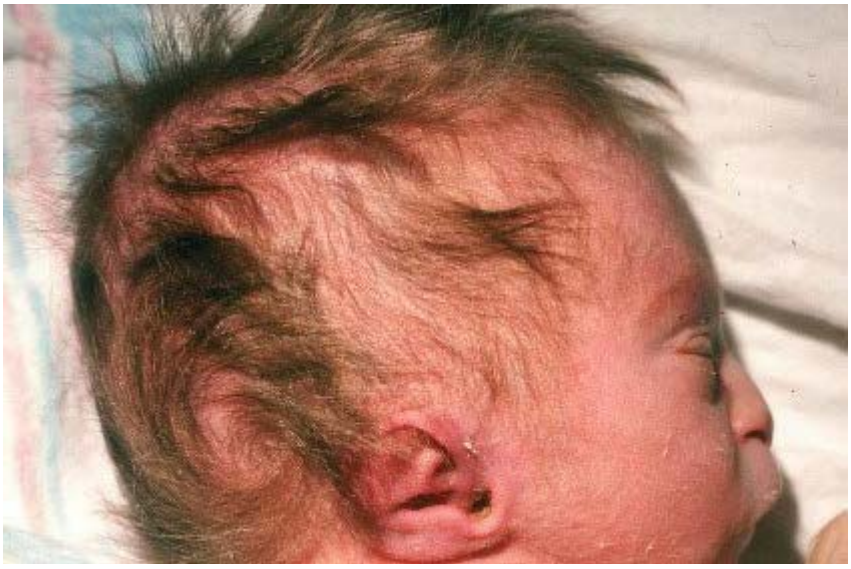
Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

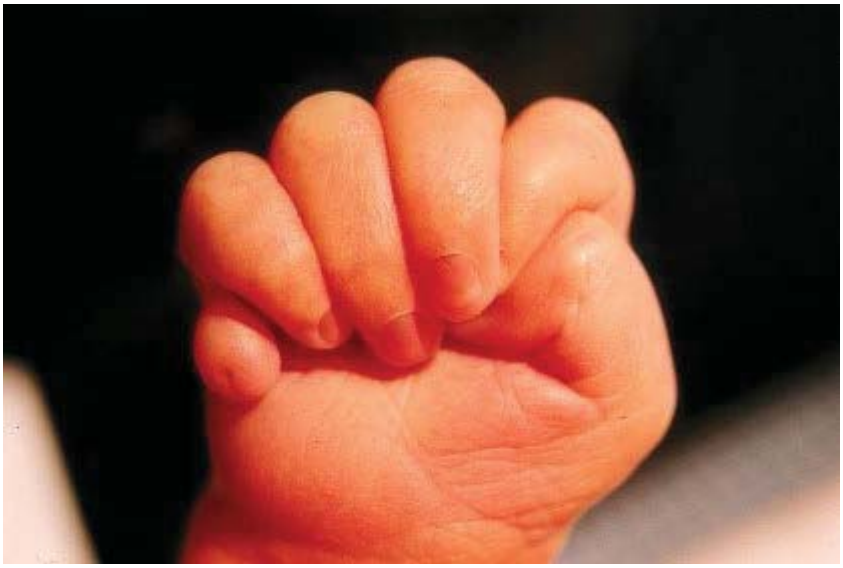
Know fetal and placental manifestations of triploidy

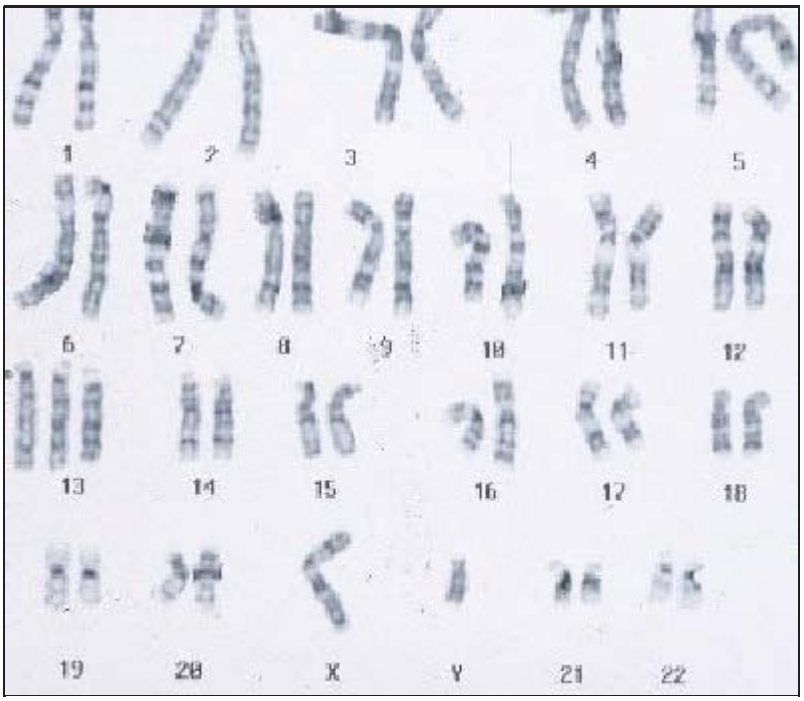
PREVIOUS NEXT







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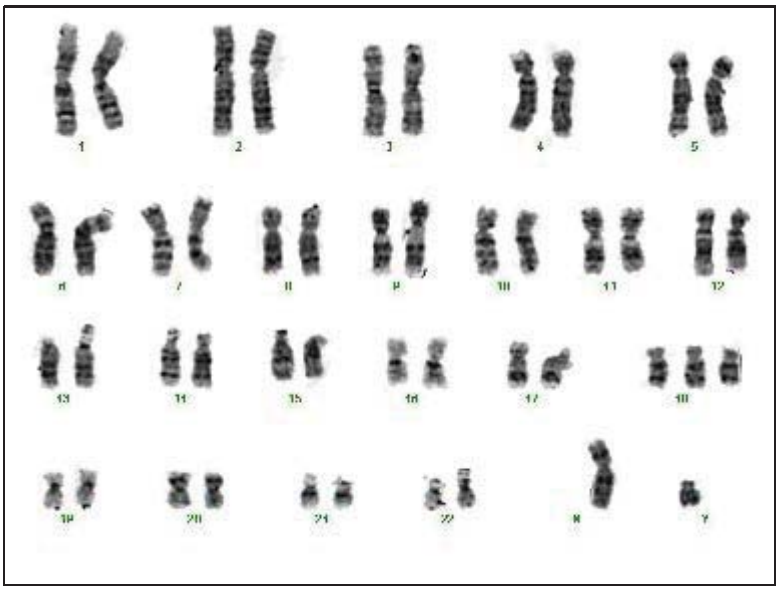

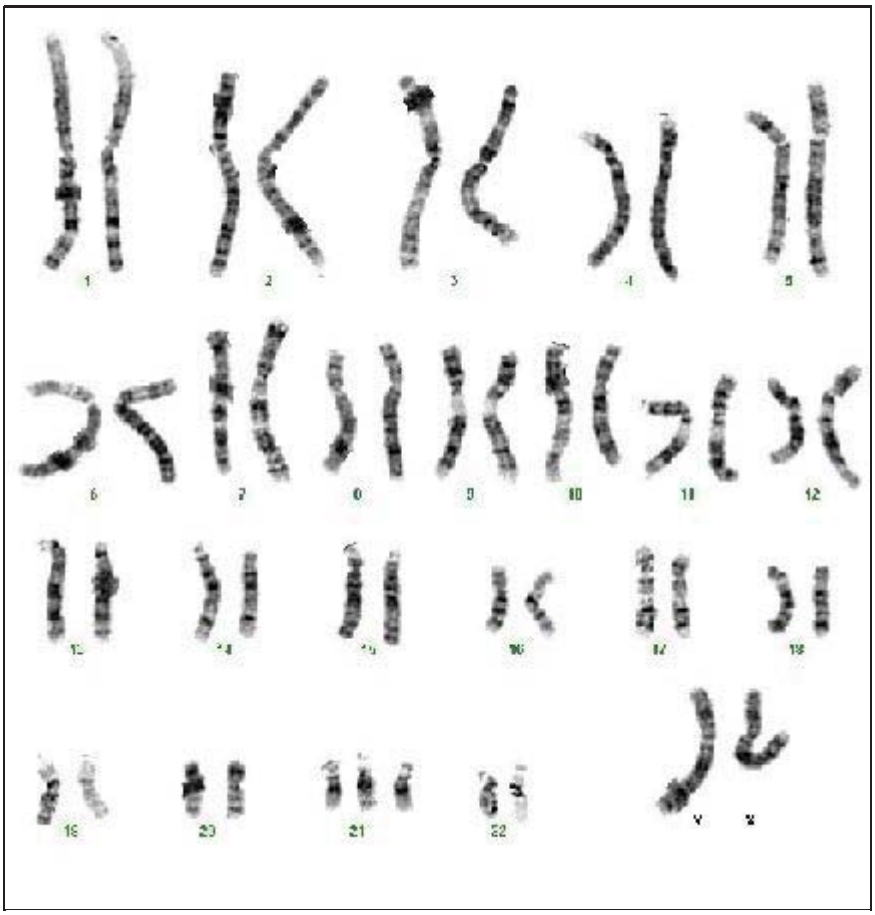

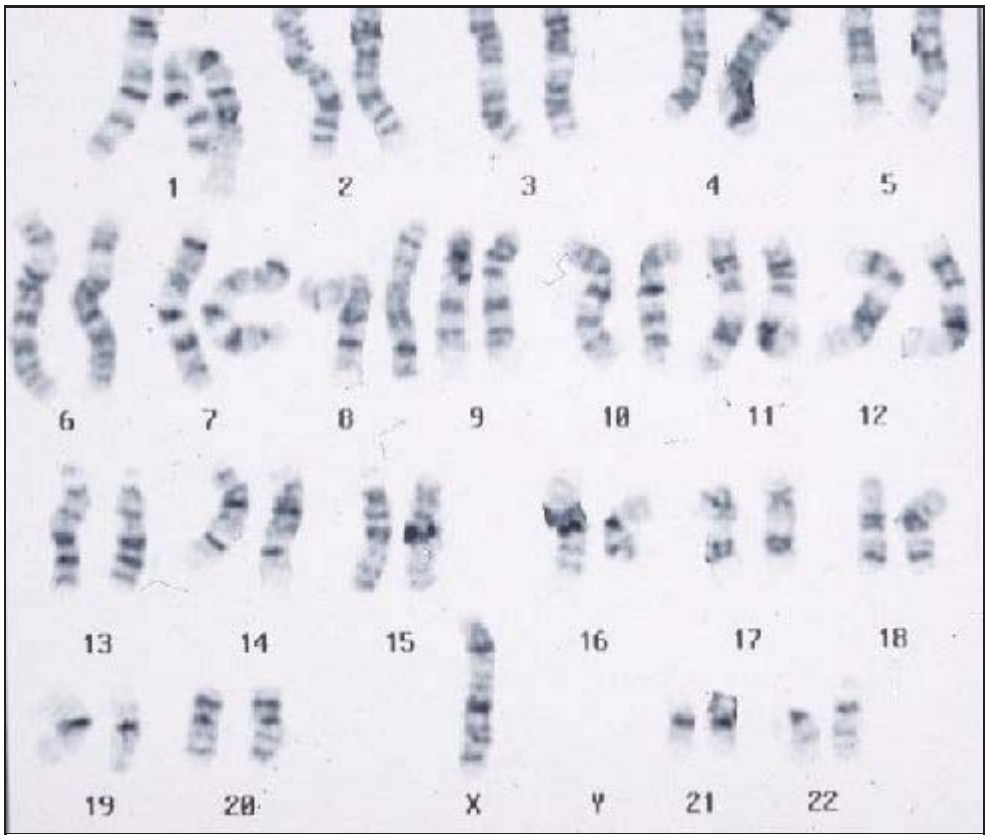
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July: Question 3

You are asked to evaluate a full-term newborn infant with intrauterine growth restriction and dysmorphic features. Birth weight is at the 4th percentile and head circumference is at the 2nd percentile for gestational age. The patient has a broad, beaked nose, hypertelorism, and low-set ears with a preauricular dimple. The parents have another child with severe mental deficiency and seizures who has been diagnosed as having Wolf-Hirschhorn syndrome.

Of the following, the MOST likely abnormality of chromosome structure causing the clinical findings in this infant is a(n):

1	deletion
2	insertion
3	inversion
4	reciprocal translocation
5	robertsonian translocation

You selected 4, the correct answer is 1.

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Abnormalities in chromosome structure result from chromosome breakage with subsequent reunion in a different configuration. Structural chromosomal rearrangements can be balanced or unbalanced. Balanced rearrangements are usually harmless because there is no loss or gain of genetic material. The exception is if one of the break points interrupts an important gene. Carriers of balanced rearrangements are at significant risk for having children with unbalanced chromosome complements. Unbalanced chromosome rearrangements are usually harmful because of the extra or missing genetic material.

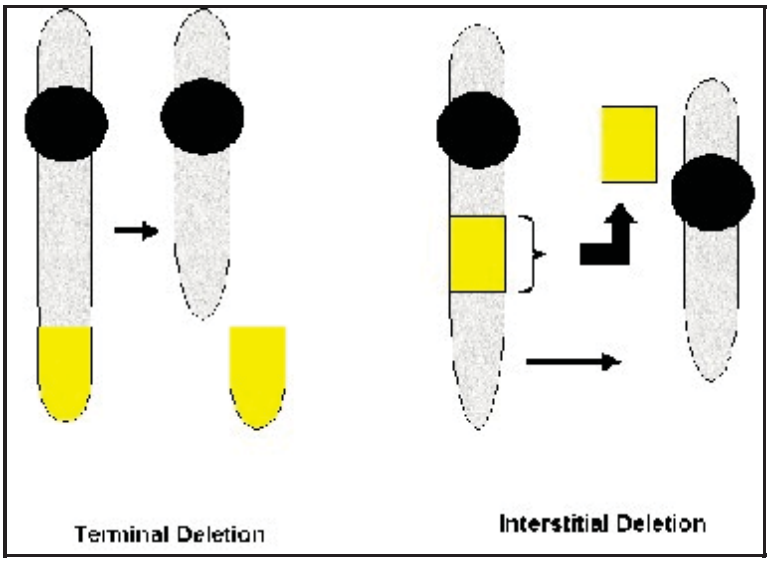
The infant and sibling described in the vignette have Wolf-Hirschhorn syndrome. Infants with Wolf-Hirschhorn syndrome have ocular hypertelorism, high arched eyebrows, and prominent glabella. Most have microcephaly and intrauterine growth restriction. The degree of developmental disability is usually severe. Approximately 40% are ambulatory, 20% perform simple household tasks, and 10% become toilet trained. The underlying chromosomal abnormality in Wolf-Hirschhorn syndrome is a partial deletion of the short arm of chromosome 4 (4p-). Approximately 87% of Wolf-Hirschhorn syndrome cases result from a sporadic de novo deletion usually of paternal origin; in 13% of cases, one of the parents, usually the mother, is a balanced translocation carrier.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

A chromosomal deletion involves a loss of part of a chromosome with resulting

monosomy for that segment of the chromosome. Deletions may occur because of chromosome breakage, abnormal segregation from a balanced translocation or inversion, or unequal crossing-over between misaligned chromatids. A chromosomal deletion (Figure 1)

Figure 1

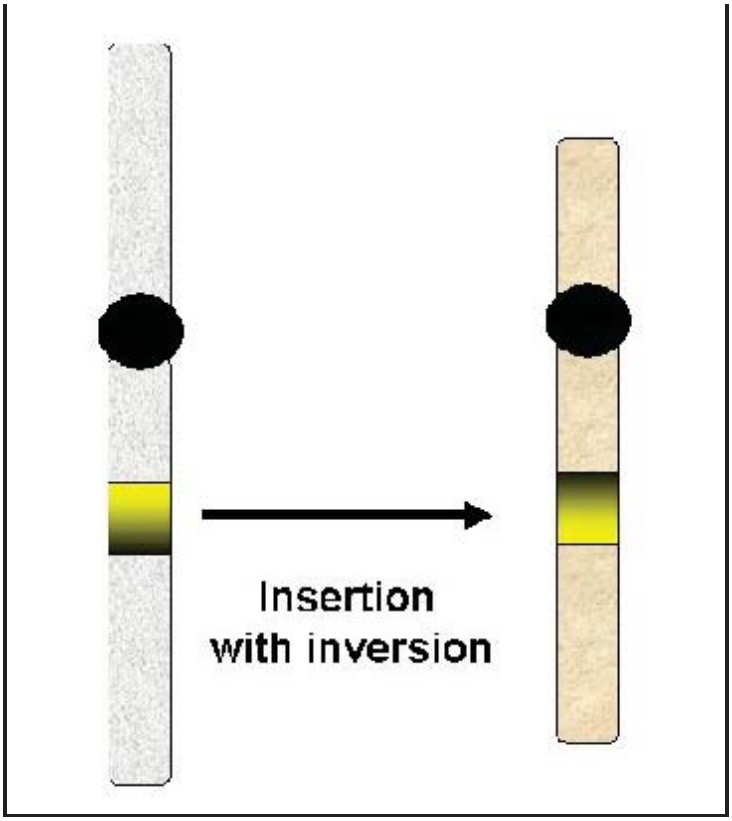


may be located at the end of a chromosome (terminal deletion) or within the chromosome (interstitial deletion). High-resolution banding techniques can identify deletions larger than 2,000 kilobases (kb).

The size of the deletion in Wolf-Hirschhorn syndrome can vary from almost half of the short arm of chromosome 4 to so small that it is cytogenically undetectable. The phenotype in Wolf-Hirschhorn syndrome does not differ based on the size of the deletion. The critical deleted region for the phenotype is 4p16.3.

An insertion occurs when a segment of one chromosome breaks off and is inserted into a different chromosome (Figure 2).

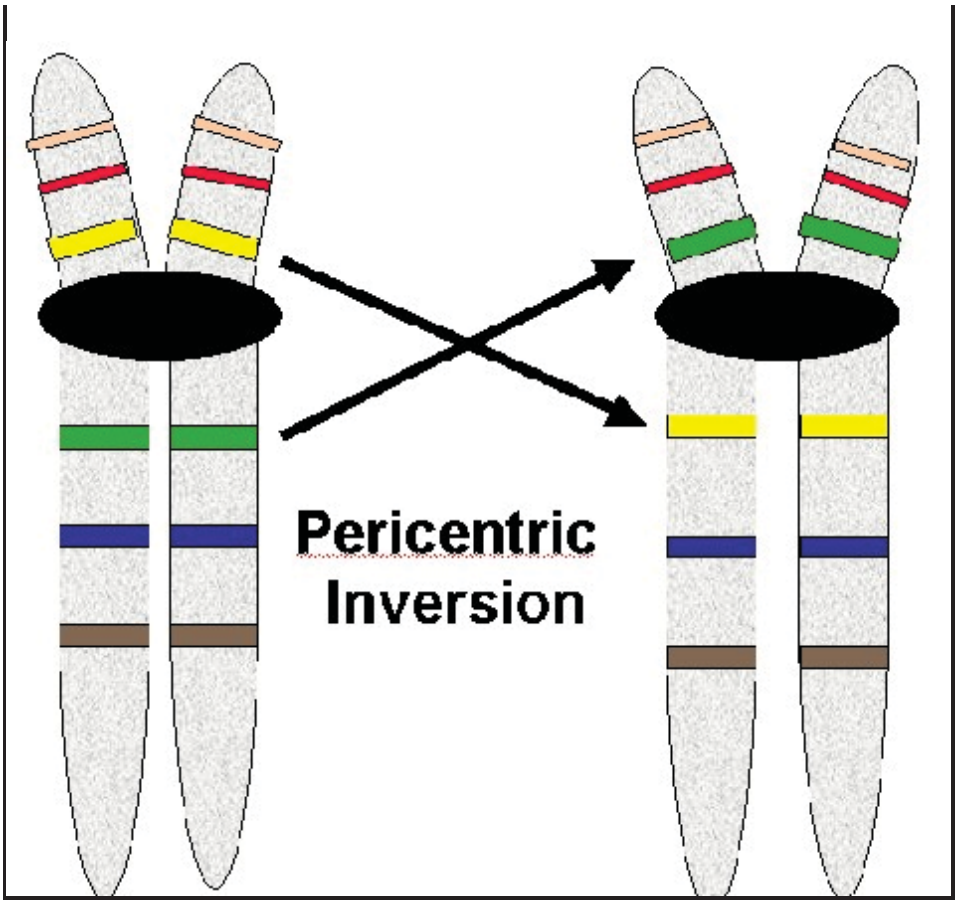
Figure 2



The insertion can be in the usual orientation or inverted. Insertions are rare because they require three chromosome breaks. Carriers of balanced deletion-insertion rearrangements are unaffected, but they are at a 50% risk of producing unbalanced gametes. Unbalanced insertions involving 4p have not been described in Wolf-Hirschhorn syndrome.

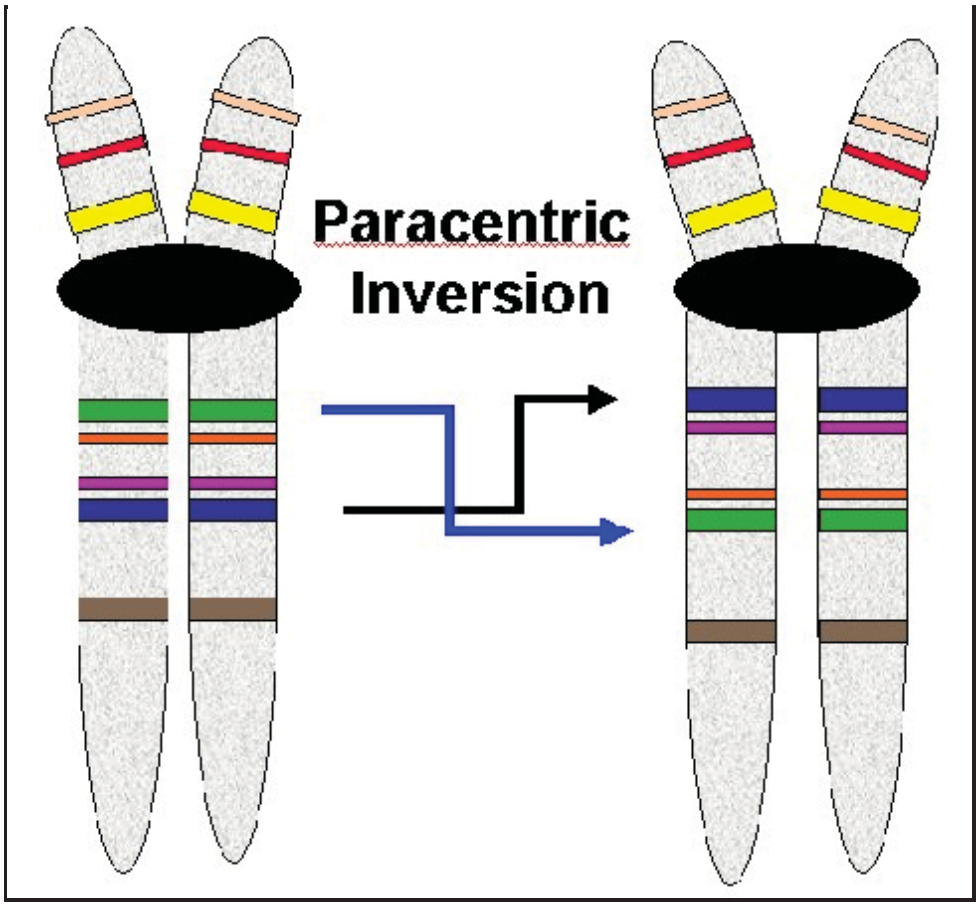
A chromosomal inversion is a two-break rearrangement involving a single chromosome in which a segment of the chromosome is reversed in position. Pericentric inversions involve the centromere (Figure 3).

Figure 3



Paracentric inversions involve one arm of the chromosome and do not involve the centromere (Figure 4).

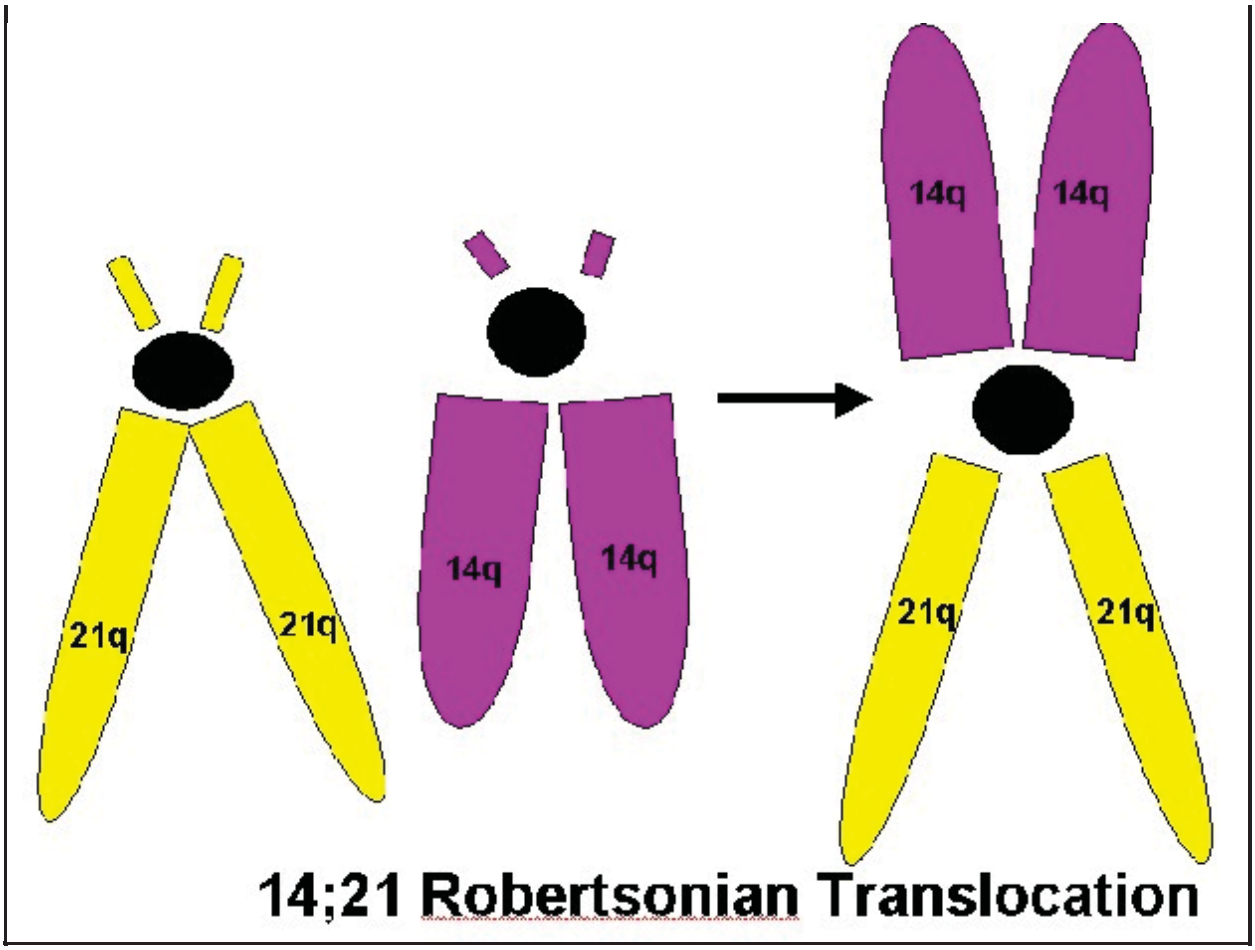
Figure 4



Paracentric inversions do not change the arm ratio of the chromosome. Paracentric inversion can only be identified by banding or fluorescence in situ hybridization with specific probes. Pericentric inversions change the proportion of chromosome arms and can be easily identified using cytogenic techniques. Inversions involving chromosome 4 have been reported in Wolf-Hirschhorn syndrome, but they are rare.

Translocations involve the exchange of chromosome segments between two nonhomologous chromosomes. There are two types of translocations, robertsonian and reciprocal. Robertsonian translocations occur when the short arms of two nonhomologous chromosomes are lost and the long arms fuse at the centromere to form a single chromosome (Figure 5).

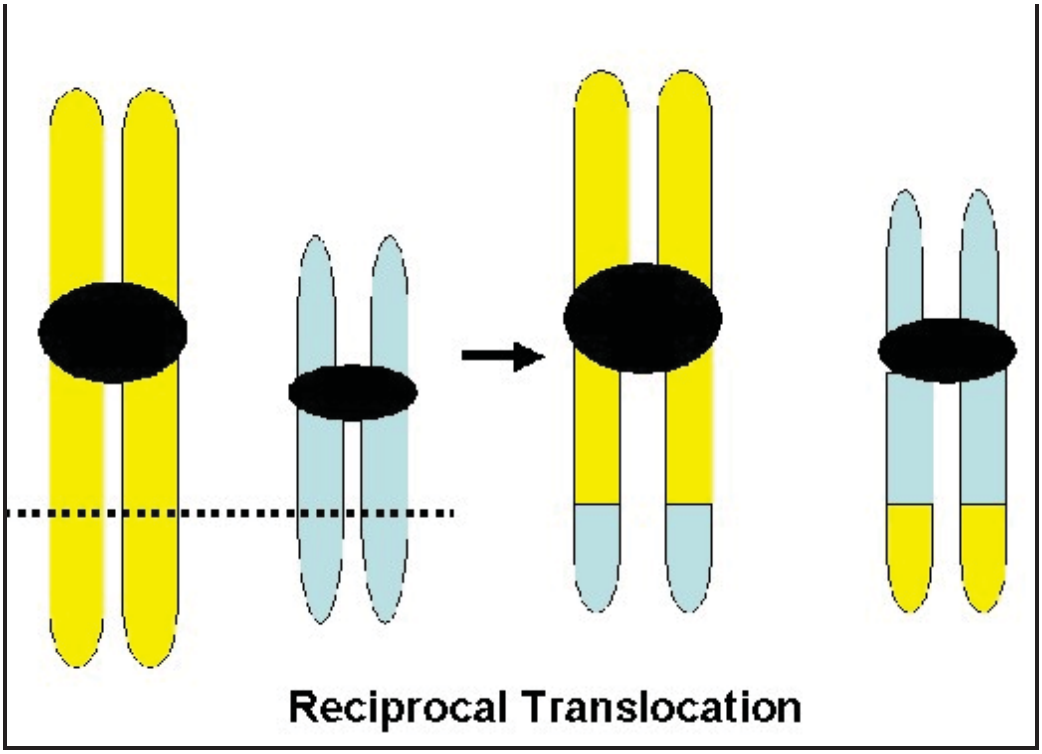
Figure 5



The resulting balanced karyotype has 45 chromosomes. Robertsonian translocations only occur with acrocentric chromosomes (13, 14, 15, 21, and 22), which have extremely small short arms. Because the short arms of these five acrocentric chromosomes contain essentially no genetic material, carriers of robertsonian translocations are phenotypically normal. However, their offspring may inherit an extra long arm of an acrocentric chromosome. Robertsonian translocations do not cause Wolf-Hirschhorn syndrome.

A reciprocal translocation is a result of breakage of nonhomologous chromosomes, with mutual exchange of the segments that are broken off (Figure 6).

Figure 6



The chromosomes that result from a reciprocal translocation are called derivative chromosomes. Carriers of balanced reciprocal translocations are phenotypically normal and have a 46-chromosome karyotype. Offspring may have partial trisomy or monosomy of the derivative chromosomes and an abnormal phenotype. Whereas 87% of Wolf-Hirschhorn syndrome cases result from a sporadic de novo deletion, 13% are the result of a deletion caused by unequal segregation of a parental translocation.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

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American Board of Pediatrics Content Specification(s):

Understand the difference between balanced and unbalanced chromosome

translocation

Know the long-term outcome and survival of infants with various congenital abnormalities

Recognize the karyotype and clinical manifestations associated with the common deletion syndromes

PREVIOUS NEXT

June: Question 9

You are asked to evaluate a 2340-gram infant born at 41 weeks of gestation with multiple anomalies (Figures 1, 2, 3, and 4).

Figure 1

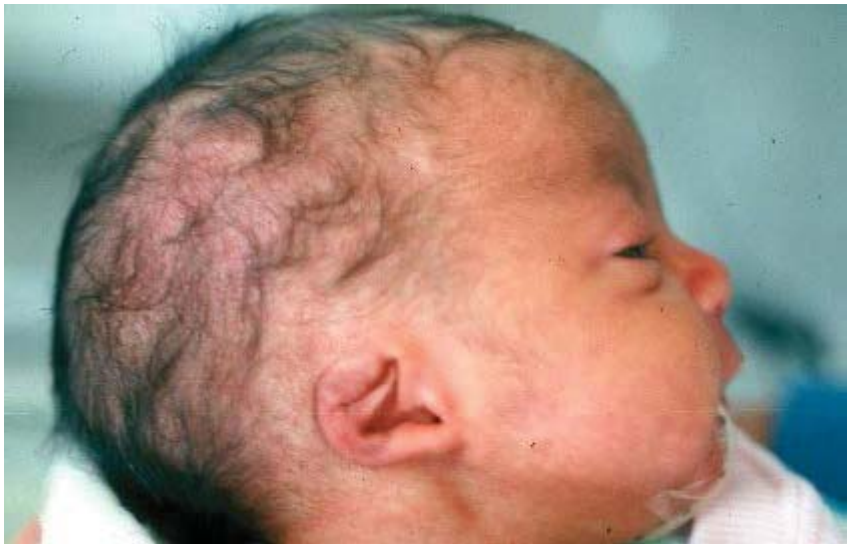


Figure 2

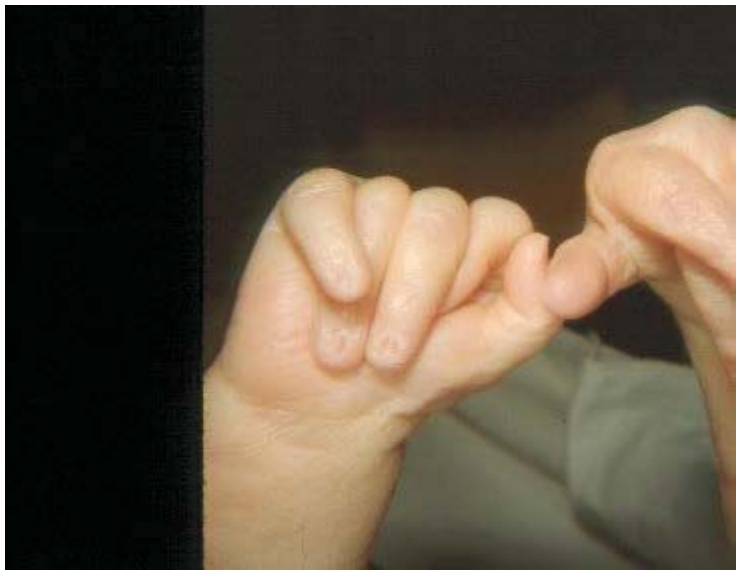


Figure 3

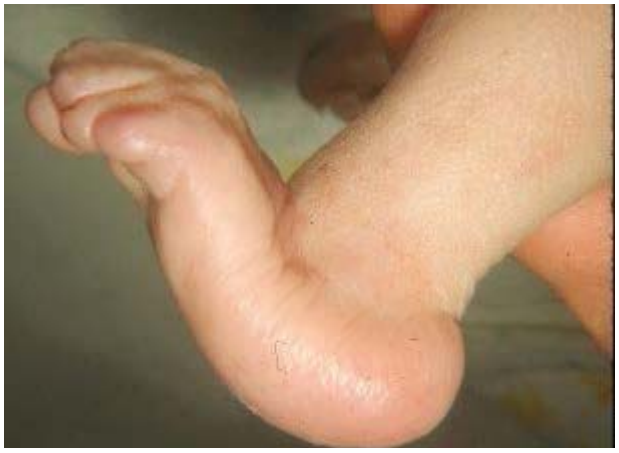
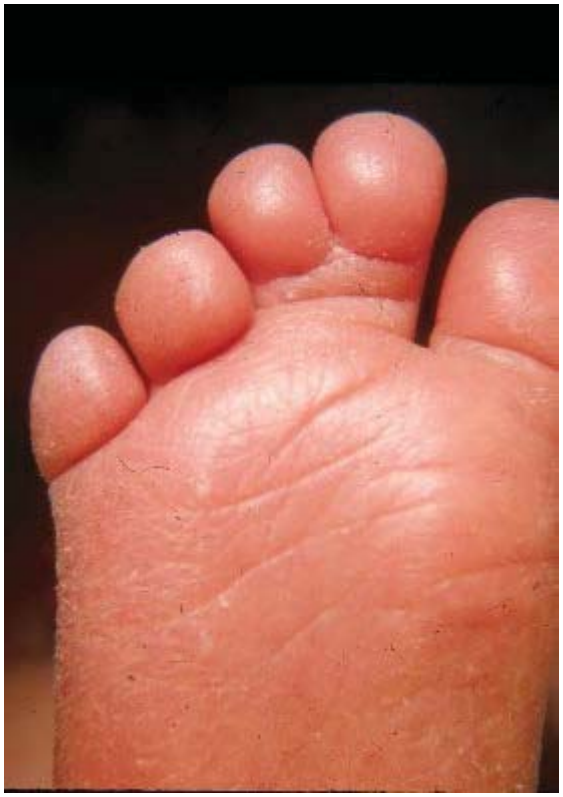


Figure 4



Additional findings on physical examination include skin redundancy, mild hirsutism of the forehead, prominent cutis marmorata, a short sternum, and limited hip abduction. The pregnancy was complicated by decreased fetal movement and polyhydramnios. Echocardiography reveals a large ventricular septal defect. The placenta is grossly normal in size and appearance.

Of the following karyotypes, the MOST likely karyotype of this infant is shown in Figure:

1	Figure 5
2	Figure 6
3	Figure 7
4	Figure 8

5 Figure 9

You selected 3, the correct answer is 2.

Do you want to add anything to your Learning Plan?
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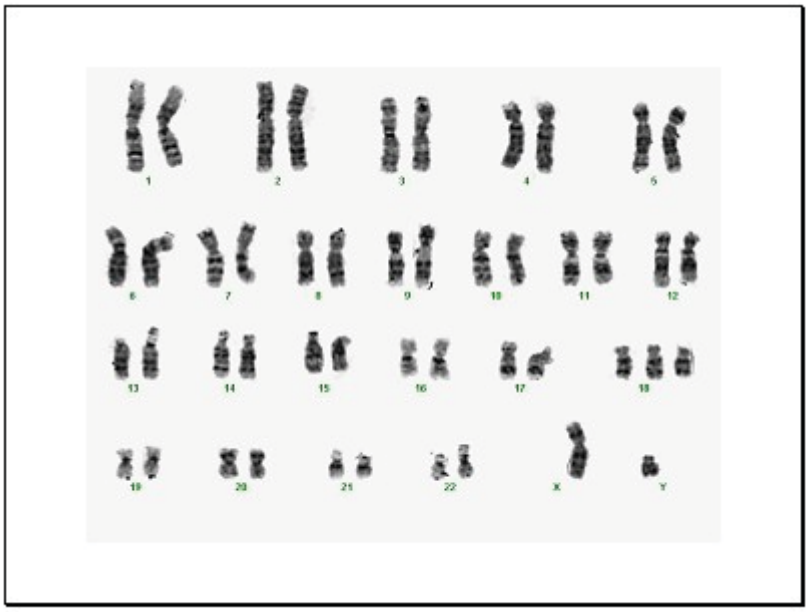
Making the diagnosis of a syndrome in an infant with multiple birth defects requires recognition of overall patterns of anomalies. It is rarely possible to make a diagnosis of a syndrome based on identification of a single birth defect. Even unusual defects such as rocker-bottom feet and a short sternum may be present in several different syndromes. Moreover, individuals with the same syndrome have varied expression of anomalies. Most clinical features are found in fewer than 80% of individuals with any given syndrome. Obtaining a karyotype is of central importance in confirming the clinical diagnosis of an infant with multiple anomalies.

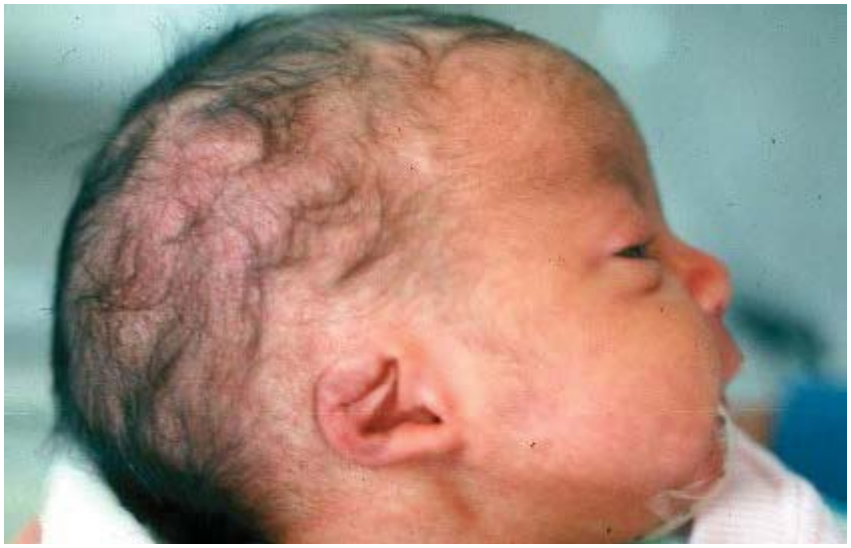
The infant described in the vignette has the pattern of anomalies consistent with trisomy 18 (Figure 5).

Figure 5



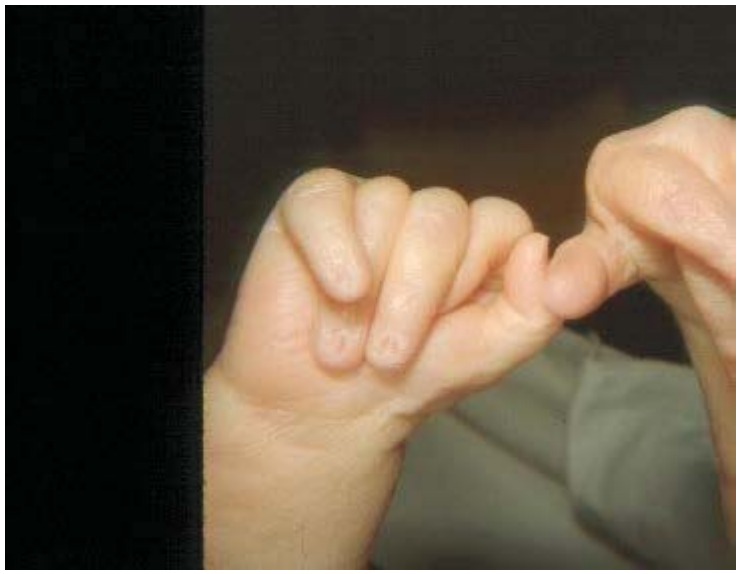
The incidence of trisomy 18 is approximately 3 in 1,000 live births. Polyhydramnios with decreased fetal movement is common with trisomy 18 pregnancies. Approximately one third of infants with trisomy 18 are born prematurely and one third postterm. Trisomy 18 infants are usually small for gestational age with a mean birth weight of 2,340 g. At birth these infants are feeble with a weak cry and frequently require resuscitation. The clinical features of trisomy 18 include a prominent occiput with low-set malformed ears (Figure 1),

Figure 1



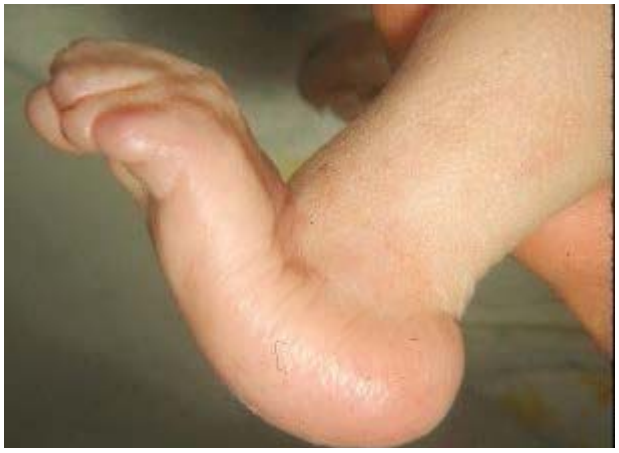
skin redundancy, mild hirsutism of the forehead, prominent cutis marmorata, clenched hands with a tendency for overlapping fingers (Figure 2),

Figure 2



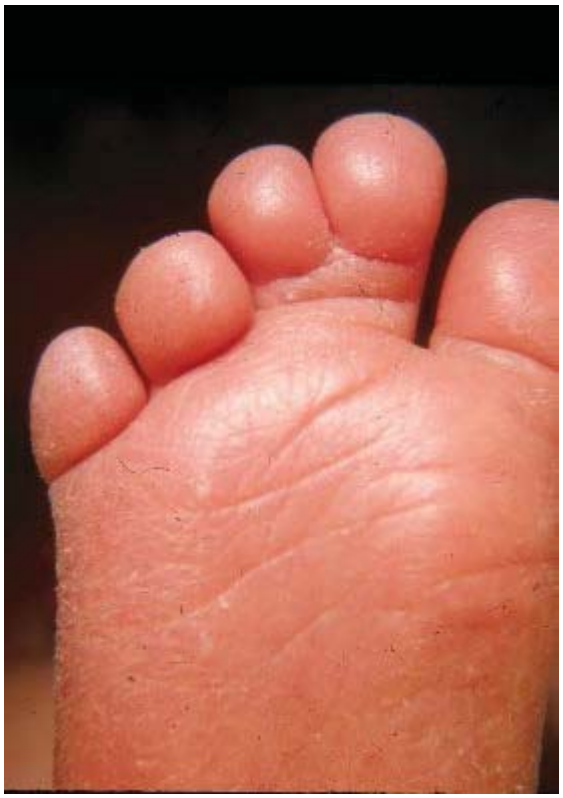
hypoplastic nails, rocker-bottom feet (Figure 3),

Figure 3



syndactyly of second and third toes (Figure 4),

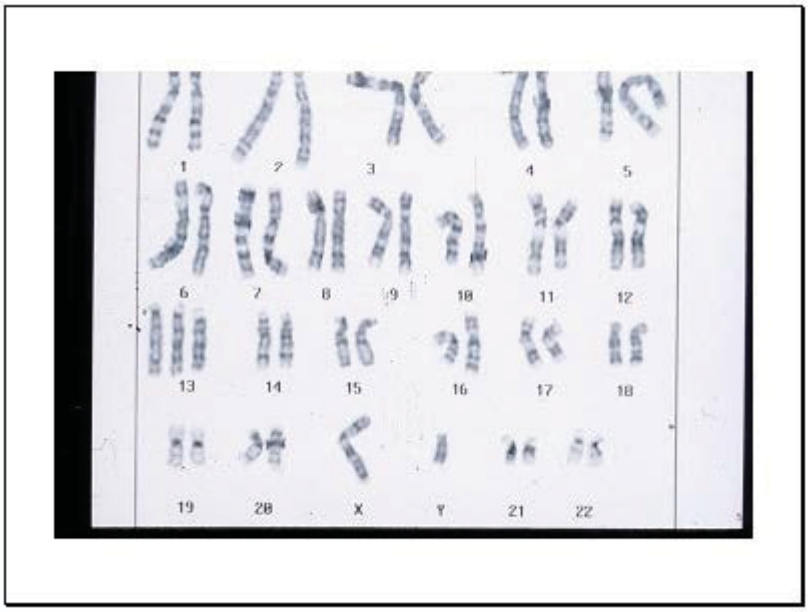
Figure 4



short sternum with reduced numbers of ossification centers, and limited hip abduction. Congenital heart disease occurs in more than 50% of patients, with ventricular septal defect (VSD) being the most common abnormality.

The karyotype in Figure 6

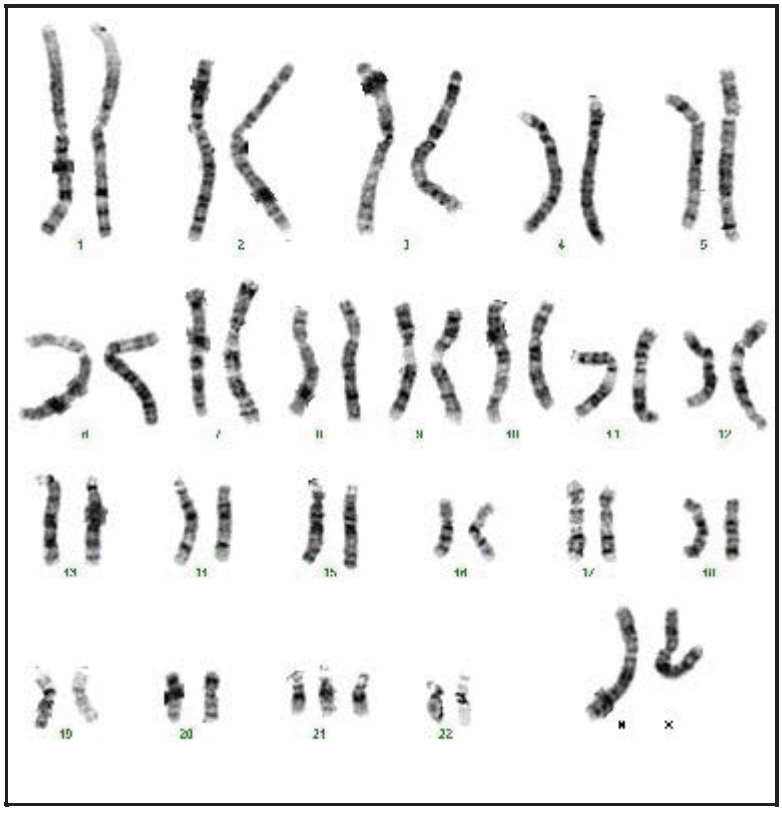
Figure 6



is trisomy 13. Trisomy 13 has an incidence of approximately 1 in 5,000 live births. Approximately 60% to 80% of patients with trisomy 13 have a cleft lip and/or a V-shaped cleft palate. Localized scalp defects in the parieto-occipital area, abnormal helices with low-set ears, holoprosencephaly, polydactyly, colobomata of irides, and retinal dysplasia occur in more than 50% of patients. Congenital heart disease occurs in 80% with VSD being the most common abnormality. Some features occur in approximately equal frequency in trisomy 13 and trisomy 18 including low-set malformed ears and cardiac anomalies such as VSD. Cleft lip and palate and cutis aplasia are common in trisomy 13 but rare in trisomy 18.

The karyotype in Figure 7

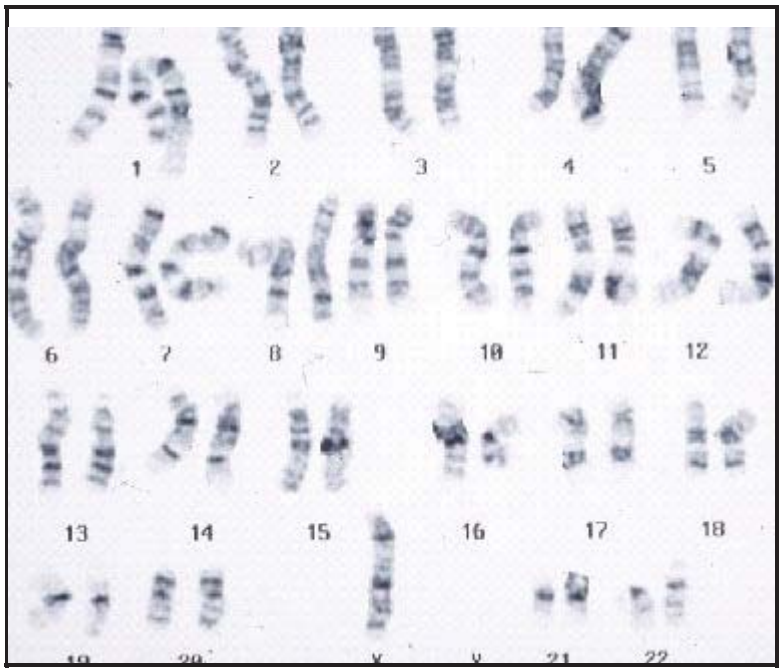
Figure 7



is trisomy 21. The clinical features of trisomy 21 include brachycephaly with flat occiput, flat facies with tendency to keep mouth open and tongue protruding, small nose with low nasal bridge, inner epicanthal folds and upward slant of eyes, cardiac anomalies, and a single palmar crease. Clenched hands with overlapping fingers, short sternum, rocker-bottom feet, syndactyly of second and third toes, and limited hip abduction are rare in trisomy 21.

The karyotype in Figure 8

Figure 8



is 45,X or Turner syndrome. The clinical features of Turner syndrome include congenital lymphedema, broad chest with widely spaced nipples, prominent auricles, and webbed posterior neck. Bicuspid aortic valve or coarctation of the aorta occurs in approximately 40% of patients with Turner syndrome. The clinical features described in the infant in the vignette would be unusual for Turner syndrome.

The karyotype in Figure 9

Figure 9

is triploidy, which is a complete extra set of chromosomes (69) in the nucleus of each cell. The clinical features of triploidy include dysplastic calvaria with a large posterior fontanel, a large bulbous nose, and hypertelorism. The clinical features described in the infant in the vignette would be unusual for triploidy.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

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American Board of Pediatrics Content Specification(s):

Recognize the physical findings and chromosomal pattern in trisomy 13

Identify the physical characteristics and chromosomal pattern in trisomy 18

Be aware of the maternal factors, incidence, and clinical manifestations of Down

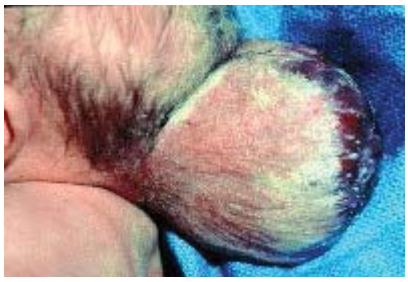
syndrome

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

Know fetal and placental manifestations of triploidy

PREVIOUS NEXT

June: Question 2



from www.inwildflower.com/MATEC1501/Encephalocele.htm

You are called to the delivery room for emergency management of a term infant who suffered intrauterine growth restriction and is experiencing severe respiratory distress. After stabilizing the infant with mechanical ventilation, oxygen, and thoracostomy tube placement for bilateral pneumothoraces, you notice multiple abnormal physical features.

These include a 3x4 cm occipital encephalocele (Figure), flattened nose, cleft palate, microphthalmia, small thorax, large bilateral flank masses (5x9 cm), single umbilical artery, polydactyly, and bilateral club feet. Facial symmetry, ears, genitalia, and lips appear normal, as are the results of cardiac examination. Both parents are normal in appearance.

Of the following, the MOST likely mode of inheritance in this case is:

1	autosomal dominant
2	autosomal recessive
3	sporadic
4	x-linked dominant
5	x-linked recessive

You selected 3, the correct answer is 2.

Do you want to add anything to your Learning Plan?
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The clinical findings described for the infant in the vignette are consistent with Meckel-Gruber syndrome, which has an autosomal recessive inheritance pattern. Meckel-Gruber syndrome classically includes the triad of encephalocele, polydactyly, and cystic dysplasia of the kidneys. In addition, there are frequently associated anomalies of growth, central nervous system, face,), neck, limbs,

kidney, liver, and genitalia (Table). There is marked heterogeneity of the clinical presentation, as seen with the infant described in the vignette. Death within days to weeks is expected due to abnormalities of the central nervous system and kidneys or occasionally to pulmonary hypoplasia.

Autosomal recessive inheritance requires the presence of a recessive gene on an autosomal chromosome from each parent. The genetic locus for Meckel-Gruber syndrome is found at 17q21-q24. An autosomal recessive inheritance pattern carries a 25% recurrence risk for future children of carrier parents. Walker-Warburg Syndrome (occipital encephalocele, lissencephaly, eye abnormalities, congenital muscular dystropy), like Meckel-Gruber Syndrome, is associated with autosomal recessive inheritance. Absence of polydactyly and renal abnormalities excludes this syndrome from consideration.

Autosomal dominant inheritance is not the inheritance pattern for Meckel-Gruber Syndrome. Autosomal dominant inheritance is evident when parents and siblings have features similar to the patient. However, this is often not present with autosomal dominant disorders because these disorders are frequently due to a fresh mutation in a family. Therefore, this baby of phenotypically normal parents could be inherited in autosomal recessive or dominant fashion. Autosomal dominant inheritance requires the presence of a dominant gene on an autosomal chromosome from one parent; the risk of inheriting this dominant gene is 50%. However, variable expression of most dominant genes accounts for the actual incidence of affected individuals being less than 50%. Genetic disorders with occipital encephaloceles occassionally present that demonstrate the impact of fresh mutations and variable expression of the dominant gene include Pallister-Hall Syndrome (occipital encephalocele, hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, postaxial polydactyly) and Adams-Oliver Syndrome (encephalocele, cutis aplasia over posterior parietal region, short fingers, hands, toes, feet and legs, cutis marmorata).

Sporadic inheritance is also the incorrect answer in this baby with Meckel-Gruber Syndrome. Sporadic inheritance is designated when the cause of the syndrome is unknown and, therefore, the risk of recurrence is small. Occipital encephaloceles may be found with Cervico-Oculo-Acoustic Syndrome (Klippel-Feil anomaly, adbucens paralysis with retracted globes, sensorineural deafness) and Oculo-Auriculo-Vertebral Spectrum (Asymmetric mandibular, maxillary and malar hypoplasia, macrostomia, ear abnormalities, vertebral abnormalities). Absence of polydactyly and renal anomalies exclude these diagnoses.

X-linked recessive and X-linked dominant inheritance is not present in the more common syndromes associated with occipital encephaloceles. X-linked recessive mutations do not overtly express phenotypic findings in females due to the presence of a normal gene; however, expression of the phenotype occurs in males because the only gene present is abnormal. X-linked dominant mutations are expressed in females but the expression is modified by presence of the normal gene. In males, however, only the abnormal dominant gene is present and the expression is often severe or lethal.

Table. Meckel-Gruber Syndrome: Frequently Associated Anomalies

Growth	variable growth deficiency
Central Nervous System	occipital encephalocele microcephaly cerebral hypoplasia cerebellar hypoplasia

	anenecephaly hydrocephaly Arnold-Chiari malformation Absence of olfactory lobes and tract Absence of corpus callosum and septum pellucidum
Face	micropthalmia cleft palate micrognathia ear anomalies
Neck	short
Limbs	polydactyly club feet
Kidney	dysplasia with variable cyst formation
Liver	bile duct proliferation fibrosis, cysts
Genetalia	cryptorchidism incomplete development of external and/or internal genitalia

Do you want to add anything to your Learning Plan?
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References:

Baraitser M, Winter RM. *Color Atlas of Congenital Malformation Syndromes*. London, England: Mosby-Wolfe; 1996

Jones KL. *Smith's Recognizable Patterns of Human Malformation*. 5th ed. Philadelphia, Pa: WB Saunders Co; 1997

American Board of Pediatrics Content Specification(s):

Demonstrate understanding of inheritance patterns and recurrence risks for autosomal recessive disorders.

Demonstrate understanding of inheritance patterns and recurrence risks for autosomal dominant disorders.

Demonstrate understanding of inheritance patterns and recurrence risks for x-linked recessive disorders.

March: Question 2

A newborn female is admitted with an unusual phenotype. Chromosomal analysis is normal, and the child fits no known pattern of single-gene syndromes. On taking a family history, you contemplate the potential recurrence risks for subsequent pregnancies.

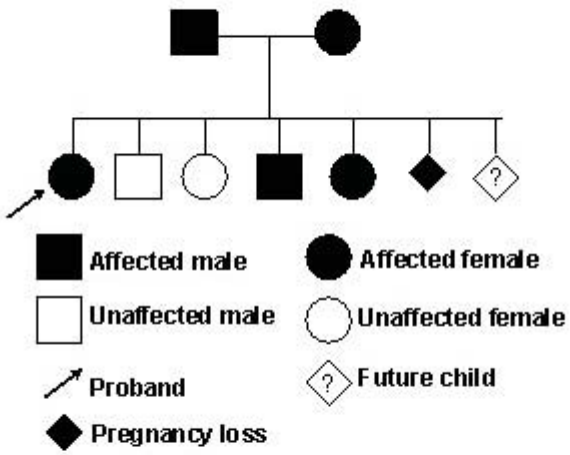
Of the following, the family history presenting the MOST risk to subsequent live-born siblings is:

1	Father affected, mother unaffected, 2 of 4 brothers and 1 sister affected.
2	Father affected, mother affected, one of 2 brothers and one of 2 sisters affected.
3	Father and mother unaffected, 4 brothers and 2 sisters unaffected.
4	Father and mother unaffected, 1 of 4 brothers and 1 sister affected, 1 sister unaffected.
5	Father unaffected, mother affected, 1 of 2 sisters affected, 1 unaffected brother, 2 pregnancy losses.

You selected 3, the correct answer is 2.

The newborn infant in the vignette presents with a condition not specifically identified as a syndrome with a known genetic inheritance pattern. The various family histories may suggest a risk to subsequent siblings.

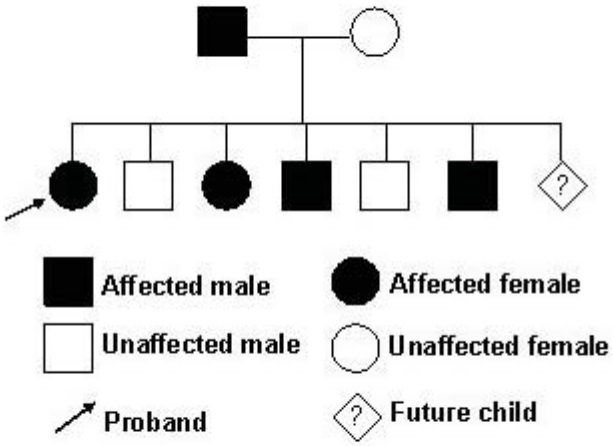
When both parents are affected and some but not all of both male and female siblings also are affected, the pattern is consistent with autosomal dominant inheritance, with possible lethality of the homozygous offspring.



autosomal dominance inheritance
with both parents affected

In this situation, 67% to 75% of the live-born siblings of both sexes will have the gene, depending on the viability of the homozygotes. Viable homozygous and heterozygous newborns could manifest the condition (depending on penetrance), and the other live-born will be disease-free. In some conditions, homozygous patients have a more pronounced phenotype than heterozygous patients. One-fourth of conceptuses may be nonviable in some autosomal dominant conditions, resulting in either loss of known pregnancies or inability of the homozygous zygote to initiate the pregnancy.A variant of autosomal dominant inheritance is sex-influenced expression, an autosomal dominant gene that is expressed in only one sex, as is seen with Familial Male Precocious Puberty. Although females have the gene and transmit it to offspring, the condition manifests clinically only in males, and male-to-male vertical transmission is seen, ruling out X-linked recessive inheritance.

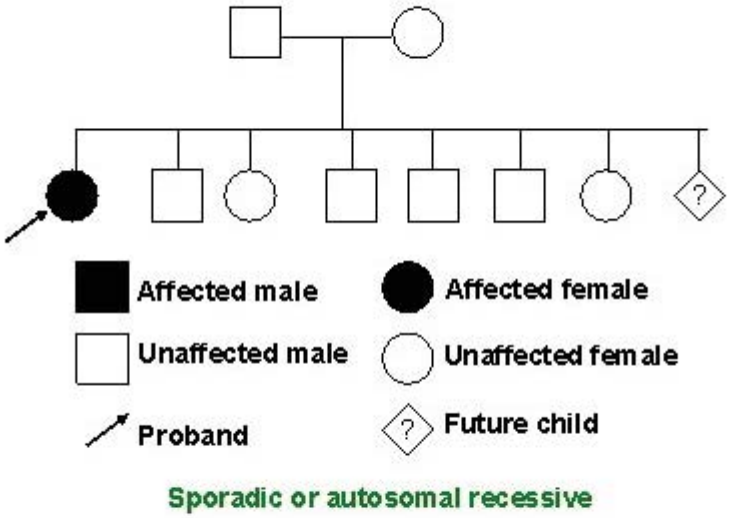
When one parent (in the given option the father, but it could be the mother as well) presents with the same phenotype as the affected children and this phenotype is seen in offspring of both sexes, autosomal dominant inheritance is likely.



Autosomal dominant inheritance pattern

Because the chance of transmitting the chromosomal allele with the abnormality is equal regardless of the sex of the offspring, each subsequent child has a 50% chance of inheriting the gene. In the option presented, several family members show the phenotype, suggesting high penetrance of the phenotype. Many autosomal dominant conditions arise as new mutations in families with no affected members, and in some autosomal dominant conditions, the gene may be inherited but no phenotypic abnormalities are seen in the offspring, a condition called nonpenetrance of the gene.

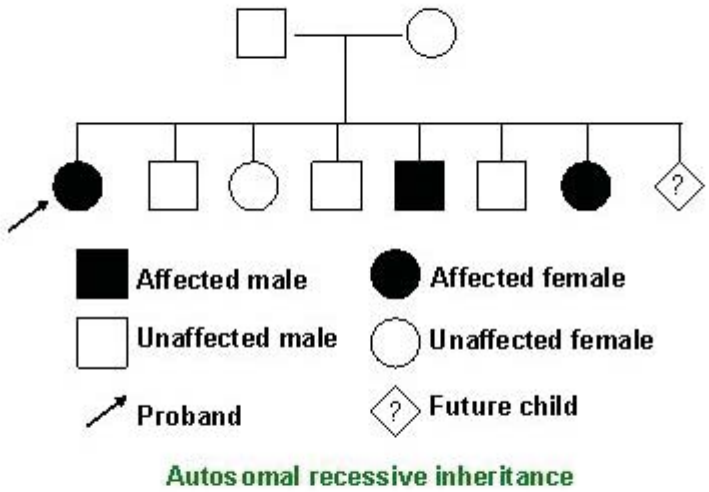
An affected child may have no affected parents nor affected siblings of either sex.



Sporadic or autosomal recessive

In this scenario, one of three situations may exist: 1.) the affected child has a sporadic condition not inherited from the parents (recurrence risk = population risk for the condition); 2.) the affected child has a new mutation of an autosomal dominant condition (risk to sibling is near population risk-proband's children have 50% risk of gene inheritance); or, 3.) the affected child has an autosomal recessive condition (25% risk to siblings if parents are carriers, minimal risk if new mutation). Because this scenario presents several options with varying recurrence risks, it is less likely to result in an affected sibling than the first two options, and it also makes counseling more difficult.

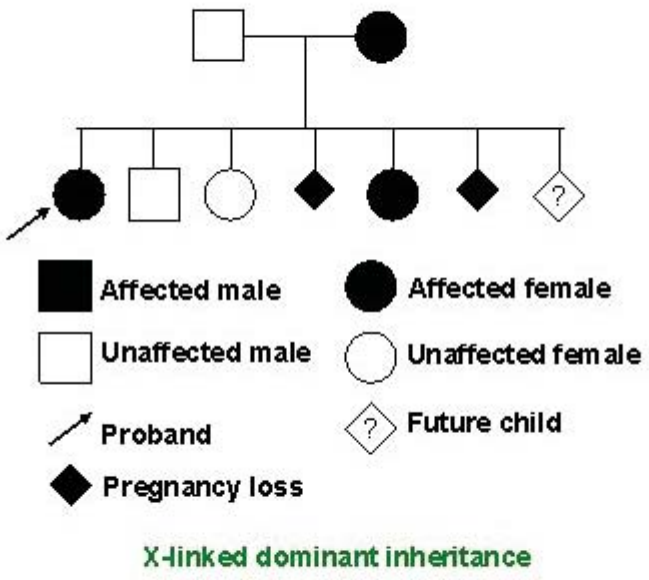
When unaffected parents have affected siblings of both genders, autosomal recessive inheritance is most likely.



Autosomal recessive inheritance

Both parents carry a recessive allele of the gene and have a 50% chance of passing the gene to each offspring. Because two recessive genes are needed to show abnormality, the risk to subsequent siblings is 25%. Most autosomal recessive conditions have very high penetrance, so homozygous infants are not likely to be normal. In some autosomal recessive conditions, heterozygotes may have reduced function of the affected gene, resulting in reduced enzyme or protein levels associated with the gene. In these conditions, both heterozygote parents would be affected, and their children would face a 1 in 4 chance of having the full effect, 2 of 4 being similar to the parents, and 1 of 4 being normal.

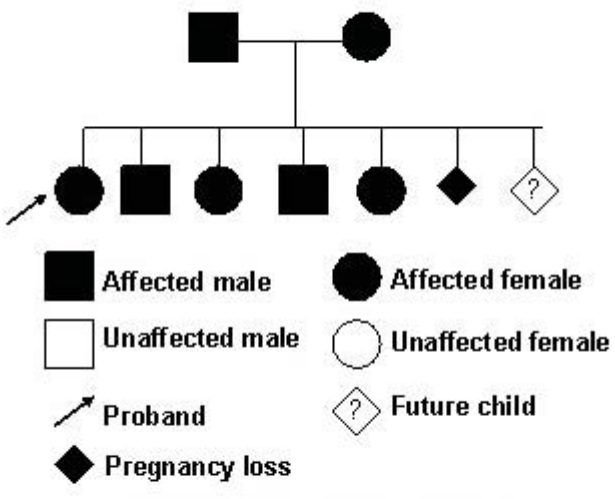
When a maternal condition transmits to some but not all of her daughters, to none of her living sons, and the mother has a history of pregnancy loss, X-linked dominant inheritance should be considered.



X-linked dominant inheritance

In this situation, all affected males would succumb in utero, and all live-born males would be unaffected since they received the normal X allele from their mothers. Female fetuses have a 50% risk of recurrence. Of live-born siblings, 50% of sisters would be at risk, but no brothers-giving an overall risk of 33.3% for live-born siblings. Genetically, the risk to a subsequent zygote is 50%, but since males with the abnormal X chromosome succumb in utero in this situation, the risk for occurrence among live-born infants is reduced.

An important situation, not presented in the options, that would pose even greater potential risk to the offspring would be both parents having the same autosomal recessive condition, in which the heterozygotes are asymptomatic carriers.



Note that in this situation, all live-born children would be affected because neither parent has the normal gene. With successful treatments for autosomal recessive conditions that heretofore did not result in survival to adulthood, the potential for individuals with given autosomal recessive conditions to seek genetic counseling is now real.

Genetic diagnosis can be difficult, but physicians can find help online from the National Library of Medicine (http://www.ncbi.nlm.nih.gov/omim and http://www.ncbi.nlm.nih.gov/Entrez). For parents and siblings facing familial genetic abnormalities, a consultation with a pediatric geneticist can be invaluable. For many of the "single-gene disorders," DNA abnormalities now can be identified by testing. Thus, rather than having to rely solely on statistical risk patterns, families can have the insights and options associated with prenatal diagnosis.

Do you want to add anything to your Learning Plan?
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Pagon RA. Internet resources in medical genetics. UpToDate Web site. Available at: http://www.uptodate.com (subscription required). Accessed October 21, 2005

Content Specification(s):

Recognize specific patterns of Mendelian inheritance

PREVIOUS NEXT

March: Question 8

A woman wishes to have a screening ultrasonogram because she will be 35 years old at the time of expected delivery. She is 11 weeks' pregnant by reliable dates. After discussing her age-related risk, you schedule the fetal ultrasonogram.

Of the following, the ultrasonographic finding MOST useful for detection of Down syndrome is:

1	absence of the nasal bone
2	atrioventricular abnormality on cardiac four-chamber view
3	nuchal translucency (NT) in the first trimester
4	NT in the second trimester
5	widened iliac angle

You selected 3, the correct answer is 3.

Nuchal translucency (NT) is noted in the space between the fetal skin and fascia of the neck in fetuses in the first trimester. NT has been well studied, and norms have been established by gestational age. When evaluated between 10 and 14 weeks' gestation, increased NT detects a greater proportion (77%) of fetuses with Down syndrome than maternal age alone (30%) or triple analyte screening (alpha-fetoprotein, human chorionic gonadotropin, and estriol) (60%). The sensitivity decreases to 40% to 50% in the second trimester, whereas the specificity of the test is 99% in the second trimester between 15 weeks' and no later than 20 weeks' gestation. Increased NT is related directly to increased risks of aneuploidy, fetal death, cardiac anomalies, and structural or metabolic abnormalities.

When used for screening, NT in the first trimester is combined with serum pregnancy-associated-plasma protein-A and free beta-subunit of human chorionic gonadotropin. This combined testing yields an 85% detection rate for aneuploidy with 5% false-positives. Operator expertise and equipment quality affect the practical application of NT measurement as a screening tool. Second-trimester quadruple screening involves measurement of alpha-fetoprotein, total human chorionic gonadotropin, unconjugated estriol, and inhibin A between 15 and 18 weeks' gestation. Screening limited to the second trimester using the 4 listed tests yields an 81% detection rate; the frequently used triple screen (inhibin A not included) results in a 69% detection rate.

The table below shows the distribution of chromosomal abnormalities detected among patients undergoing karyotyping based on increased NT. Overall, about

one-third of the abnormalities detected after increased NT involve the chromosomes.

Chromosomal abnormality	Percent of abnormal chromosomal tests
Trisomy 21	50%
Trisomy 13 or Trisomy 18	25%
Monosomy X (Turner syndrome)	10%
Triploidy	5%
Other	10%

Absence of the nasal bone is being evaluated as a marker for Down syndrome. In one study, 69% of fetuses with trisomy 21 lacked a nasal bone, in contrast with 1.4% of normals. In normal practice, the fetal nasal bone is difficult to discern: in another screening study, all 11 cases of Down syndrome were missed. Overall, nasal bone absence is considered to have a sensitivity of 40% in detecting Down syndrome, but its practicality for screening is limited by technical factors.

Four chamber views of the fetal heart are optimum at 18 to 22 weeks' gestation. Although atrioventricular canal defects are associated with Down syndrome, congenital heart disease occurs in about 40% of Down syndrome patients, and not all of these have this defect. The sensitivity of this test would be low.

Widened iliac angle has a low positive predictive value and is not recommended for screening.

The combination of increased NT, pyelectasis (greater than 4 mm), and short humerus has a sensitivity of 87% for predicting Down syndrome, with a false-positive rate of 6.7%. This is the best grouping of sonographic markers for Down syndrome.

In clinical practice, first trimester screening using the combination of NT, PAPP-A, and HCG is recommended, and is superior to second-trimester screening. Improved detection in the first trimester may be enhanced with further experience in assessment for absence of the nasal bone. Newer genetic techniques are evolving using fetal cells from maternal blood, cell-free DNA in maternal blood, or fetal trophoblasts exfoliated into the cervix. If these or other novel techniques prove reliable, direct genetic testing of the fetus using chromosomal microarrays may replace serum screening and ultrasonography.

Do you want to add anything to your Learning Plan?
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Content Specification(s):

Identify appropriate cases in which to obtain chromosomal studies

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

PREVIOUS NEXT

March: Question 9

You are asked to evaluate a newborn with dysmorphic features:

Figure 1.

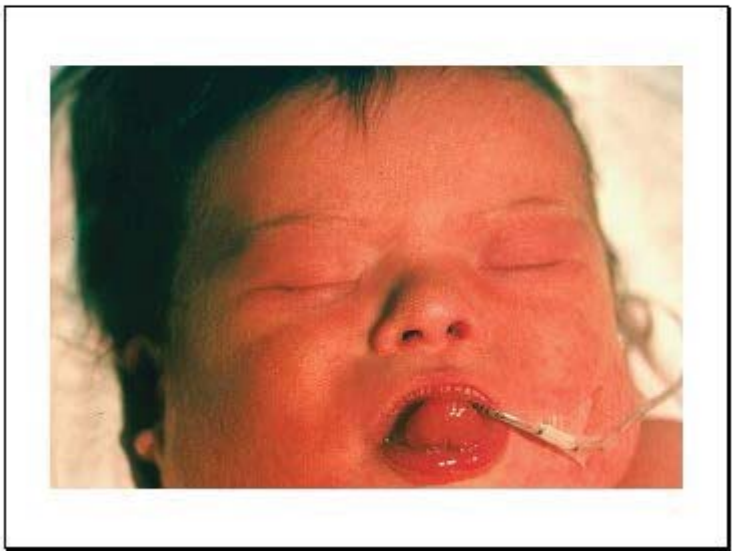

Figure 2.

Of the following, the MOST likely mechanism for the clinical features seen in this infant is chromosomal nondisjunction that occurred at:

1	meiosis I during maternal oogenesis
2	meiosis II during maternal oogenesis
3	meiosis I during paternal spermatogenesis
4	meiosis II during paternal spermatogenesis
5	mitosis after fertilization

You selected 3, the correct answer is 1.

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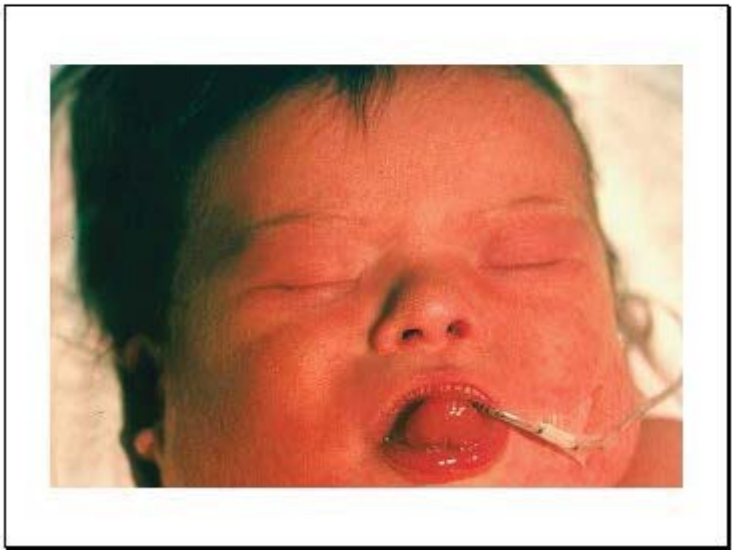
The infant in the vignette has clinical features of Down syndrome (DS), including flat facies with a tendency to keep the mouth open and the tongue protruding, and to have a small nose with a low nasal bridge, inner epicanthal folds, upward slant

Figure 1.



of eyes (Figure 1)

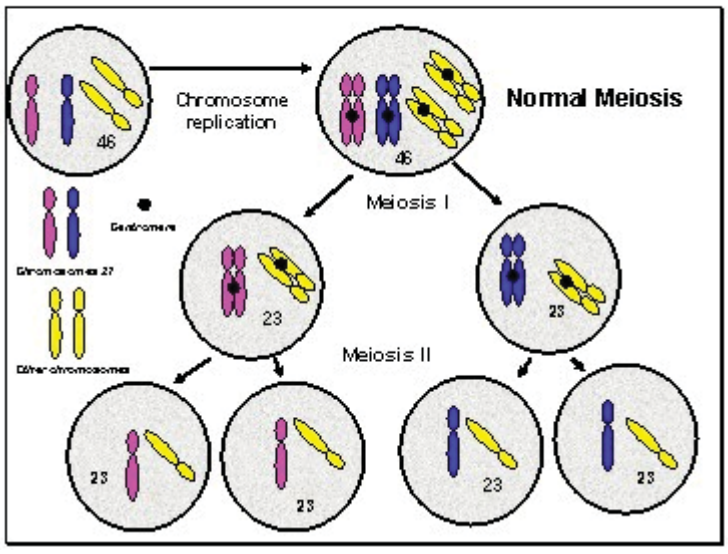
and a single palmar crease and (Figure 2).

Figure 2.

DS occurs in approximately 1 in 800 live births and is the most common aneuploid disorder compatible with survival to term. Aneuploidy is an abnormal chromosome number due to an extra or missing chromosome. The most common cause of aneuploidy is nondisjunction, the failure of chromosomes to disjoin during meiosis.

Meiosis is the method of cell division that occurs in cells of the germline. Meiosis results in formation of gametes with half the number of chromosomes (haploid) as somatic cells (diploid). In the first stage of meiosis, DNA replication occurs (Figure 3).

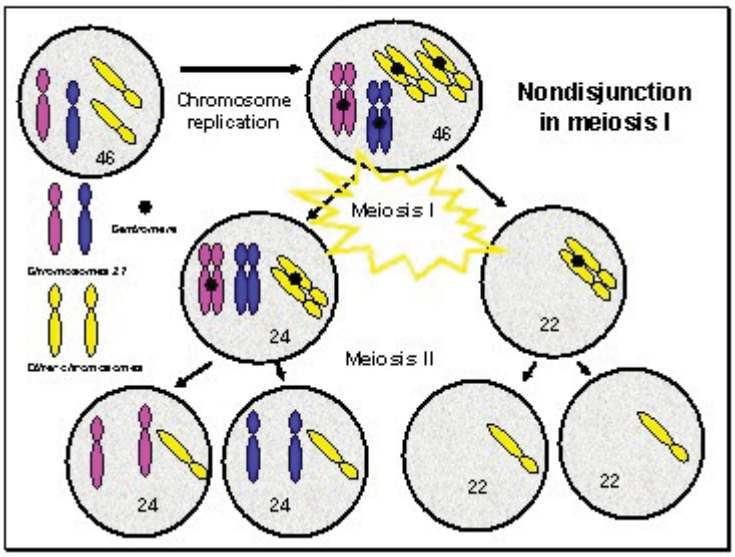
Figure 3.



The cell now contains two identical copies of each of the 46 chromosomes. These identical chromosomes are called sister chromatids and are attached at the centromere. After DNA replication, two successive meiotic divisions, called meiosis I and meiosis II, take place.

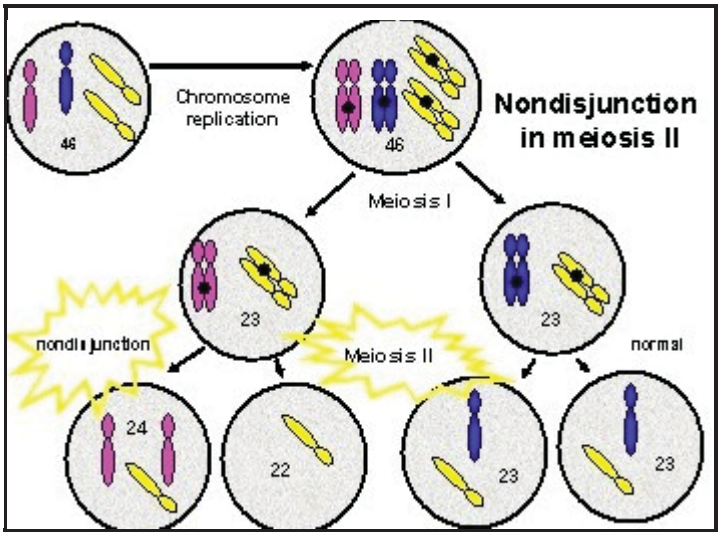
Meiosis I, also known as the reduction division stage, is the stage in which the chromosome number is reduced from diploid (46 chromosomes) to haploid (23 chromosomes). During meiosis II, the sister chromatids separate, and one chromatid from each chromosome passes to each daughter gamete. Nondisjunction can occur during meiosis I (Figure 4)

Figure 4.



or meiosis II (Figure 5).

Figure 5.



The resulting abnormal gamete either lacks a chromosome or has two copies of it. Fertilization of such a gamete produces a zygote that has either a monosomy or a trisomy.

DS is caused by trisomy of all or a large part of chromosome 21. Complete trisomy 21 accounts for 94% of DS cases. Chromosome translocation accounts for 4%, and trisomy 21/normal mosaicism accounts for 2% of DS cases.

Complete trisomy 21 is caused by nondisjunction during meiosis in one of the parents.

The nondisjunction event can occur in the first or second meiotic division of either parent. By comparing microsatellite polymorphisms on chromosome 21, the extra chromosome has been traced to an abnormality in maternal oogenesis in 90% of DS cases. Approximately 75% of maternal nondisjunction events occur during meiosis I.

Faulty chromosome distribution leading to DS is more likely to occur with advanced maternal age:

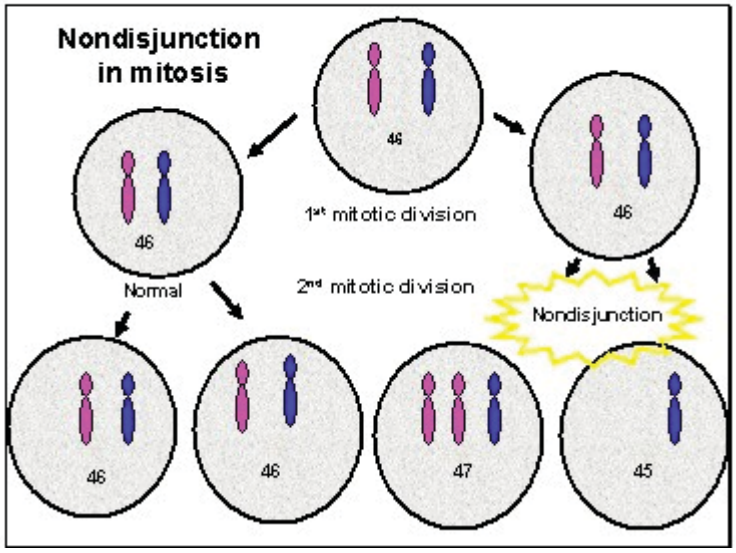
Maternal age	Odds of DS
15-29 years	1 in 1500
30-34 years	1 in 800
35-39 years	1 in 270
40-44 years	1 in 100
> 45 years	1 in 50

The cause of the increased rate of nondisjunction in older mothers is not known. The process of oogenesis begins before birth. Oocytes are formed during the mother's embryonic development. These oocytes remain suspended in the earliest phase of meiosis I (prophase I) until sexual maturity. After puberty, usually one oocyte per month completes meiosis I shortly before ovulation. A prolonged period of suspension in prophase I (up to 45 years) may account for the relatively high frequency of nondisjunction that occurs with increasing maternal age.

In 10% of DS cases, the extra chromosome is the result of nondisjunction during spermatogenesis. The incidence of nondisjunction in meiosis I and meiosis II of spermatogenesis is approximately equal. In contrast to oogenesis, spermatogenesis is ongoing throughout adult life. Advanced paternal age is a lower risk factor for DS than advanced maternal age.

Chromosomal nondisjunction that occurs during an early embryonic mitotic division results in mosaicism with the persistence of more that one cell line. If the two chromatids of chromosome 21 fail to separate at the second mitotic division of a zygote, the four-cell zygote would have two cells with 46 chromosomes, one cell with 47 (trisomy 21) and one cell with 45 (monosomy 21) (Figure 6).

Figure 6.



The monosomy 21 cell line usually does not survive, so the resulting embryo has approximately 33% mosaicism for trisomy 21. Trisomy 21/normal mosaicism usually leads to a less severe phenotype. Intellectual ability ranges from severe mental retardation to normal.

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Content Specification(s):

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Understand how mosaicism modifies clinical presentation

PREVIOUS NEXT

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March: Question 1

A term male infant is admitted for hypoglycemia and intrauterine growth restriction. His mother received no prenatal care, and this is her first live-born infant, three previous pregnancies having ended in miscarriage. She reports no illnesses during this pregnancy, is not on any medications, is healthy, but smokes cigarettes. Maternal drug testing is positive for cocaine, amphetamines, and alcohol. The infant's uncle has Williams syndrome. Physical examination is remarkable for microcephaly, small palpebral fissures, smooth philtrum, thin vermilion border of the upper lip, redundant folds of the pinnae, "hockey stick" upper palmar creases, and a heart murmur.

Of the following, the MOST likely cause for the physical findings in this infant is:

1	Cornelia de Lange syndrome
2	Dubowitz syndrome
3	fetal alcohol syndrome
4	velocardiofacial syndrome
5	Williams syndrome

You selected 3, the correct answer is 3.

The physical findings in the infant in this vignette are consistent with a diagnosis of one of the fetal alcohol spectrum disorders (FASD).

FASD are estimated to affect as many as 40,000 infants born each year in the United States and are the leading cause of preventable mental retardation. Nearly 13% of women drink alcohol during their pregnancies; 3% admit to drinking five or more alcoholic products during a single occasion. The incidence of miscarriage, stillbirth, and delivery of low birthweight infants is also higher in mothers who consume alcohol. In addition to the medical and social impact on the fetus, the cost to society of one infant with FASD has been estimated to exceed $1.4 million for the lifetime of each affected infant. The FASD spectrum is listed in the Table below.

Table

Proposed Clarification of the 1996 IOM Criteria for Diagnosis of FASD

I. FAS With Confirmed Maternal Alcohol Exposure (requires all features A-D)
A. Confirmed maternal alcohol exposure

B. Evidence of a characteristic pattern of minor facial anomalies, including 2 of the following

1. Short palpebral fissures (10th percentile)

2. Thin vermilion border of the upper lip (score 4 or 5 with the lip/philtrum guide)

3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide)

C. Evidence of prenatal and/or postnatal growth retardation

1. Height or weight 10th percentile, corrected for racial norms, if possible

D. Evidence of deficient brain growth or abnormal morphogenesis, including 1 of the following

1. Structural brain abnormalities

2. Head circumference 10th percentile

II. FAS Without Confirmed Maternal Alcohol Exposure

IB, IC, and ID, as above

III. Partial FAS With Confirmed Maternal Alcohol Exposure (requires all features, A-C)

A. Confirmed maternal alcohol exposure

B. Evidence of a characteristic pattern of minor facial anomalies, including 2 of the following

1. Short palpebral fissures (10th percentile)

2. Thin vermilion border of the upper lip (score 4 or 5 with the lip/philtrum guide)

3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide)

C. One of the following other characteristics

1. Evidence of prenatal and/or postnatal growth retardation

a. Height or weight 10th percentile corrected for racial norms, if possible

2. Evidence of deficient brain growth or abnormal morphogenesis, including 1 of the following

a. Structural brain abnormalities

b. Head circumference 10th percentile

3. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone

a. This pattern includes marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits;

and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

IV. Partial FAS Without Confirmed Maternal Alcohol Exposure

IIIB and IIIC, as above

V. ARBD (requires all features, A-C)

A. Confirmed maternal alcohol exposure

B. Evidence of a characteristic pattern of minor facial anomalies, including 2 of the following

1. Short palpebral fissures (10th percentile)

2. Thin vermilion border of the upper lip (score 4 or 5 with the lip/philtrum guide)

3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide)

C. Congenital structural defects in 1 of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, 2 must be present): *cardiac*: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects; *skeletal*: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis; *renal*: aplastic/hypoplastic/dysplastic kidneys, "horseshoe" kidneys/ureteral duplications; *eyes*: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia; *ears*: conductive hearing loss, neurosensory hearing loss; *minor anomalies*: hypoplastic nails, short fifth digits, clinodactyly of fifth fingers, pectus carinatum/excavatum, camptodactyly, "hockey stick" palmar creases, refractive errors, "railroad track" ears

VI. ARND (requires both A and B)

A. Confirmed maternal alcohol exposure

B. At least 1 of the following

1. Evidence of deficient brain growth or abnormal morphogenesis, including 1 of the following

a. Structural brain abnormalities

b. Head circumference 10th percentile

2. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone.

a. This pattern includes marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

http://pediatrics.aappublications.org/cgi/reprint/115/1/39

The amount of alcohol needed to induce teratogenicity is unknown. Most infants born to mothers who consume large quantities of alcohol do not have FASD, suggesting a multifactorial causation rather than a critical concentration effect. The gestational age at exposure, amount of alcohol ingested, placental transfer, pattern of consumption (such as binge drinking), peak concentration of alcohol, maternal alcohol metabolism and fetal susceptibility likely alter the degree to which a fetus is affected. The mechanisms of teratogenicity are likewise variable. Animal models have demonstrated that alcohol and its byproduct, acetaldehyde, have specific negative interactions with molecules that control and regulate key developmental processes.

FASD refers to a group of disorders caused by fetal alcohol exposure. Fetal alcohol syndrome (FAS) is defined by the presence of maternal alcohol exposure (confirmed), characteristic minor facial features (such as short palpebral fissures, thin vermilion border of the upper lip, and smooth philtrum), prenatal and/or postnatal growth restriction, and deficient brain growth or structural anomaly (such as microcephaly or structural brain defects). The infant in the vignette has all four of these findings.

Partial fetal alcohol syndrome is subcategorized according to maternal alcohol exposure (confirmed or not confirmed) and defined by the presence of minor facial features as in FAS and either growth restriction, deficient brain growth or morphogenesis, or behavioral and cognitive abnormalities that cannot be explained by genetic factors, family background or environment (such as impairment in performance of complex tasks, higher-level receptive and expressive language deficits, and disordered behaviors).

Alcohol-related birth defect (ARBD) is another FASD. It is defined by confirmed maternal alcohol use during pregnancy, characteristic facial features, congenital structural defects of the heart, skeleton, kidneys, eyes, ears, and miscellaneous minor anomalies (such as "hockey stick" upper palmar creases, "railroad track" ears, hypoplastic nails, short fifth digits, clinodactyly of fifth fingers, pectus carinatum/excavatum and camptodactyly). These features can be quantified using the following scoring system.

Dysmorphology Scoring System

Feature	Points
Height <10%	1
Weight <10%	2
Occipitofrontal circumference <10%	3
Inner canthal distance <10%	0
Palpebral fissure length <10%	3
Attention-deficit/hyperactivity disorder	1
Fine motor dysfunction	1
Midfacial hypoplasia	2
"Railroad track" ears	1
Strabismus	0

Ptosis	2
Epicanthal folds (nonracial)	1
Flat nasal bridge	1
Anteverted nares	2
Long philtrum	2
Smooth philtrum	3
Thin vermilion border of upper lip	3
Prognathism cardiac murmur	0
Cardiac malformation (confirmed)	1
Hypoplastic nails	0
Decreased pronation/supination of elbow	2
Clinodactyly of fifth fingers	1
Camptodactyly	1
"Hockey stick" palmar creases	1
Hirsutism	1
Total possible dysmorphology score	36

The dysmorphology score is a weighted calculation based on assigning points to clinical findings characteristic of FASD (the highest point values are assigned to the cardinal findings of FAS, ie., growth deficiency, microcephaly, short palpebral fissures, smooth philtrum, and thin upper lip). The score provides an objective method of quantifying dysmorphologic features but is not used in assigning clinical diagnoses in the FASD continuum.

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Alcohol-Related Neurodevelopmental Disorder (ARND) also is defined by confirmed maternal alcohol exposure. The diagnosis requires evidence of either deficient brain growth/abnormal morphogenesis or behavioral/cognitive abnormalities.

The diagnosis of FASD during the neonatal period is a clinical challenge. Most children with FASD are diagnosed after age 6 years. Evidence of maternal alcohol use during pregnancy is required in all specific FASD categories except partial FAS without confirmed maternal alcohol exposure. Therefore, the diagnosis is nearly always dependent on maternal acknowledgement of her alcohol use. Blood alcohol concentrations, if obtained, only remain elevated for a few days. There is no laboratory method that determines the presence of prolonged fetal exposure to alcohol. Metabolites in meconium (such as ethyl livoleate) are under investigation for their ability to provide evidence of fetal exposure. Establishing the diagnosis of one of the FASD is complicated further by the presence of minor physical anomalies in many infants. If the characteristic pattern of anomalies and prenatal growth restriction are not evident, the diagnosis may not even be considered during the perinatal period. In addition, some of the evidence for FASD, such as developmental abnormalities and behavioral dysfunction, generally is not present until later in childhood.

Cornelia de Lange syndrome may present with intrauterine growth restriction, a long philtrum and a thin upper lip; mental retardation also becomes evident during childhood. Distinctive findings include synophrys, down-turned angles of the mouth, and limb defects, such as micromelia. These findings were not reported in the infant in the vignette. Cornelia de Lange syndrome also is inherited in an autosomal dominant pattern. Women who consume alcohol during pregnancy may have additional children with FASD but not in an autosomal dominant genetic pattern.

Dubowitz syndrome also has features in common with FASD, including intrauterine growth restriction, microcephaly, short palpebral fissures, and ptosis. Mental retardation becomes evident later. Infants with Dubowitz syndrome also have eczema-like rashes, limb anomalies, cryptorchidism, and eye abnormalities, none of which was found in the infant in the vignette. Dubowitz syndrome is inherited in an autosomal recessive pattern.

Velocardiofacial syndrome is associated with a microdeletion on chromosome 22q11 and inherited in an autosomal dominant pattern. In common with FASD, these infants have short palpebral fissures, malar hypoplasia (and smooth philtrum), congenital heart disease, and microcephaly. However, they also have a broad nasal root and a cleft or high arched palate, neither of which is present in the infant in the vignette. Other velocardiofacial syndrome findings not found in infants with FASD include deficiency of the alae nasi, long slender fingers, predisposition to conotruncal congenital heart lesions, and laboratory evidence of hypocalcemia. Children with velocardiofacial syndrome, like those with FASD, may demonstrate learning disabilities, psychiatric disorders, and behavioral problems during childhood or as an adult.

Williams syndrome, like FASD, may present with mild intrauterine growth restriction, microcephaly, short palpebral fissures, a long smooth philtrum, nail hypoplasia, and later learning and behavior problems. In contrast to children with FASD, children with Williams syndrome usually have full upper lips, periorbital fullness of subcutaneous tissues, epicanthal folds, characteristic "stellate" pattern to the iris, and hallux valgus. These findings were not evident in the infant in the vignette. Supravalvular aortic stenosis or peripheral pulmonic stenosis often are found in these children. Williams syndrome is caused by a microdeletion of chromosome 7q11. Although usually a sporadic disorder, parent-to-child transmission has been reported.

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May: Question 9

You are asked to evaluate a term infant because of intrauterine growth restriction and subtle dysmorphic features. Birthweight is at the 4th percentile and head circumference is at the 2nd percentile for gestational age. The patient has downward slanting palpebral fissures, epicanthal folds, and hypertelorism. During your examination, you notice that the infant has an unusual, high-pitched cry that resembles the mewing of a cat.

Of the following, the MOST likely abnormality of chromosome structure causing the clinical findings in this infant is a(n):

1	deletion
2	insertion
3	inversion
4	reciprocal translocation
5	Robertsonian translocation

You selected 5, the correct answer is 1.

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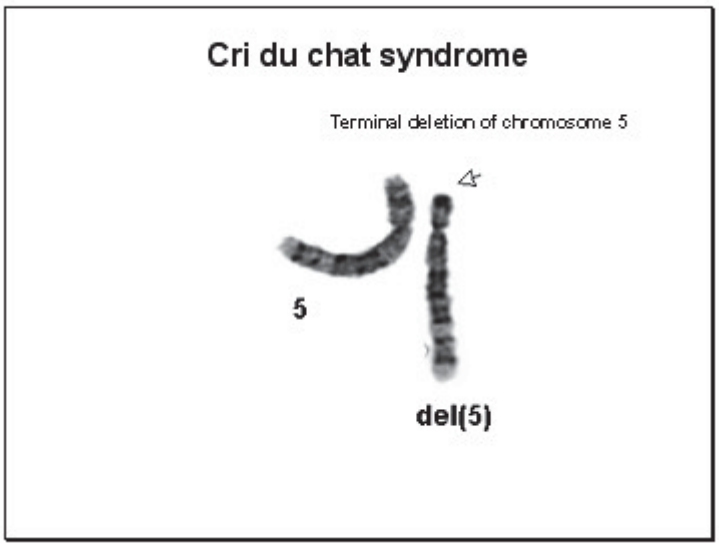
Abnormalities in chromosome structure result from chromosome breakage with subsequent reunion in a different configuration. Structural chromosomal rearrangements can be balanced or unbalanced. Balanced rearrangements are usually harmless since there is no loss or gain of genetic material. The exception is a breakpoint that interrupts an important gene. Carriers of balanced rearrangements are at significant risk for having children with unbalanced chromosome complements. Unbalanced chromosome rearrangements usually are harmful because of the extra or missing genetic material.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

The infant described in the vignette has cri du chat syndrome. The famous and distinctive cry that resembles the mewing of a cat is due to abnormal laryngeal development. Infants with cri du chat syndrome have round faces, hypertelorism, epicanthal folds and downward slanting palpebral fissures. Most have microcephaly and intrauterine growth restriction. Approximately 30% have cardiac malformations. Developmental disability is usually severe. Cri du chat syndrome occurs in approximately 1 in 50,000 live births.

The underlying chromosomal abnormality in cri du chat syndrome is a partial deletion of the short arm of chromosome 5 (5p-), as shown in Figure 1:

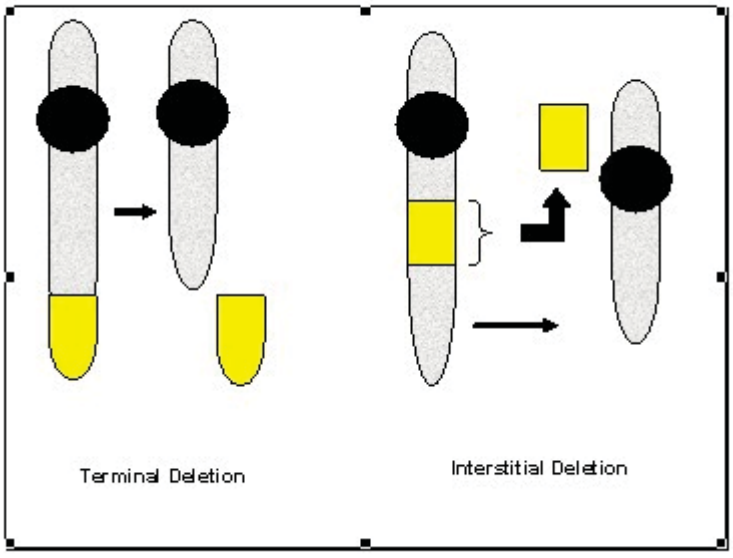
Figure 1



Approximately 85% of cri du chat syndrome cases result from a sporadic de novo deletion; in 80% of these cases, the de novo deletion is of paternal origin.

A chromosomal deletion involves a loss of part of a chromosome with resulting monosomy for that segment of the chromosome. Deletions may occur because of chromosome breakage, abnormal segregation from a balanced translocation or inversion, or unequal crossing over between misaligned chromatids. A chromosomal deletion may be located at the end of a chromosome (terminal deletion) or within the chromosome (interstitial deletion) (Figure 2):

Figure 2

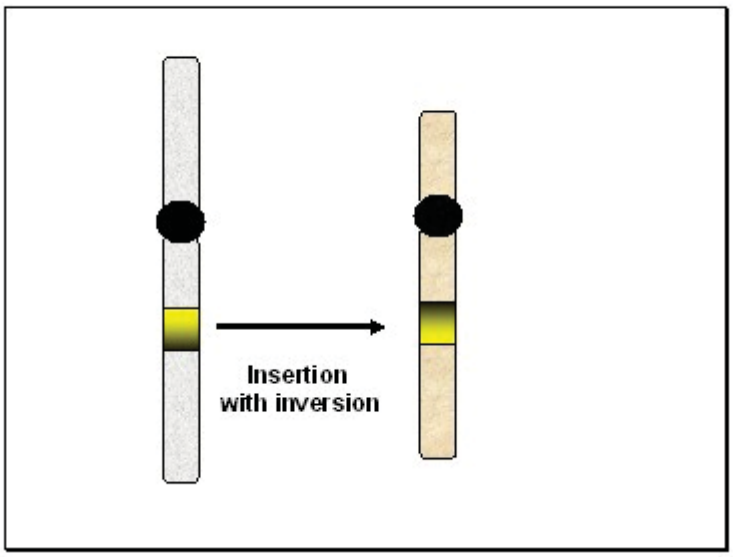


High-resolution banding techniques can identify deletions >2000 kb.

The size of the deletion in cri du chat syndrome is variable. The high-pitched cry maps to 5p15.3. The developmental disabilities and other phenotypic features map to 5p15.2. Individuals with deletions only involving 5p15.3 have the catlike cry but may have normal development and facial features.

An insertion occurs when a segment of one chromosome breaks off and is inserted into a different chromosome (Figure 3):

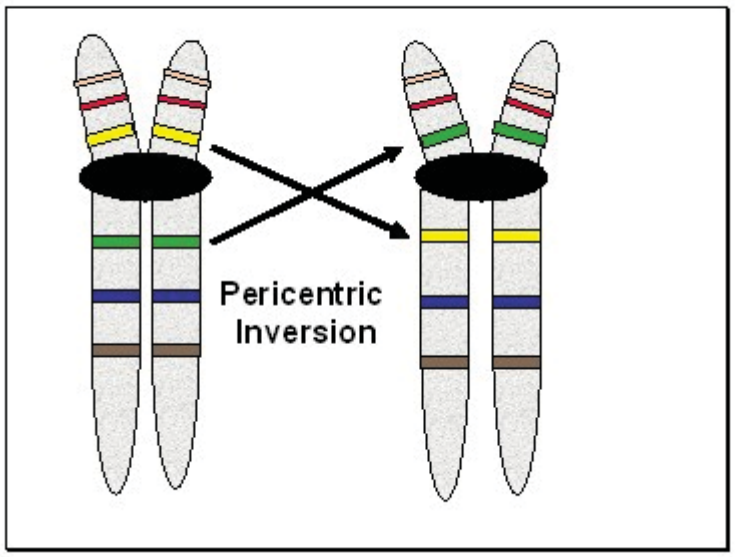
Figure 3



The insertion can be in the usual orientation or inverted. Insertions are rare because they require three chromosome breaks. Carriers of balanced deletion-insertion rearrangements are unaffected, but they are at a 50% risk of producing unbalanced gametes. There is a single case report in the literature of an unbalanced insertion involving 5p that resulted in offspring with monosomy 5p and clinical features of cri du chat.

A chromosomal inversion is a two-break rearrangement in which a segment of a single chromosome is reversed in position. Pericentric inversions involve the centromere (Figure 4):

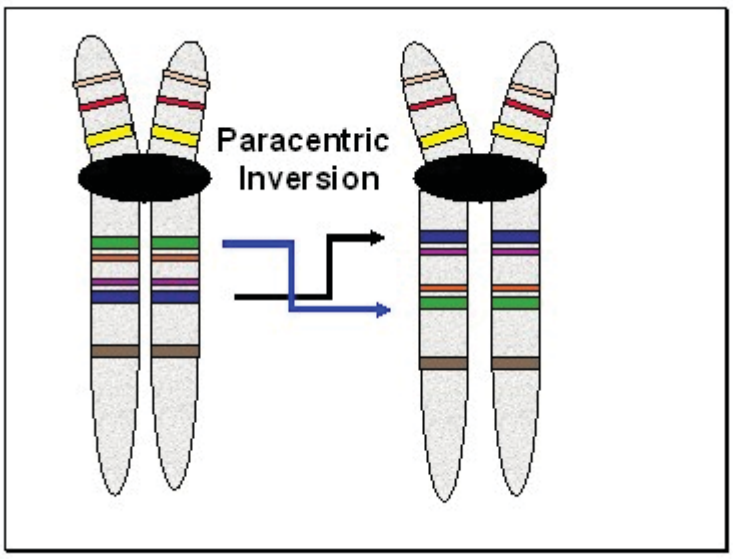
Figure 4



Paracentric inversions involve one arm of the chromosome and do not involve the

centromere (Figure 5):

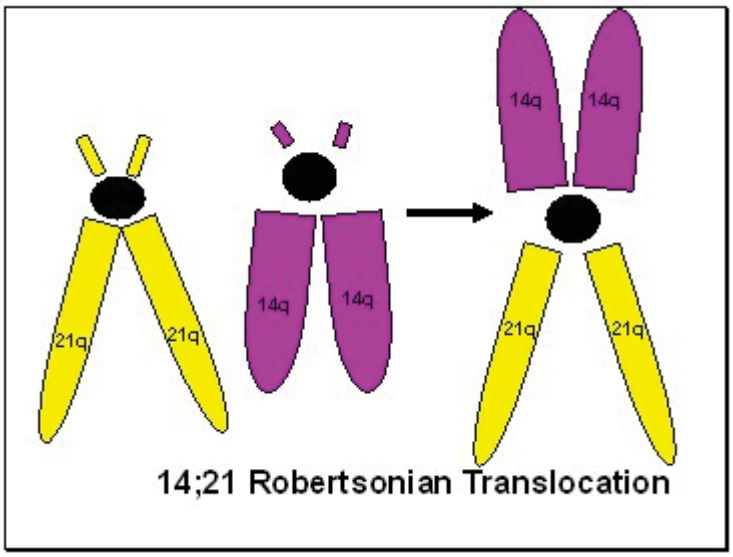
Figure 5



Paracentric inversions do not change the arm ratio of the chromosome. Paracentric inversions can be identified only by banding or fluorescent in situ hybridization with specific probes. Pericentric inversions change the proportion of chromosome arms and easily can be identified using cytogenic techniques. Inversions involving chromosome 5 have been reported in cri du chat syndrome, but they are rare.

Translocations involve the exchange of chromosome segments between two nonhomologous chromosomes. There are two types of translocations, Robertsonian and reciprocal. Robertsonian translocations occur when the short arms of two nonhomologous chromosomes are lost, and the long arms fuse at the centromere to form a single chromosome (Figure 6):

Figure 6

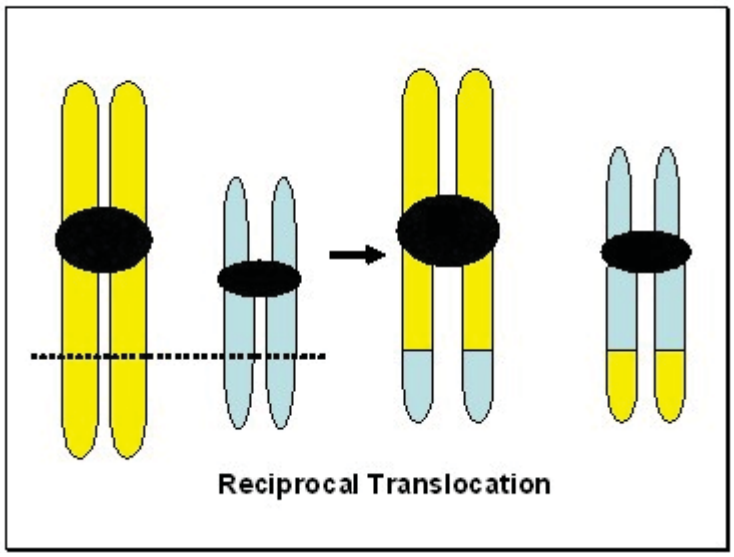


The resulting balanced karyotype has 45 chromosomes. Robertsonian translocations only occur with acrocentric chromosomes (13, 14, 15, 21, and 22) that have extremely small short arms. Because the short arms of these five

acrocentric chromosomes contain essentially no genetic material, carriers of Robertsonian translocations are phenotypically normal. However, their offspring may inherit an extra long arm of an acrocentric chromosome. Robertsonian translocations do not cause cri du chat syndrome.

A reciprocal translocation is a result of breakage of nonhomologous chromosomes with mutual exchange of the broken-off segments (Figure 7):

Figure 7



The chromosomes that result from a reciprocal translocation are called derivative chromosomes. Carriers of balanced reciprocal translocations are phenotypically normal and have a 46-chromosome karyotype. Offspring may have partial trisomy or monosomy of the derivative chromosomes and an abnormal phenotype. Whereas 85% of cri du chat syndrome cases result from a sporadic de novo deletion, 15% result from a deletion caused by unequal segregation of a parental translocation.

References:

Jones KL. Deletion 5p syndrome. In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2006:40-43

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Marinescu RC, Mamunes P, Kline AD, Schmidt J, Rojas K, Overhauser J. Variability in a family with an insertion involving 5p. *Am J Med Genet.* 1999;86:258-263

Nussbaum RL, McInnes RR, Willard HF. Clinical cytogenetics: disorders of the autosomes and sex chromosomes. In: Nussbaum RL, McInnes RR, Willard HF, eds. *Thompson & Thompson Genetics in Medicine.* 6th ed. Philadelphia, Pa: WB Saunders; 2004:157-179

Nussbaum RL, McInnes RR, Willard HF. Principles of clinical cytogenetics. In: Nussbaum RL, McInnes RR, Willard HF, eds. *Thompson & Thompson Genetics in Medicine.* 6th ed. Philadelphia, Pa: WB Saunders; 2004:135-155

Turnpenny PD, Ellard S. Chromosomes and cell division. In: Turnpenny PD, Ellard S, eds. *Emery's Elements of Medical Genetics.* 12th ed. Edinburgh, Scotland: Elsevier; 2005:31-58

Content Specification(s):

Understand the difference between balanced and unbalanced chromosome translocation

Know the long-term outcome and survival of infants with various congenital abnormalities

Recognize the karyotype and clinical manifestations associated with the common deletion syndromes

PREVIOUS NEXT

May: Question 2

You are asked to evaluate a newborn with dysmorphic features (Figures 1 and 2).

Figure 1

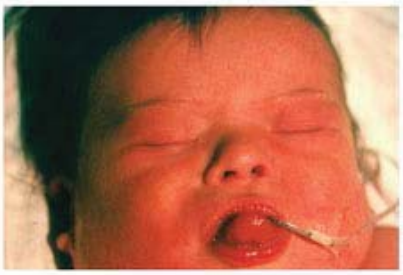
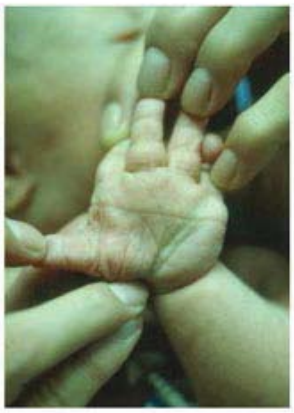


Figure 2



Of the following, the MOST likely abnormality of chromosome structure causing the clinical findings in this infant is a chromosomal:

1	deletion
2	insertion
3	inversion
4	reciprocal translocation
5	Robertsonian translocation

You selected 5, the correct answer is 5.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

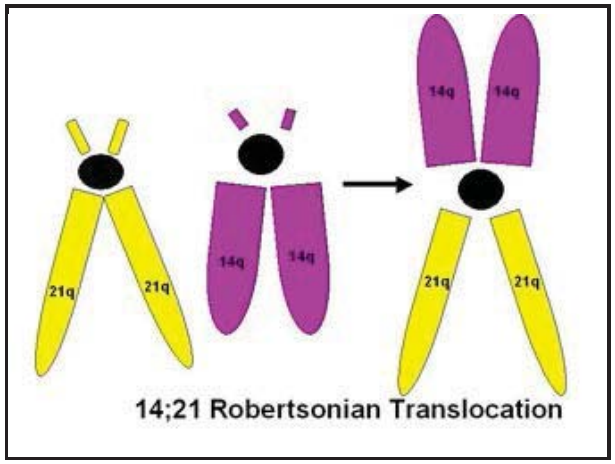
The infant in the vignette has clinical features of Down syndrome (DS), including flat facies with tendency to keep mouth open and tongue protruding, small nose with low nasal bridge, inner epicanthal folds, upward slant of eyes (Figure 1), short fingers with hypoplasia of fifth finger, and a single palmar crease (Figure 2).

DS, which occurs in approximately 1 of every 800 live births, is caused by trisomy of all or a large part of chromosome 21. The most common cause of DS is complete trisomy 21 (94% of cases) due to nondisjunction during meiosis. However, the most common structural chromosomal abnormality causing DS is a Robertsonian translocation (4% of cases). The remaining 2% of individuals with DS have trisomy 21/normal mosaicism or other rare structural chromosomal abnormalities.

Abnormalities in chromosome structure result from chromosome breakage with subsequent reunion in a different configuration. Structural chromosomal rearrangements can be balanced or unbalanced. Balanced rearrangements usually are harmless since there is no loss or gain of genetic material. The exception is if one of the break points interrupts an important gene. Carriers of balanced rearrangements are at significant risk for having children with unbalanced chromosome complements. Unbalanced chromosome rearrangements are usually harmful because of the extra or missing genetic material.

Translocations involve the exchange of chromosome segments between two nonhomologous chromosomes. There are two types of translocations, Robertsonian and reciprocal. Robertsonian translocations occur when the short arms of two nonhomologous chromosomes are lost and the long arms fuse at the centromere to form a single chromosome (Figure 3):

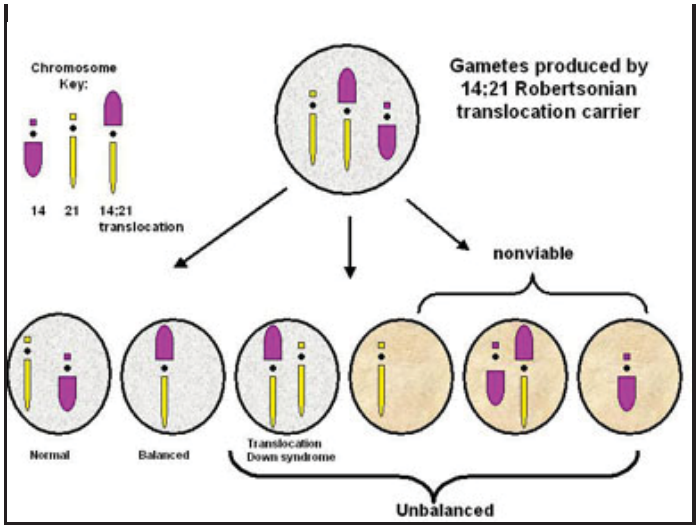
Figure 3



The resulting balanced karyotype has 45 chromosomes. Robertsonian translocations only occur with acrocentric chromosomes (13, 14, 15, 21, and 22) that have extremely small short arms. Because the short arms of these five acrocentric chromosomes contain essentially no genetic material, carriers of Robertsonian translocations are phenotypically normal. However, their offspring may inherit an extra long arm of an acrocentric chromosome. The Robertsonian translocation of the long arms of chromosomes 21 and 14 is the most common structural abnormality leading to DS. These DS patients have 46 chromosomes but are trisomic for 21q.

Unlike the risk for DS due to nondisjunction in meiosis, the risk for DS due to a Robertsonian translocation is not increased by advanced maternal age. Furthermore, DS due to nondisjunction in meiosis has a relatively low recurrence risk (1%); DS due to a parent being a carrier of a balanced Robertsonian translocation has a relatively high recurrence risk. The potential gametes that can be formed by a Robertsonian translocation carrier are illustrated in Figure 4:

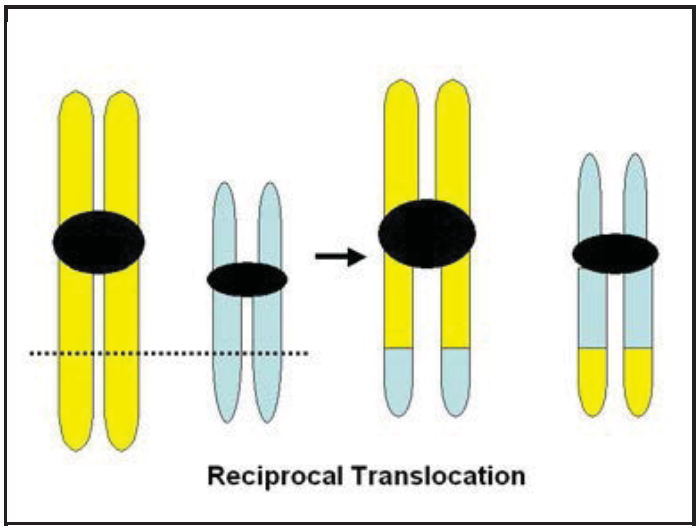
Figure 4



There are six possible types of gametes, but three lead to nonviable fetuses. The three viable gamete types lead to one normal, one balanced, and one unbalanced trisomic 21q DS. Since all three of the gamete types that can lead to a viable infant are produced equally, the risk of DS in a carrier of a Robertsonian translocation should be 1 in 3. However, the function of the unbalanced trisomic 21q gamete is diminished such that the risk of DS is 15% if the mother is a Robertsonian carrier and 2% to 3% if the father is a carrier.

A reciprocal translocation is a result of breakage of nonhomologous chromosomes, with mutual exchange of the broken-off segments (Figure 5):

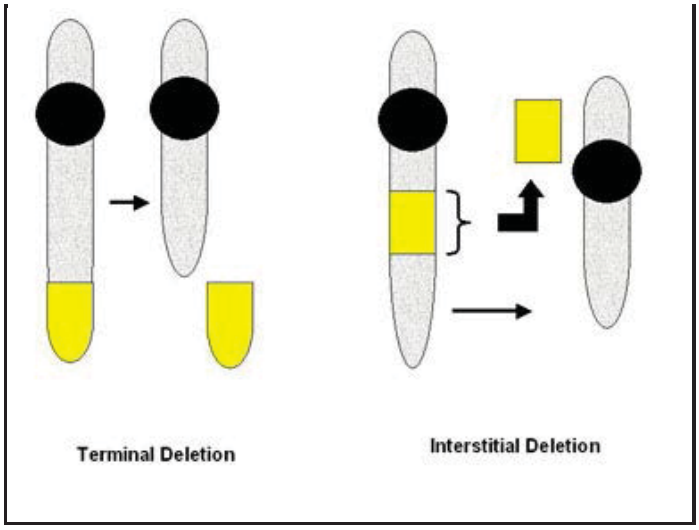
Figure 5



The chromosomes that result from a reciprocal translocation are called derivative chromosomes. Carriers of balanced reciprocal translocations are phenotypically normal and have a 46-chromosome karyotype. Offspring may have partial trisomy or monosomy of the derivative chromosomes and an abnormal phenotype. Reciprocal translocations are extremely rare causes of DS.

A chromosomal deletion involves a loss of part of a chromosome with resulting monosomy for that segment of the chromosome. Chromosomal deletion may be located at the end of a chromosome (terminal deletion) or within the chromosome (interstitial deletion) (Figure 6):

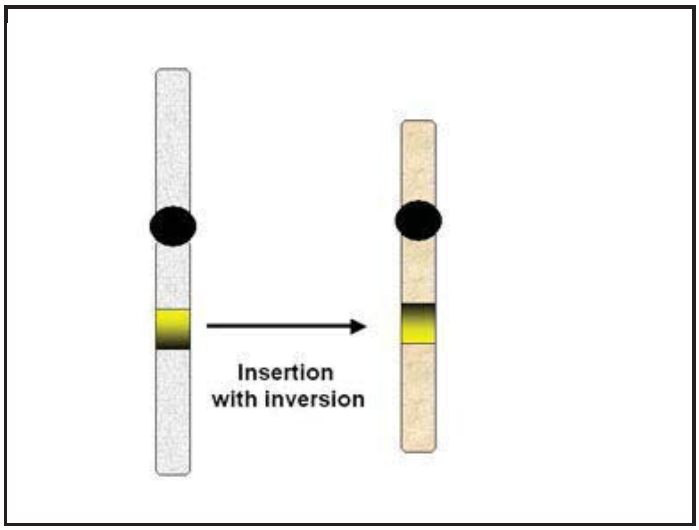
Figure 6



Large deletions (>2% of the haploid genome) are usually incompatible with life. Several large-deletion syndromes have been described, including Cri du chat syndrome (5p-) and Wolf-Hirschhorn syndrome (4p-). Microdeletions have been identified using fluorescent in situ hybridization techniques. Angelman syndrome and Prader-Willi syndrome are caused by microdeletions. Deletions do not cause DS.

An insertion occurs when of a segment of one chromosome breaks off and is inserted into a different chromosome. The insertion can be in the usual orientation or inverted (Figure 7):

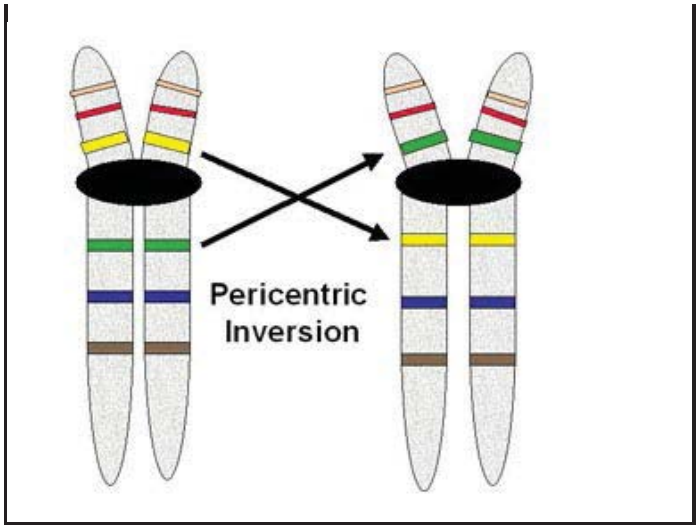
Figure 7



Insertions require three chromosome breaks. Carriers of balanced deletion-insertion rearrangements are unaffected, but they are at a 50% risk of producing unbalanced gametes. DS caused by partial trisomy 21 due to an insertion can occur but is extremely rare.

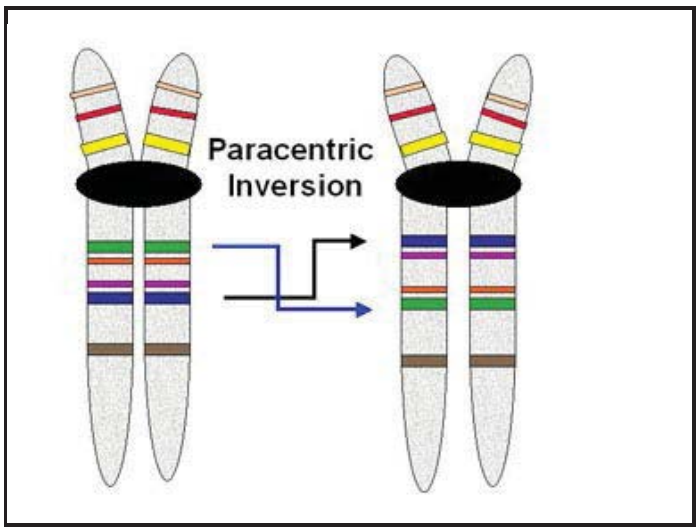
A chromosomal inversion is a two-break rearrangement involving a single chromosome in which a segment is reversed in position. Pericentric inversions involve the centromere (Figure 8):

Figure 8



Paracentric inversions involve one arm of the chromosome (Figure 9):

Figure 9



Carriers of inversions are usually normal. However, during meiosis, recombination events may lead to unbalanced gametes, particularly with pericentric inversions. Partial trisomy 21 due to an unbalanced pericentric inversion can occur but is extremely rare.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Jones KL. Down syndrome. In: Jones KL ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2006:7-12

Jorde LB, Carey JC, Bamshad MJ, White RL. Clinical cytogenetics: the chromosomal basis of human disease. In: Jorde LB, Carey JC, Bamshad MJ, White RL, eds. *Medical Genetics.* 3rd ed. St. Louis, Mo: Mosby; 2003:107-135

Moore KL, Persaud TVN. The beginning of human development: the first week. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 6th ed. Philadelphia, Pa: WB Saunders; 1998:18-24

Moore KL, Persaud TVN. Human birth defects. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 6th ed. Philadelphia, Pa: WB Saunders; 1998:170-179

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chromosomes. In: Nussbaum RL, McInnes RR, Willard HF, eds. *Thompson & Thompson Genetics in Medicine*. 6th ed. Philadelphia, Pa: WB Saunders; 2004:157-179

Nussbaum RL, McInnes RR, Willard HF. Principles of clinical cytogenetics. In: Nussbaum RL, McInnes RR, Willard HF, eds. *Thompson & Thompson Genetics in Medicine.* 6th ed. Philadelphia, Pa: WB Saunders; 2004:135-155

Turnpenny PD, Ellard S. Chromosomes and cell division. In: Turnpenny PD, Ellard S, eds. *Emery's Elements of Medical Genetics.* 12th ed. Edinburgh, Scotland: Elsevier; 2005:31-58

Content Specification(s):

Know when to obtain chromosomes on parents or other family members

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Understand the difference between balanced and unbalanced chromosome translocation

PREVIOUS NEXT

October: Question 8

You are asked by a pediatrician to see a child newly born to a deaf mother. On your way to her hospital room to take a family history, you review the hereditary syndromic causes of neonatal deafness and related diagnostic tests.

Of the following, electroretinography is the MOST appropriate test for the diagnosis of:

1	Alport syndrome
2	Jervell Lang-Neilsen syndrome
3	Pendred syndrome
4	Usher syndrome
5	Waardenburg syndrome

You selected 4, the correct answer is 4.

The incidence of neonatal hearing loss is about 1 per 1,000 live births for profound loss and 3 to 4 per 1,000 live births for significant loss. The incidence for infants born at less than 32 weeks' postmenstrual age ranges from 5% to 10%.

The causes of neonatal hearing loss are myriad. One classification scheme is shown in the Table.

Table. Major Causes of Deafness in the Neonatal Period*

Familial

Associated with malformations of external ears, eyes, skin, or skeleton

Isolated – autosomal dominant, autosomal recessive, x-linked recessive, mitochondrial

Toxins

Bilirubin

Other – aminoglycosides, furosemide

Infections

Congenital – cytomegalovirus, rubella, toxoplasmosis, syphilis

Neonatal – meningitis

Defects of the head and neck

Treacher-Collins syndrome, Goldenhar syndrome, branchio-oto-renal syndrome

Low birthweight

Perinatal asphyxia

Persistent fetal circulation

* Adapted from Volpe.

Another scheme divides the causes into acquired (eg, infection, hypoxia) and genetic or familial. Genetic causes compose about half of cases of neonatal hearing loss. Genetic causes are further divided into syndromic and nonsyndromic. Nearly 400 syndromes have been associated with deafness.

Of the above syndromes, Usher syndrome is unique in having ophthalmologic findings involving the retina, which makes electroretinography the most appropriate test for its diagnosis. Usher syndrome is an autosomal recessive disorder of deafness associated with retinitis pigmentosa. Vestibular dysfunction may accompany the decline of visual function, usually in the first decade. Twelve loci have been associated with various kindreds, each with a different gene product.

Alport syndrome is an X-linked recessive disorder. It is characterized by renal disease, usually presenting in late childhood or adolescence with chronic nephritis. Hematuria is usually the first renal manifestation. It has been linked to a mutation of a type 4 collagen gene (COL4A5).

Jervell Lang-Neilsen syndrome is an autosomal recessive disorder. Prolongation of the QT interval on electrocardiography reflects a defect in cardiac repolarization. Defects in genes coding for certain potassium channels map to chromosome 11p15.5 (KVLQT1) or 21q22.1 (KCNE1).

Pendred syndrome is an autosomal recessive disorder. It involves goiter and malformation of the inner ear. The goiter involved with this syndrome is usually not associated with hypothyroidism. The gene for the syndrome, SLC26A4 on chromosome 7, produces the protein pendrin, which is involved in the transport of iodide and chloride ions. The goiter results from a defect in the organification of

iodine, demonstrated by the perchlorate release test (http://www.medicine.uiowa.edu/pendredandbor/perchlorate_test.htm). Radioactive iodine is given, and radioactivity over the thyroid gland is measured. Perchlorate is administered, and any unorganified iodine is allowed to leave the thyroid. An unaffected thyroid should show no significant drop in radioactivity (less than 10% change), as most of the iodine is rapidly organified and held in the cell. In Pendred syndrome, the slowly organifying iodine is released from the cell during perchlorate administration, causing a significant decrease in radioactivity.

Waardenburg syndrome is an autosomal dominant disorder. It comprises a white forelock of hair, heterochromia of the irides, vitiligo, synophrys, a broad nasal root, and dystopia canthorum (lateral displacement of the inner canthi). The syndrome has been traced to mutations of the PAX3 gene on chromosome 2q37.

Nonsyndromic causes of neonatal hearing loss account for more than half of the genetic cases. Half of the autosomal recessive nonsyndromic cases are caused by mutations of the connexin 26 gene. Testing for this gene is recommended as part of the evaluation of a neonate with bilateral hearing loss. Other suggested tests include urine analysis, electrocardiography, and computed tomography or magnetic resonance imaging of the head.

The American Academy of Pediatrics has endorsed universal hearing screening by 3 months of age and intervention by 6 months of age. Currently, 41 states mandate universal screening.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

March of Dimes. Hearing loss. http://www.marchofdimes.com/professionals/681_1232.asp. Accessed March 18, 2006

Nance WE. The genetics of deafness. *Mental Retard Dev Disabil Res Rev.* 2003;9:109-119

Volpe JJ. *Neurology of the Newborn.* 4th ed. Philadelphia, Pa: WB Saunders; 2001:121-123

American Board of Pediatrics Content Specification(s):

Recognize the dysmorphic syndromes associated with hearing loss, such as the Waardenburg and Goldenhar syndromes

Recognize the association of abnormalities of the ear and congenital syndromes

Know the incidence of congenital hearing loss in the neonate

Understand the approaches to the evaluation of congenital hearing loss in the neonate

PREVIOUS NEXT

January: Question 8

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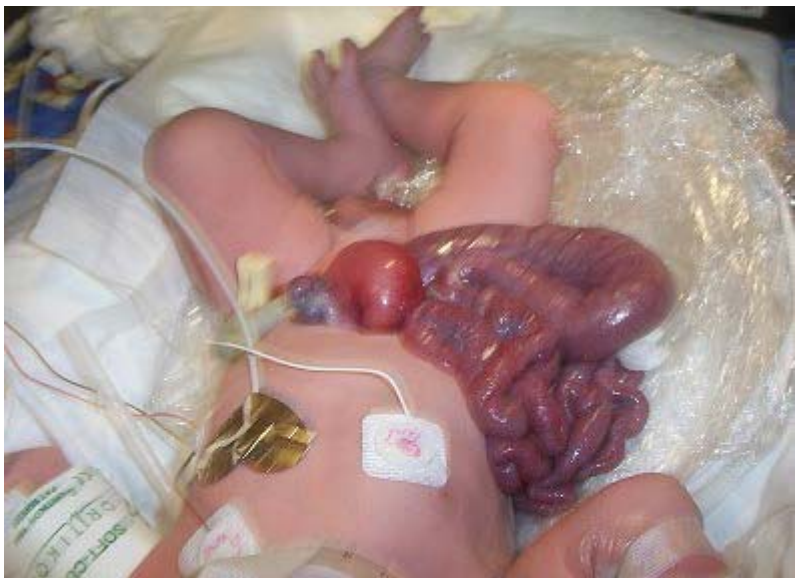
11 November 07

12 December 07

You attend the delivery of an infant at 35 weeks' gestational age. The infant appears growth restricted and presents with herniated intestines from the anterior abdominal wall (Figure 1).

Figure 1



Of the following, review of this infant's prenatal history is MOST likely to reveal:

1	abnormal fetal karyotype
2	advanced maternal age
3	elevated alpha-fetoprotein levels
4	maternal cocaine use
5	polyhydramnios

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in the vignette has an abdominal wall defect consistent with gastroschisis. The bowel protrudes from a defect located to the right of a normally inserted umbilical cord. The herniated viscera lack a covering sac and typically include small intestine and ascending colon. These characteristics distinguish gastroschisis from abdominal wall defects such as omphalocele, in which the

defect involves the umbilical ring, resulting in a herniated, membrane-covered bowel and insertion of the umbilical cord into the covering membrane. Antenatally, the diagnosis of gastroschisis is often made with ultrasonography, performed as a routine procedure or for evaluation of elevated maternal alpha-fetoprotein (AFP). Up to 75% of affected fetuses may be detected based on an elevated maternal serum AFP (with an average elevation of more than nine multiples of the mean).

Gastroschisis is thought to result from vascular compromise to the developing fetal body wall. During the sixth week of gestation, the bowel migrates through the umbilical ring and into the umbilical cord. By the 10th to 12th week, the intestines rotate and return to the abdominal cavity for fixation. The right paraumbilical area is vulnerable to ischemia, as this is the site of regression of the right umbilical vein and right omphalomesenteric artery. Disturbed involution of these vessels could produce a weak spot in the lateral umbilical ring that could rupture and permit herniation of the bowel.

The incidence of gastroschisis is approximately 1 to 4 per 10,000 births, and has been increasing worldwide over the past several decades. Although the cause of the defect remains elusive, low maternal age is the most consistent risk factor, with about 30% of affected infants born to mothers aged 20 years or younger. Other associated factors include maternal tobacco smoking and the use of vasoactive drugs (such as phenylephrine). Cocaine use has not been consistently associated with gastroschisis. Familial cases have been reported, but aneuploidy or other chromosomal derangements are not associated with gastroschisis.

The pregnancy diagnosed with gastroschisis should be considered high risk. Due to loss of transmural proteins and other nutrients, up to 70% of fetuses with gastroschisis experience growth restriction. Oligohydramnios is common (25% of cases), and polyhydramnios may occur in association with bowel atresias. Amniotic fluid is frequently meconium- or bile-stained, and in nearly 25% of cases, fetal distress occurs. Intrauterine fetal death is reported to be as high as 15%, and may be related to in utero midgut volvulus or acute compromise of umbilical blood flow by the herniated bowel. The exposure of bowel to amniotic fluid likely contributes to bowel edema and frequently to inflammatory "peel" or serositis, which results in a matted appearance to the bowel. Elevated concentrations of acute inflammatory mediators are found in this amniotic fluid and may also contribute to the increased incidence of preterm labor seen with gastroschisis (mean gestational age at delivery, approximately 36 weeks). Antenatal surveillance to detect the compromised fetus decreases perinatal mortality, but cesarean delivery has not been shown to reduce bowel injury or improve outcomes.

Neonatal management of gastroschisis targets the increased heat and fluid losses resulting from the large surface area of exposed bowel. In the delivery room, enclosure of exposed bowel (generally enclosure of the lower half of the newborn into a sterile plastic bag) reduces fluid loss and aids in thermoregulation. Care must be taken to avoid twisting and strangulation of the bowel at the site of herniation. Fluid management should compensate for increased sodium and protein losses. Surgical correction may be a primary, delayed primary, or staged repair (silo placement), and is influenced by the infant's general medical condition and capacity of the abdominal cavity. Current evidence suggests equivalent outcomes among the surgical options.

Mortality from gastroschisis remains as high as 10%, and is influenced by the degree of associated intestinal injury and complications of prematurity. The incidence of associated anomalies is low (6%); however, intestinal atresias may be present in up to 20% of cases. Deaths from gastroschisis most often result from catastrophic bowel loss, sepsis, and the long-term complications of short bowel syndrome. Survivors frequently experience prolonged feeding intolerance,

with full enteral feeds often not attained until 6 weeks of age or later. Necrotizing enterocolitis, central line infections, and cholestasis related to prolonged parenteral nutrition plague convalescence. Long-term morbidity has not been well studied, but gastrointestinal and growth outcomes appear favorable. Limited data exist describing the neurodevelopmental outcomes of survivors with gastroschisis.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Brantberg A, Blaas H-G, Salvesen KA, Haugen SE, Eik-Nes SH. Surveillance and outcome of fetuses with gastroschisis. *Ultrasound Obstet Gynecol.* 2004;23:4-13

Eggink BH, Richardson CJ, Malloy MH, Angel CA. Outcome of gastroschisis: a 20-year case review of infants with gastroschisis born in Galveston, Texas. *J Pediatr Surg.* 2006;41:1103-1108

Ledbetter DJ. Gastroschisis and omphalocele. *Surg Clin North Am*. 2006;86:249-260

American Board of Pediatrics Content Specification(s):

Understand the embryology, clinical manifestations, and associated abnormalities of gastroschisis

Know the approach to therapy, the complications, and the difficulties in providing enteral nutrition to neonates with gastroschisis

PREVIOUS NEXT

January: Question 5

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11 November 07

12 December 07

A nurse-midwife calls you to see an infant immediately after birth to "tell the parents if the baby is a boy or a girl." Family and pregnancy histories are noncontributory. Physical examination of the infant reveals ambiguous genitalia. The parents and grandparents are anxiously awaiting your decision.

Of the following, the MOST appropriate comment regarding gender assignment at this time is:

1	"Chromosomes will tell."
2	"He's a boy."
3	"Let the baby choose when older and able."
4	"She's a girl."
5	"We'd best get experts involved."

You selected 1, the correct answer is 5.

Gender assignment is one of the most important clinical decisions made by professionals at the time of delivery. Occurring in 1 in 4,500 births, disorders of sexual development (DSD) (the term now proposed by the Consensus Statement on Management of Intersex Disorders) requires a multidisciplinary team approach and long-term planning process involving professionals and the family.

The term DSD is preferred over terms such as intersex, pseudohermaphroditism, hermaphroditism, sex reversal, or other sex-based terms. DSD includes those congenital conditions characterized by abnormal development of chromosomal, gonadal, or anatomic sex.

When presented with an infant with DSD, the appropriate behavior at delivery is to formulate a plan for evaluation, diagnosis, gender assignment, and treatment options. This plan requires contributions from experienced subspecialists in the fields of neonatology, endocrinology, genetics, urology/pediatric surgery, and gynecology with support from psychiatry, social work, nursing, and (perhaps) ethics. In this vignette, calling in this expert team is the most appropriate response.

Gender assignment in the newborn period is recommended for all individuals according to the consensus statement. First-line testing includes karyotyping with X- and Y-specific probes. Most virilized 46,XX infants will have congenital adrenal

hyperplasia. More than 90% of such infants assigned as female in infancy subsequently identify themselves as female. Therefore, evidence supports the current recommendation that virilized 46,XX infants be raised as females. Although usually not diagnosed in the newborn period unless detected by a discrepancy between a prenatal karyotype and anatomic features at birth, 46,XY individuals with the complete androgen insensitivity syndrome assigned female in infancy uniformly identify themselves as female in later life.

In addition to karyotyping, testing may include:

- **Abdominopelvic ultrasonography**
- **Hormone concentrations (17-hydroxyprogesterone, testosterone, gonadotropins, antimüllerian hormone)**
- **Serum electrolytes**
- **Urinalysis**
- **Stimulation tests (human chorionic gonadotropin and corticotropin)**
- **Urinary steroids**
- **Gonadal biopsy**

Factors that influence gender assignment in the remainder of infants include specific diagnosis (only 50% of 46,XY infants with DSD will receive a definitive diagnosis), genital appearance, surgical options, need for lifelong replacement therapy, potential for fertility, and family or cultural views. This decision needs family participation, respect for their concerns, and confidentiality.

Although chromosomal analysis is an essential component of the diagnostic evaluation, karyotype is not necessarily decisive regarding gender assignment. As noted before, virilized 46,XX infants should be raised as females, but appropriate gender assignment for other conditions involves the aforementioned considerations, as in the case of androgen insensitivity or severe genital malformation.

Taking a "best guess" to mollify the family in the immediate situation is fraught with difficulty. Gender assignment is hard to reverse once the information is shared with family, medical records, care-giving staff, and the state (birth certificate). Management of ambiguous genitalia is an urgent situation, but not so urgent as to condone guessing.

Gender identity is established by age 3 years. Gender role is influenced by societal and cultural factors in addition to biological factors. Atypical gender role behavior is more common in DSD, but should not be used for gender reassignment. As the youngest age of gender identity is not known, the oldest age for gender reassignment is likewise not known. As the child grows older, disclosure of karyotype, gonads, fertility, and related issues are introduced and discussed. Although popular media have focused on the views of some DSD individuals who are not happy with their assigned gender and who advocate for delay in assigning gender until individuals can make their choices, current recommendations continue to promote assigning a gender to all individuals after careful evaluation and family counseling.

Do you want to add anything to your Learning Plan?
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References:

Houk CP, Levitsky LL. Management of the infant with ambiguous genitalia. Available at: www.uptodate.com. Accessed August 7, 2006

Hughes IA, Houk C, Ahmed SF, Lee PA, LWPES Consensus Group, ESPE Consensus Group. Consensus statement on management of intersex disorders. *Arch Dis Child.* 2006;91:554-563

American Board of Pediatrics Content Specification(s):

Understand normal fetal sexual differentiation

Understand the management of abnormal sexual differentiation

Know the approach to therapy of an infant with ambiguous genitalia, including congenital adrenal hyperplasia

PREVIOUS NEXT

February: Question 6

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11 November 07

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A female infant was transferred to your neonatal intensive care unit with respiratory distress, hypotonia, and dysmorphic features. She was born by elective primary caesarian section after a 37-week gestation; the mother was a 25-year-old gravida III woman, with a history of two spontaneous abortions. The infant had Apgar scores of 5 and 7 at 1 and 5 minutes after birth, respectively; mild respiratory distress which improved by 42 hours; and no family history of similar problems. The parents were unrelated. Physical examination showed birthweight at the 20th percentile, length at the 50th percentile, and head circumference at the 10th percentile. The infant was hypotonic and sleepy. The anterior fontanel measured 4 x 5 cm, forehead appeared high, and orbits shallow. Bilateral Brushfield spots were noted. Single transpalmar creases were found on both hands, and both thumbs were mildly broad and somewhat short. Physical examination findings of the thorax and abdomen were unremarkable. An ultrasonograph of the abdomen and a radiograph of the knee were obtained (Figures 1 and 2).

Figure 1: Radiograph of left knee showing stippled calcification of the patella.

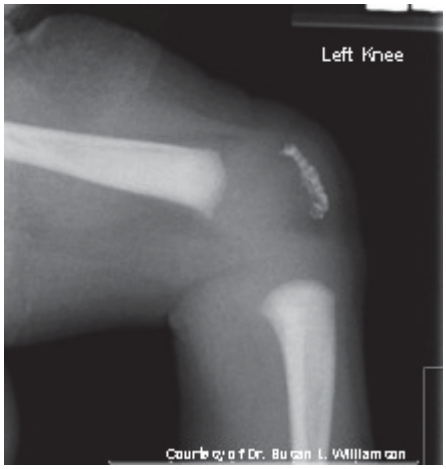
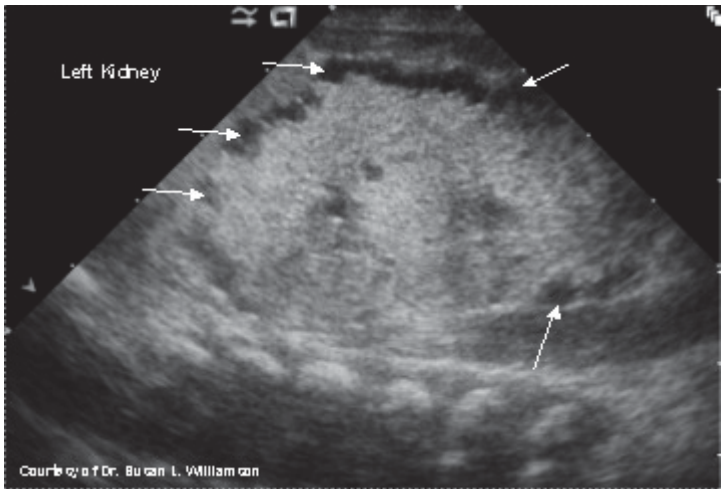


Figure 2: Sonogram of left kidney showing multiple peripheral cysts.



Of the following, the MOST likely diagnosis in this infant is:

1	Conradi Hünermann syndrome
2	Down syndrome
3	Fetal warfarin syndrome
4 (selected)	Smith-Lemli-Opitz syndrome
5	Zellweger syndrome

You selected 4, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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The infant in the vignette has Zellweger syndrome also known as cerebrohepatorenal syndrome. Typical features include hypotonia, high forehead, Brushfield spots, large fontanel (normal mean, 2.1 cm; upper limit, 3.5 cm at birth), shallow orbits, multiple cysts in the kidneys, and radiographic calcifications of the patella (see Figures). Other affected infants have exhibited seizures, defects in brain development on imaging, hepatomegaly, redundant skin of the neck, patent ductus arteriosus, limb contractures, and high blood concentrations of iron and copper. Zellweger syndrome is a peroxisomal disorder. It is the most common peroxisomal disorder to be seen in early infancy (1 in 50,000 to 100,000 births). Peroxisomal disorders taken together, however, have been estimated to occur in 1 in 20,000 individuals.

The peroxisome (originally called the microbody) is a cytoplasmic organelle measuring 0.5 µm in diameter. It participates in beta-oxidation of very-long-chain fatty acids (VLCFAs), biosynthesis of ether phospholipids (including plasmalogen and platelet activating factor), synthesis of cholesterol and bile acids, detoxification of glycolate to glycine, and oxidation of L-pipecolic acid. Abnormal accumulation of VLCFAs in blood confirms the diagnosis of Zellweger syndrome. VLCFAs adversely affect membrane structure and function. In the brain, VLCFA accumulation leads to demyelination, an intense white matter inflammatory response along with increased concentrations of leukotrienes secondary to beta-oxidation deficiency, and perivascular infiltration of T cells and B cells. VLCFAs are likely components of gangliosides and cell-adhesion molecules in growing axons, and their accumulation may account for the migration defects seen in Zellweger syndrome.

The peroxisomal disorders are divided into two classes based on the underlying mechanism (Table).

Table. Types of Peroxisomal Disorders*

Disorders of Peroxisome Biogenesis (Mutations of =1 of the 14 *PEX* genes)	Disorders of Single Functions (Intact Peroxisomal Structure)
Zellweger syndrome	Adrenoleukodystrophy (ie, VLCFA synthesis deficiency)
Neonatal adrenoleukodystrophy	Adrenomyeloneuropathy
Infantile Refsum disease	Pseudoneonatal adrenoleukodystrophy (acyl-CoA oxidase deficiency)
Hyperpipecolic acidemia	Metabolic kinase deficiency
	Hyperoxaluria type I (alanine glyoxylate aminotransferase deficiency)
	Acatalasemia
	DHAP acyltransferase deficiency (RCPD type II)
	Alkyl DHAP synthase deficiency (RCPD, type III)
	Glutaric aciduria type III
	Refsum disease (phytanoyl-CoA hydroxylase deficiency)

DHAP, dihydroxy acetonephosphate; RCPD, rhizomelic chondrodysplasia punctata; VLCFA, very-long-chain fatty acid.

The first group includes disorders in which the organelle itself is not formed properly (abnormal biogenesis) and is deficient in multiple functions. The second group includes defects of individual functions/enzymes with intact peroxisomal structure.

Chondrodysplasia punctata, also known as Conradi Hünermann syndrome, is an X-linked dominant disorder associated with mild to moderate growth deficiency, flat facies, and punctate mineralization of epiphyses. Infants with chondrodysplasia punctata, however, do not have hypotonia, large fontanels, or cystic kidneys.

Some of the features seen in the infant in this vignette can also be seen in infants with Down syndrome (trisomy 21). These include hypotonia, Brushfield spots, single transpalmar creases, and mild growth failure. However, although brachycephaly is typical in Down syndrome, a large fontanel or high forehead is not. Calcification of the patella and renal cysts are not features of Down syndrome either. Brushfield spots, which are depigmented speckles arranged in a ring concentric to the pupil, are found most often in infants with Down syndrome. However, they can occur in normal infants (with low incidence) and more frequently in infants with Zellweger syndrome.

Stippled epiphyses are seen in fetal warfarin syndrome, but generally in the uncalcified epiphyses of the axial skeleton, proximal femora, and calcanei. Calcification of the patella is not typical. These infants tend to have low birthweights, mental retardation, and seizures. There is no history of warfarin exposure in the vignette.

Infants with Smith-Lemli-Opitz syndrome, a disorder of cholesterol biosynthesis, are also moderately small at birth, and can have hypotonia, single transpalmar creases, and renal cysts. They tend to have microcephaly, including a small fontanel (not high forehead), and do not have abnormal limb calcifications.

References:

Chedrawi AK, Clark GD. Peroxisome disorders. Available in: http://www.emedicine.com/NEURO/topic309.htm. Accessed May 27, 2006.

Jones KL. *Smith's Recognizable Patterns of Human Malformation*. 6th ed. Philadelphia, Pa: Elsevier Saunders; 2005.

American Board of Pediatrics Content Specification(s):

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Recognize the clinical features and know how to manage craniofacial anomalies

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

Recognize the clinical features, inheritance pattern, and laboratory values associated with the Smith-Lemli-Opitz syndrome

Understand the etiology, clinical manifestations, laboratory features, treatment, and management of infants with lysosomal and peroxisomal, and mitochondrial disorders

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids

PREVIOUS NEXT

May: Question 5

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A couple meets with you for a prenatal consultation at 17 weeks' gestation. They report a remote family history of a severe congenital metabolic derangement for which the mother's large extended family has undergone linkage analysis. They want to know the probability of the current pregnancy resulting in that severe congenital metabolic derangement.

Of the following, the concept MOST central to linkage analysis is:

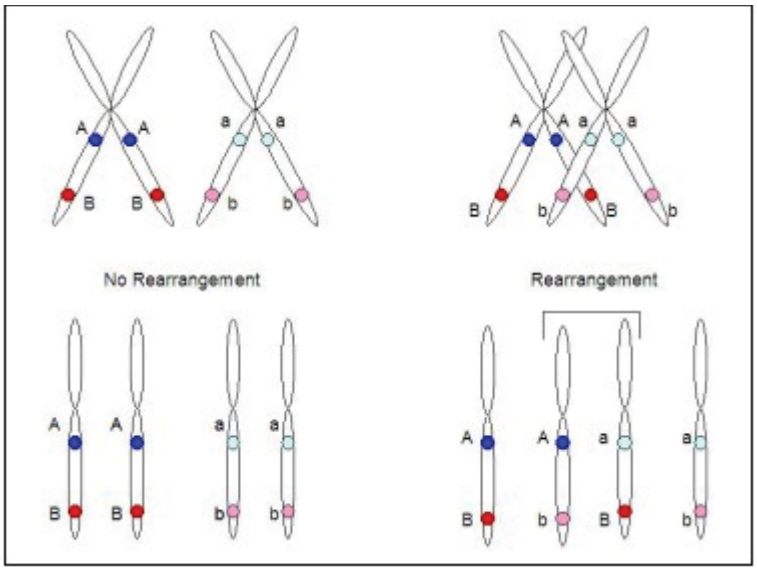
1	chromosomal recombination
2	logarithm-of-odds (LOD) scores
3	polymorphism of each haplotype
4	restriction fragment length polymorphisms (RFLPs)
5	short tandem repeats (STRs)

You selected 5, the correct answer is 1.

Genetic recombination of chromosomal DNA is the concept most central to linkage analysis. Each individual's genetic haplotype is polymorphic, or different, from another individual's. The specific points of polymorphism represent differences in the DNA from one person to another, and occur on average once every few hundred base pairs. Recombination is a fundamental concept that helps explain how those polymorphisms can be rearranged from one generation to the next. The strength of the linkage to resist rearrangement between any two points in the genome can be estimated by a logarithm-of-odds (LOD) score. Short tandem repeats (STRs) and restriction fragment length polymorphisms (RFLPs) are some of the polymorphic elements that vary from one individual's haplotype to another's, and can be aids in identifying cases in which recombination has occurred. Polymerase chain reaction (PCR) is a laboratory technique for dramatically amplifying the quantity of DNA under study, and can help with some linkage analyses.

Recombination is one of the processes during prophase I of meiosis by which DNA is rearranged. Homologous chromosomes are paired at this phase. The proximity of sister chromatids to each other allows an occasional exchange, or crossover, of segments of DNA between the sister chromatids (Figure).

Figure: Chromosomal rearrangement.



This exchange can occur at any point on the chromosome. Given any two points on a chromosome, the probability of a recombination event between those two points is low if the points are close to each other, higher if far apart. For small distances, a recombination rate of 1% (referred to as one centiMorgan) corresponds to approximately one million base pairs. To put that in perspective, the human genome is composed of approximately three billion base pairs.

The probability of linkage between two points is expressed as the LOD score. An LOD score of 3 represents a 1,000:1 odds in favor of a close linkage between the two points, and a low probability that a rearrangement will occur from one generation to the next.

Linkage analysis is useful clinically when a point on the chromosome corresponds to an inherited trait or disease. If the disease does not manifest in utero or has no easily detectable DNA defect or gene product, then linkage analysis might help to identify if a given fetus or newborn has the disease. If the gene for the disease is closely linked to another point on the chromosome that is easily detectable, then that easily detectable point can be used as an approximate marker for the disease. If the marker is found, using chorionic villous sampling or amniocentesis, then existence of the disease in the fetus can be inferred.

Linkage studies initially used only specific phenotypic traits (eg, blood type) or isoenzymes (eg, alcohol dehydrogenase variants) as markers for specific reference points on a chromosome. With the advent of PCR, genetic polymorphisms without a gene product or trait could be used as marker points on a chromosome. Several types of polymorphisms, such as STRs and RFLPs, are now used in linkage analysis.

Restriction fragment length polymorphisms are produced in the laboratory by digesting genomic DNA with restriction endonucleases. The nucleases derive their name from their function in bacteria, digesting the DNA of invading bacteriophages without digesting the bacterial genome, and so restricting the phage from infecting the bacteria. Each restriction enzyme cuts double-stranded DNA at a specific recognition sequence made of 4 to 12 base pairs. The specific recognition sequence is repeated at various points in the eukaryotic DNA under study, resulting in a genome cut into many stretches of DNA of different lengths. The different lengths of DNA migrate at different speeds under gel electrophoresis,

forming a pattern of bands.

If there is a benign genetic polymorphism at one of the recognition sites, the endonuclease fails to cleave and a different band pattern is seen on electrophoresis. The different band patterns made by different polymorphisms can be used in linkage analysis in the pedigrees of large families to find which RFLP pattern is linked to the disease in question.

Short tandem repeats also are polymorphisms that are useful in linkage analysis. They are made of sequences of 2 to 10 base pairs, repeated in tandem from 4 to 30 times. Their polymorphic aspect is the number of times the tandem repetition occurs at a specific site. They most often occur in the stable intron portions of the human genome and are highly conserved from generation to generation. They are detected with PCR amplification of specific STR sites followed by electrophoresis, mass spectrophotometry, or direct sequencing. There are more than 10,000 STR sites in the human genome, providing an excellent well-distributed basis for linkage analysis.

Polymerase chain reaction starts with a specimen of DNA and amplifies it using cycles of priming, synthesis, and denaturation. The process is automated in most laboratories and results in more than a millionfold multiplication in the mass of the DNA under study. When selective primers are used, one discrete segment of the original DNA can be selectively amplified and studied. PCR is a valuable tool that supports the performance of additional studies on the amplified DNA, including treatment with restriction endonucleases, gel electrophoresis, Southern blot analysis, and sequencing. Although a useful tool in linkage analysis, PCR is not essential to the concept of linkage analysis.

References:

Hamilton BA, Wynshaw-Boris A. Basic genetics and patterns of inheritance. In: Creasy RK, Resnik R, Iams JD, eds. *Maternal-Fetal Medicine* 5th ed. Philadelphia, Pa: Elsevier Saunders; 2004:3-36

Levine F. Basic genetic principles. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology*. 3rd ed. Philadelphia, Pa: Elsevier Saunders; 2004:1-15

Schwartz S. Genetic aspects of perinatal disease and prenatal diagnosis. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Elsevier Mosby; 2006:113-140

Taeusch HW. Impact of the human genome project on neonatal care. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:171-185

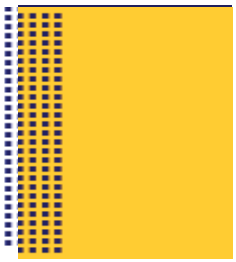
American Board of Pediatrics Content Specification(s):

Understand how linkage studies are used clinically

Understand the meaning of the terms point mutation, polymorphism, and haplotype

Understand the principal of polymerase chain reaction (PCR) procedure and application for genetic diagnosis

Understand the function and research utility of restriction endonucleases



May: Question 8

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A term male infant with an antenatal diagnosis of transposition of great arteries is admitted to the intensive care unit. A karyotype is obtained and the results are shown in the Figure.

Figure

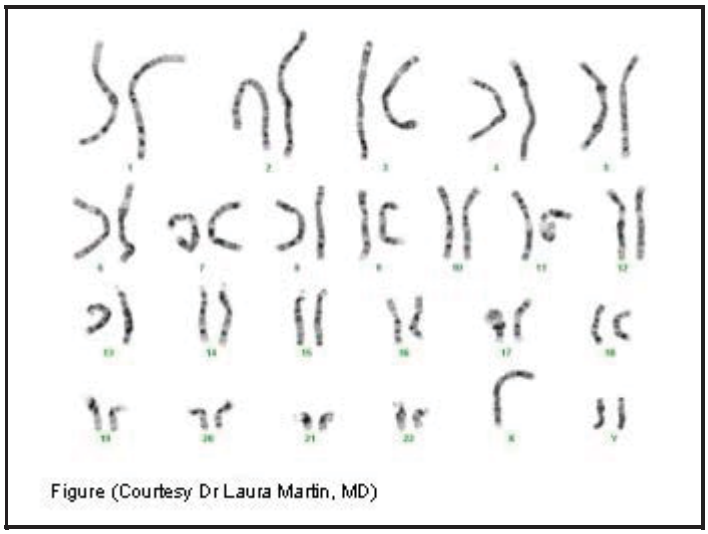

Figure (Courtesy Dr Laura Martin, MD)

Of the following, the MOST accurate statement about this karyotype is that it:

1	includes congenital heart disease in the spectrum of abnormalities
2	is associated with high testosterone levels
3	is inherited in an autosomal dominant fashion
4	is overrepresented in institutionalized male delinquents
5	results from nondisjunction in sperm cells

You selected 4, the correct answer is 5.

The Figure shows the presence of an extra Y chromosome. The 47,XYY karyotype represents an aneuploidy (specifically a trisomy) of the sex chromosomes in which a human male receives an extra Y chromosome. One in 840 males have the 47,XYY genotype. Five to 10 boys with 47,XYY syndrome are born in the United States each day. Most 47,XYY males are phenotypically normal and do not know their karyotype. For these reasons, some medical geneticists question whether the term "syndrome" is appropriate for this condition. Because there are no distinct

physical characteristics, the condition usually is only detected during genetic analysis for another reason. In fact, the first diagnosis of this condition was a karyotypic rather than a phenotypic discovery. The relatively small gene content of the Y chromosome is in keeping with the absence of congenital defects that characterize other types of sex chromosome imbalance. However, a pattern of characteristics has come to be appreciated, which may raise suspicion for the XYY syndrome in childhood. These characteristics include:

- acceleration of growth during middle childhood
- IQ in the low-normal range
- large teeth; prominent glabella; long ears; and increased anteroposterior length of cranial vault
- long hands and feet
- severe nodulocystic acne during adolescence
- occasional abnormalities include radioulnar synostosis, cryptorchidism, small penis, hypospadias, and abnormal electroencephalographic and electrocardiographic (prolonged PR interval) findings

The 47,XYY karyotype usually is not inherited, but occurs as a random event during the formation of sperm cells. The presence of the extra Y chromosome is paternally derived in all cases, and the extra Y originates at meiosis II. An error in cell division called "nondisjunction" can result in 47,XYY karyotype. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra Y chromosome in each of the body's cells. In some cases, the addition of an extra Y chromosome results from nondisjunction during cell division in early embryonic development. These cases are usually 46,XY/47,XYY mosaics. The incidence of 47,XYY is not affected by advanced paternal (or maternal) age. The first published report of a man with a 47,XYY karyotype was by Sandberg and associates in 1961. It was an incidental finding in a phenotypically normal 44-year-old, 6 feet (183 cm) tall man of average intelligence who had chromosomal analysis because he had a daughter with Down syndrome.

Although affected patients are occasionally long at birth, the tendency toward tall stature is usually not evident until 5 to 6 years of age. 47,XYY boys and men are usually taller than average and several centimeters taller than their parents and siblings. Despite the large size, these boys are usually not strong or well coordinated, and tend to have poorly developed pectoral and shoulder girdle musculature.

Behavioral problems, especially distractibility, hyperactivity, and temper tantrums are present in childhood and early adolescence. The XYY karyotype was once thought to cause aggressive or violent criminal behavior, but this theory has been disproved. Although early reports suggested that there existed an overrepresentation of 47,XYY individuals among institutionalized male juvenile delinquents, prospective longitudinal studies of unselected 47,XYY males showed that such linkage reflected a strong bias of ascertainment.

Boys with 47,XYY karyotype have an increased risk of learning disabilities (10%-50%) and delayed speech and language skills. Average IQ scores of 47,XYY boys are 10 to 15 points below controls and, while variability is large, most are within the average range.

Onset of puberty is delayed by approximately 6 months. Severe acne was noted in a few early case reports, but an association between acne and the 47,XYY karyotype has not been confirmed. Testosterone levels (prenatally and postnatally) are normal in 47,XYY males. Most 47,XYY males are fertile and have chromosomally normal offspring. However, an increased risk for offspring with chromosomal abnormalities as well as miscarriage and perinatal death has been

suggested. These individuals are not at increased risk of developing gonadal tumors.

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Jones KL. XYY Syndrome. In: Jones KL, editor. *Smith's Recognizable Patterns of Human Malformations.* 5th ed. Philadelphia, Pa: WB Saunders Co; 1997:70-71

47,XYY syndrome. Accessed October 25, 2006, at: http://ghr.nlm.nih.gov/condition=47xyysyndrome/show/print

Ratcliffe SG, Read G, Pan H, Fear C, Lindenbaum R, Crossley J. Prenatal testosterone levels in XXY and XYY males. *Horm Res.* 1994;42(3):106-109.

Robinson DO, Jacobs PA. The origin of the extra Y chromosome in males with a 47,XYY karyotype. *Hum Mol Genet.* 1999;8:2205-2209

Robinson A, Linden MG, Bender BG. Prenatal diagnosis of sex chromosome abnormalities. In: Milunsky A, ed. *Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment.* 4th ed. Baltimore, Md: The Johns Hopkins University Press; 1998:249-285

Sandberg AA, Koepf GF, Ishihara T, Hauschka TS. An XYY human male. *Lancet.* 1961;2:488-489

American Board of Pediatrics Content Specification(s):

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

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11 November 07

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May: Question 3

The infant depicted in Figures 1, 2, 3, and 4 was transferred for management of severe respiratory failure. The pregnancy, labor, and delivery were uncomplicated. Antenatal testing and sonography had been declined. The infant died despite intensive medical management.

Figure 1: Face and head of the infant in the vignette.

Figure 2: Frontal image of the face, head, torso, and extremities of the infant in the vignette.

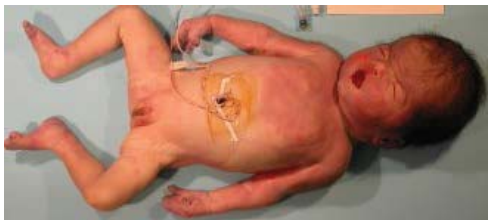


Figure 3: Right hand and feet of the infant in the vignette.

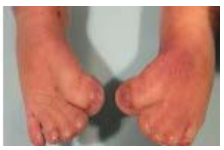
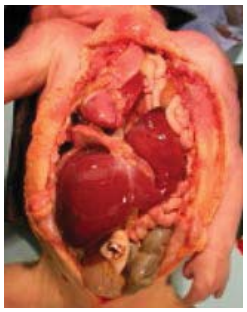


Figure 4: Autopsy of the infant in the vignette showing the intestines and left lope of the liver herniated into the left chest. The heart is located in the right thorax and lungs are hypoplastic.



Of the following disorders, the MOST likely diagnosis in this infant is:

1	Apert syndrome
2	craniofrontonasal dysplasia
3	Crouzon syndrome
4	Pfeiffer syndrome
5	Saethre-Chotzen syndrome

You selected 4, the correct answer is 1.

Abnormal head shapes and sizes that are present at birth are often caused by extracranial pressure or trauma (such as molding, caput succedaneum, cephalohematoma, subgaleal hemorrhage, and skull fractures) and central nervous system disorders (such as hydrocephalus, macrencephaly, anencephaly, microcephaly, tumors, vascular lesions, and encephaloceles). Heads of infants also may be misshapen because of craniosynostosis or deformational plagiocephaly.

Craniosynostosis results from premature closure of the sutures of the skull and is often accompanied by facial dysmorphism. When multiple sutures are fused, increased intracranial pressure and neurocognitive impairment may occur. Surgical intervention may be indicated.

Craniosynostosis is classified in a number of ways. It may be categorized as either primary or secondary. Primary craniosynostosis results from premature closure of one or more sutures without a known precipitating systemic illness. In contrast, secondary craniosynostosis is associated with systemic factors that alter the membranous growth of the cranial bones (eg, rickets, hyperthyroidism, glycogen storage disease, polycythemia vera, thalassemia, teratogens, intrauterine constraint).

Craniosynostosis also may be classified by the presence or absence of associated congenital anomalies. Nonsyndromic, or simple, craniosynostosis occurs when there is isolated fusion of one or more cranial sutures. Approximately 0.34 to 0.40 per 1,000 live births are affected by nonsyndromic craniosynostosis. The most commonly affected sutures are the sagittal (55% of cases, 3:1 male predominance) and coronal (25% of cases, slight female predilection) sutures. Multiple suture synostosis occurs in 15% of cases. Metopic and lambdoidal synostosis are unusual. Although most cases of nonsyndromic synostosis are sporadic, 10% of coronal and 2% of sagittal synostosis cases are familial. Syndromic craniosynostosis is defined by the presence of closed sutures, facial dysmorphism, skeletal abnormalities, and extraskeletal malformations. The prevalence of syndromic craniosynostosis is estimated to be a fraction of craniosynostosis cases (10% to 20%).

The neurocranium is composed of tissues derived from mesoderm and neural crest cells. The membranous neurocranium, or the bones and sutures of the skull, and cartilaginous neurocranium, or the bones that form the base of the cranium (such as the occipital, sphenoid, ethmoid, temporal, and ear ossicles) are derived from mesodermal embryonic cells. Sutures allow for growth of both the brain and cranium and, in humans, molding during vaginal delivery.

The development, differentiation, and pathobiology of the membranous neurocranium that leads to craniosynostosis are not well understood. The cranial bones are derived from bony spicules in five primary ossification centers located in the paired frontal and parietal centers, and a single occipital center by membranous ossification. The ossification centers grow in a radial direction with osteoblastic activity at the edges and osteoclastic activity within the center. The sutures develop at the junction where two ossification centers meet, and fontanels form where more than two ossification centers come together. The expansion of the brain, specifically the dura, stimulates growth of the cranial bones and sutures. The mechanisms associated with dural stimulation, growth of the sutures, and development of craniosynostosis are complex, and likely different in nonsyndromic and syndromic craniosynostosis. Molecular, cellular, and genetic studies have implicated a number of factors important in this process. Examples include fibroblast growth factor receptors 1 through 3, heparin-binding factors such as transforming growth factors beta 1 through 3, basic fibroblast growth factors, insulinlike growth factor 1, osteocalcin, collagen types 1 and 3, and several genes (eg, fibroblast growth factor receptor genes 1 through 3, *GLI3*, *MSX2*, and *TWIST*).

The infant depicted in the vignette has brachyturricephaly (towering head) (Figures 1, 2, and 5), symmetric syndactyly of the hands (mitten hands) and feet (sock toes) (Figure 3), and a left congenital diaphragmatic hernia (Figure 4) that is consistent with a syndromic form of craniosynostosis. Symmetric polysyndactyly of the hands and feet, usually involving the second, third, and fourth digits, and craniosynostosis affecting multiple sutures are distinguishing features of Apert syndrome (Table, Figure 3).

Table. Craniosynostosis Syndromes

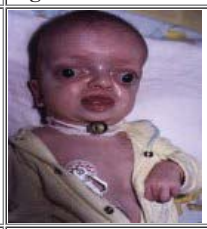
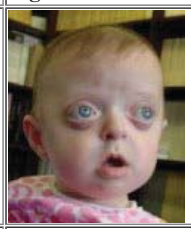
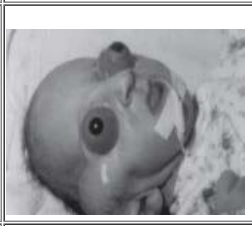
Features	Apert Syndrome	Craniofacial Dysplasia	Crouzon Syndrome	Pfeiffer Syndrome	Saethre-Chotzen Syndrome
Craniofacial	• Brachiturricephaly • Wide sagittal suture vs large anterior and posterior fontanels • Exorbitism (rare orbital subluxation) • Maxillary hypoplasia • Mandibular prognathism • Hypertelorism • Downslanting palpebral fissures • Small nose • Cleft palate/high arched and narrow palate	• Brachycephaly (coronal suture synostosis) • Male:Female difference (see text)	• Brachiturricephaly • Exorbitism (prominent with relatively common orbital subluxation) • Hypertelorism • Divergent strabismus • Maxillary hypoplasia • Curved parrotlike nose • Inverted V-shaped palate	• Brachiturricephaly • Exorbitsm • Maxillary hypoplasia • Small, beaked nose • Type 1: Craniosynostosis, broad thumbs and great toes, variable syndactyly, normal to near normal mental function • Type 2: Cloverleaf skull, severe ocular proptosis, severe CNS abnormalities, elbow ankylosis/synostosis, broad thumbs and great toes, various infrequently occurring anomalies in other organ systems, early death • Type 3: Similar to	• Brachycephaly • Wide sagittal vs large anterior and posterior fontanels • Shallow orbits • Hypertelorism • Ptosis • Lacrimal duct abnormalities • Prominent ear crust • Small, posteriorly rotated ears • Low frontal hairline • Maxillary hypoplasia with narrow palate • Facial asymmetry

				type 2 but without cloverleaf skull, early death	• Deviated nasal septum
Hands, feet, and limbs	• Syndactyly of the hands and feet (both cutaneous and osseous, symmetric) • Broad thumbs and toes, valgus positions	• Females and males: Longitudinal splitting of nails, syndactyly of toes, broad first toe, clinodactyly • Females: Syndactyly of fingers	• Normal	• Variable and partial syndactyly of the fingers • Broad thumbs and toes, valgus positions	• Syndactyly of the hands and feet (cutaneous, variable but usually partial) • Brachydactyly • Clinodactyly • Single palmar crease • Short and angulated, fingerlike, or flat thumbs • Broad great toes, valgus position • Limited elbow mobility
Other common features	• Mental deficiency • Megencephaly • Agenesis of corpus callosum • Hydrocephalus-progressive and nonprogressive • Gyral and hippocampal abnormalities • Growth deceleration • Fusion of C5-6		• Frontal bossing • Poor visual acuity • Optic atrophy • Nystagmus • Conductive hearing loss	• External auditory canal and middle ear abnormalities with hearing loss	• Short clavicles with distal hypoplasia
Occasional	• Humerus short with synostosis with radius • Genu valga • Pyloric stensosis, esophageal atresia, ectopic anus • Pulmonary aplasia, anomalous tracheal cartilage, congenital diaphragmatic hernia • Pulmonic stenosis, overriding aorta, VSD or endocardial fibroelastosis • Polycystic kidney, hydronephrosis, bicornuate uterus, vaginal atresia, cryptorchidism	• Females: Telecanthus • Exotropia • Nystagmus • Strabismus • Hearing loss • Axillary pterygium • Sprengel deformity • Restricted joint motion • Poland sequence • Dry, curly hair • Females and males: Cleft lip/palate • Webbed neck • Mental retardation • Males: Short stature • Pectus excavatum • Pseudoarthrosis of clavicles • Brachydactyly • Pre- and postaxial polydactyly • Deviated distal phalanges of fingers and	• Mental deficiency • Hydrocephalus • Seizures • Agenesis of the corpus callosum • Chiari I malformation • Syringomyelia • Keratoconus • Iris coloboma • Jugular foraminal stenosis • Auditory meatus atresia • Cleft lip/palate • Pulmonary valve stenosis • Tracheobronchomalacia • Subluxation of radial heads	• Mental deficiency • Hydrocephalus • Seizures • Choanal atresia • Ocular anterior chamber dysgenesis • Cartilaginous trachea; laryngo-, tracheo-, and bronchomalacia • Kleeblattschadel anomaly (cloverleaf skull) • Rediohumeral synostosis • Symphalangism of index finger • Fused cervical vertebra • Arnold-Chiari malformation	• Mental deficiency • Increased intracranial pressure • Small stature • Cleft palate • Deafness • Radioulnar synostosis • Cervical spine and other vertebral anomalies • Short 4th metacarpals • Hallucal reduplication • Duplicated phalanges of the great toe • Cyrptorchidism • Renal anomalies

		• toes • Wide space between first and second toes • Hypospadias • Shawl scrotum • Diaphragmatic hernia			
Etiology	• Fibroblast growth factor receptor 2 mutation (chromosome 10q25-10q26)	• Gene defect on Xp22	• Fibroblast growth factor receptor 2 mutation (chromosome 10q25- 10q26)	• Fibroblast growth factor receptor 1 (chromosome 8p11.22-p12) or fibroblast growth factor receptor 2 mutation (chromosome 10q25-10q26)	• *TWIST* gene mutation (chromosome 7-21-p22)
Prevalence	• 0.015/1,000 live births	• Rare	• 0.015/1,000 live births	• 0.0025/1,000 live births	• > 0.015/1,000 live births, uncertain estimate due to variable expression
Inheritance	• Autosomal dominant • Sporadic in majority of cases • Association with advanced paternal age	• X-linked dominant	• Autosomal dominant, with variable penetrance • Sporadic in 25% of cases	• Autosomal dominant and sporadic (type 1) • Sporadic only (types 2 and 3)	• Autosomal dominant with variable expression

Of note, large anterior and posterior fontanels, a wide sagittal suture, and megencephaly are frequently found in Apert syndrome. The presence of additional congenital anomalies affecting nonfacial structures, such as the congenital diaphragmatic hernia in the infant in the vignette, is also more common with Apert syndrome than in other syndromes associated with craniosynostosis. Physical features that may be shared with other craniosynostosis syndromes, especially Pfeiffer and Crouzon syndromes, include brachiturricephaly, exorbitism, maxillary hypoplasia, and mandibular prognathism. Cases of Apert syndrome are commonly sporadic, with a small percentage occurring due to autosomal dominant inheritance. Older paternal age is a risk factor. The genetic defect involves the fibroblast growth factor receptor 2 gene located on chromosome 10q25-q26.

Craniofrontonasal dysplasia is a rare disorder that involves craniosynostosis of one or more sutures (Table). It is unique in that female infants are more severely affected than male infants. Craniosynostosis, brachycephaly, and frontal bossing are found in female infants. Male infants have hypertelorism but craniosynostosis is unusual. Facial features (hypertelorism, asymmetry, broad nasal root, bifid nasal tip) and some limb anomalies (longitudinal splitting of nails, syndactyly of toes, broad first toe, clinodactyly) are similar in males and females. Syndactyly of the fingers, however, is present in female infants. Occasional abnormalities in noncraniofacial systems include diaphragmatic hernia, as seen in the infant in the vignette. However, symmetric polysyndactyly is not seen in infants with craniofrontonasal dysplasia. The inheritance pattern appears to be X-linked dominant; all daughters of affected males have been affected but no male-to-male transmission has been reported. The gene defect is located on chromosome Xp22. The reason for the milder phenotype in male infants is not known.

Figure 5a	Figure 5b	Figure 5c	Figure 5d
			
Infant with Apert syndrome	Infant with Crouzon syndrome	Infant with Pfeiffer syndrome type 1	Infant with Pfeiffer syndrome type 2

Crouzon syndrome is the most frequently encountered craniosynostosis syndrome, with an incidence of approximately 1 in 25,000 births. Because signs and symptoms may not be present at birth but evolve during the first year, Crouzon syndrome may go unrecognized initially whereas Apert syndrome is clinically evident at birth. Crouzon syndrome presents primarily with craniofacial abnormalities (Table, Figure 5B). Skeletal and extraskeletal abnormalities are unusual. Craniosynostosis of coronal, lambdoid, and sagittal sutures with palpable ridging accompanied by shallow orbits, prominent ocular proptosis, and maxillary hypoplasia are the characteristic clinical features. Sagittal craniosynostosis is unusual. A curved parrotlike nose and inverted V-shaped palate may accompany the maxillary hypoplasia. Strabismus, exposure conjunctivitis, hypertelorism, visual loss, optic atrophy, and conductive hearing loss are also common features. Hands and feet are normal. Hence, the infant in the vignette does not have Crouzon syndrome. Autosomal dominant inheritance with variable expression characterizes this syndrome. New mutations account for only about 25% of cases, in contrast to Apert

syndrome in which most cases are new mutations. The mutation involves the fibroblast growth factor receptor 2 gene mapped to chromosome 10q25-10q26, similar to that found in Apert syndrome.

The clinical features of Pfeiffer syndrome are similar to those of Apert syndrome except for the presence of variable syndactyly and less frequent association with noncraniofacial anomalies. Pfeiffer syndrome has been classified into three clinical subtypes, each with different dominant features. Type 1 is characterized by craniosynostosis, broad thumbs and great toes, variable syndactyly, and normal to near-normal mental function (Figure 5C). Type 2 is the most severe phenotype with the poorest survival. Frequently associated anomalies include a cloverleaf skull, severe ocular proptosis, central nervous system abnormalities, elbow ankylosis/synostosis, broad thumbs and great toes, various infrequently occurring anomalies in other organ systems, and early death (Figure 5D). Type 3 is similar to type 2 but without a cloverleaf skull. The inheritance pattern in type 1 is autosomal dominant, although sporadic gene mutations also occur. Inheritance in type 2 and 3 is sporadic. More than one genetic defect has been identified in Pfeiffer syndrome. Mutations of the fibroblast growth factor receptor 1 gene on chromosome 8p11.22-p12 and the fibroblast growth factor receptor 2 gene on chromosome 10q25-q26 (like Apert and Crouzon syndromes) have been identified.

Saethre-Chotzen syndrome is characterized by asymmetric craniosynostosis, brachycephaly, plagiocephaly, shallow orbits with rare orbital subluxation, maxillary hypoplasia, facial asymmetry, ptosis, prominent ear crust, posteriorly rotated and small ears, low frontal hairline, long and pointed nose, variable soft tissue syndactyly of toes and fingers, brachydactyly, short clavicles, and fusion of the second and third cervical vertebrae. The infant in the vignette has symmetric polysyndactyly and craniofacial features that are not characteristic of Saethre-Chotzen syndrome. The inheritance pattern is autosomal dominant. Mutations of the *TWIST* gene on chromosome 7p21-p22 are responsible for this disorder. The extremely variable phenotypic expression accounts for many cases being unrecognized and an underestimation of its true prevalence at birth.

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Strong Health. Image of infant with Apert syndrome. Accessed July 11, 2006, at: http://www.stronghealth.com/services/surgical/plastic/craniofacial/images/Pic7.jpg

The Craniofacial Center. Image of infant with Pfeiffer syndrome type 1. Accessed July 11, 2006, at: http://www.thecraniofacialcenter.org/pfeiffer.html

American Board of Pediatrics Content Specification(s):

Know the different factors that influence an infant's head shape

Recognize the clinical features of the syndromes associated with craniosynostosis

June: Question 7

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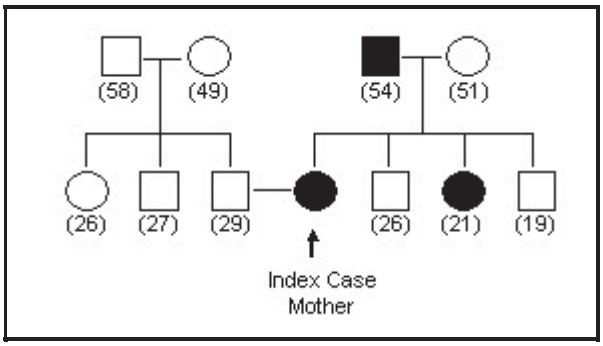
11 November 07

12 December 07

A 28-year-old primigravida has tuberous sclerosis with a strong family history (Figure 1).

Figure 1: Pedigree showing autosomal dominant pattern of inheritance of tuberous sclerosis.



Her pregnancy is dated at 24 weeks of gestation and has been uncomplicated thus far. She inquires about the effects of her disease on the offspring.

Of the following, the clinical feature of tuberous sclerosis MOST likely to manifest during fetal life is:

1	cardiac rhabdomyoma
2	facial angiofibroma
3	pulmonary lymphangiomyoma
4	renal angiomyolipoma
5	retinal hamartoma

You selected 3, the correct answer is 1.

Tuberous sclerosis is an autosomal dominant genetic disorder with multisystem manifestations. Two clinically indistinguishable, but genetically different, conditions comprise the tuberous sclerosis complex (TSC). TSC1 is caused by a mutation in the gene *TSC1* located on chromosome 9q34.3, which encodes a 140-kD protein called hamartin. TSC2 is caused by a mutation in the gene *TSC2* located on chromosome 16p13.3, which encodes a 200-kD protein called tuberin. *TSC1* mutation accounts for most familial cases of tuberous sclerosis and is associated with less severe disease. *TSC2* mutation accounts for most sporadic cases of tuberous sclerosis and is associated with more severe disease. Approximately

15% to 20% of patients with tuberous sclerosis have no identifiable mutations in the *TSC1* and *TSC2* genes, and generally manifest milder disease. Somatic mosaicism may account for failure to detect mutations in the *TSC1* and *TSC2* genes in some of these cases.

The proteins hamartin and tuberin interact physically with high affinity to form heterodimers and are coexpressed in cells within multiple organs. Within each cell, hamartin is localized to the centrosome, whereas tuberin is localized to the Golgi apparatus and the nucleus. The hamartin-tuberin heterodimers inhibit a cellular cascade called the mammalian target of rapamycin (mTOR) cascade, which is a critical regulator of cell growth and proliferation. Abnormal hamartin-tuberin heterodimers resulting from mutations in the *TSC1* and *TSC2* genes account for uncontrolled activation of the mTOR cascade and promote excessive cell growth (cytomegaly) and proliferation (increased cell number). The net result is the formation of tumors within many tissues, particularly in the mesenchymal tissue, that are pathognomonic of tuberous sclerosis.

The clinical features of tuberous sclerosis manifest at different developmental stages varying from fetal life to adulthood (Table).

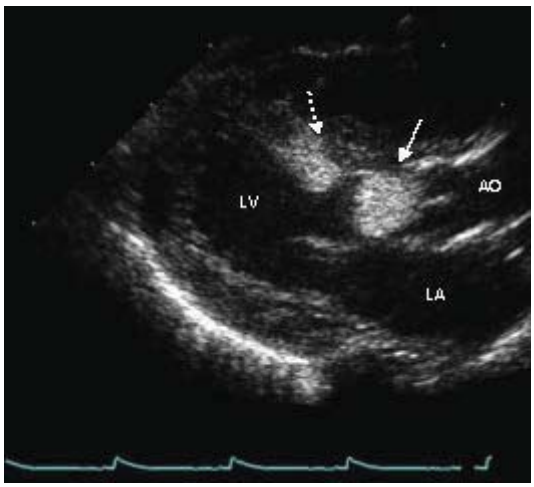
Table. Major Clinical Features of Tuberous Sclerosis

Clinical Feature	Age at Onset
Cardiac rhabdomyoma	Fetal life
Cerebral cortical tuber	Fetal life
Retinal hamartoma	Infancy
Hypomelanotic macule	Infancy to childhood
Shagreen patch	Childhood
Subependymal giant cell tumor	Childhood to adolescence
Facial angiofibroma	Childhood to adolescence
Renal angiomyolipoma	Childhood to adulthood
Periungual fibroma	Adolescence to adulthood
Pulmonary lymphangiomyoma	Adolescence to adulthood

The clinical features most likely to manifest during fetal life include cardiac rhabdomyoma and cerebral cortical tubers.

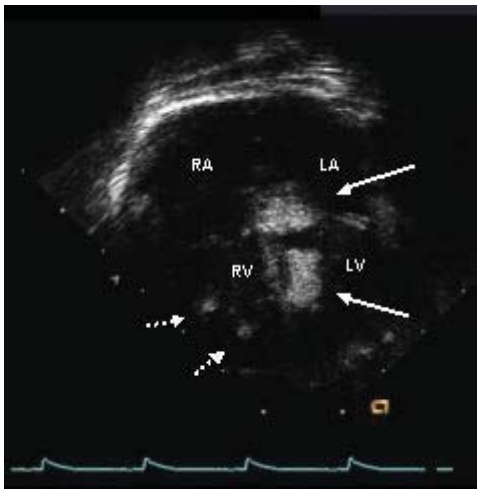
Cardiac rhabdomyoma is an intracavitary or intramural tumor of the heart that can be detected on fetal or neonatal ultrasonography (Figure 2 and Figure 3).

Figure 2: Neonatal echocardiography (long axis view) showing cardiac tumors of rhabdomyoma.



(Courtesy Dr Ann Kavanaugh-McHugh.)

Figure 3: Neonatal echocardiography (four chamber view) showing cardiac tumors of rhabdomyoma.



(Courtesy Dr Ann Kavanaugh-McHugh.)

It represents the most common cardiac tumor diagnosed in utero. Multiple tumors of varying sizes are common and found in 50% to 70% of affected infants. Conversely, 80% to 90% of infants with cardiac rhabdomyomas have tuberous sclerosis. These tumors can interfere with cardiac output by obstructing the flow and cause cardiac failure. Approximately 50% of infants with cardiac rhabdomyomas have cardiac dysrhythmias, including atrial tachycardia, ventricular tachycardia, complete heart block, and Wolff-Parkinson-White syndrome. Cardiac rhabdomyomas can be asymptomatic and often peak in size at approximately 32 weeks' gestation. These tumors often regress spontaneously and completely, mostly during infancy.

The cutaneous features of tuberous sclerosis include hypomelanotic macules, facial angiofibromas, collagenomas (shagreen patches), periungual fibromas, forehead fibrous plaques, and gingival fibromas. In infancy, only the hypomelanotic lesions are likely to be found. Facial angiofibromas, located predominantly around the nose and over the chin, typically do not manifest until 4 years of age or older and show progressive worsening of the lesions over time.

Pulmonary lymphangiomyoma typically manifests in adolescence and affects females almost exclusively. It is characterized by widespread proliferation of abnormal smooth muscle cells in the lung and cystic degeneration of the lung parenchyma. The aberrant migration of smooth muscle cells is promoted by estrogen, which explains the predisposition of adolescent females to this disease.

Renal angiomyolipoma manifests in late childhood, typically by the age of 10 years. It represents a benign tumor composed of abnormal blood vessels, immature smooth muscle cells, and fat cells. Often multiple tumors of varying sizes are found in each kidney. An estimated 2% to 3% of patients with tuberous sclerosis carry on chromosome 16 a contiguous germ line deletion that affects both the *TSC2* gene and one of the genes that causes autosomal dominant polycystic kidney disease. Such patients have a polycystic kidney phenotype that is detectable in infancy. Renal carcinoma is a potential complication of renal tumors in tuberous sclerosis.

Retinal hamartoma typically manifests during infancy. It represents a developmental abnormality in which there is an excess of one or more mature or nearly mature tissue structures normally found in the retina. Multiple nodular tumors of the retina are common and can be diagnosed with a fundoscopic examination.

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American Board of Pediatrics Content Specification(s):

Recognize the cardiac manifestations of maternal diseases and of common perinatal syndromes in the newborn infant

Know the effects on the fetus of maternal connective disorders and their treatment

Understand the pathophysiology, including genetics, of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Recognize the clinical features of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Recognize the laboratory and radiographic features of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

PREVIOUS NEXT

July: Question 8

A term male newborn is referred to you at 2 days of age because of feeding difficulty, hypotonia, and muscle weakness since birth. His mother is in good health. She had a distant history of genital herpes infection with occasional recurrences. This is her first child and she did not notice decreased fetal movement. Delivery was via cesarean section due to breech presentation, with membranes ruptured at delivery. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. Physical examination reveals a well-developed term infant with normal vital signs. He has poor suck, poor head control, generalized hypotonia, and weakness. The muscles in his arms and legs are normal in size. Deep tendon reflexes are present in all extremities. Complete blood count is normal. Cerebrospinal fluid (CSF) shows normal glucose and protein concentrations, and cell count, but an increased lactate concentration. Blood gases reveal a mild mixed respiratory and metabolic acidosis.

Of the following, the MOST likely diagnosis in this infant is:

1	cerebral palsy
2	herpes encephalitis
3	Leigh syndrome
4	Pompe disease
5	Werdnig-Hoffmann disease

You selected 3, the correct answer is 3.

The infant in this vignette has Leigh (pronounced Lee) syndrome which is a disorder of mitochondrial function. Leigh syndrome, first described in 1951, typically becomes symptomatic later in infancy or early childhood. However, increasing numbers of cases with neonatal onset are reported. The classic findings include hypotonia, weakness, hypoventilation (from mild to as severe as in central hypoventilation syndrome), oculomotor abnormalities, feeding disorders, and facial weakness. Increased lactate concentration is seen in cerebrospinal fluid (CSF) and, in many cases, in the blood. Cranial ultrasonography may show increased echogenicity in the caudate and putamen. Magnetic resonance imaging may show increased T2-weighted signals from the same areas. The prognosis is poor, with progressive neurologic deterioration, including the onset of seizures, and progression to death typically in 1 to 2 years. Earlier onset is associated with a shorter course. The last stage may be accompanied by heart failure because of an associated cardiomyopathy.

Leigh syndrome can be caused by one of several genetic defects that lead to mitochondrial dysfunction. Enzyme deficiencies associated with the disorder

include:

- cytochrome *c* oxidase
- the pyruvate dehydrogenase complex
- reduced form of nicotinamide adenine dinucleotide coenzyme (NADH)-CoQ reductase
- or adenosine triphosphatase (ATPase) subunit 6

Of these four, the defect in cytochrome *c* oxidase is most commonly associated with Leigh syndrome, with enzyme activity reduced to 4% to 24% of normal.

In most cases of Leigh syndrome, the molecular defect is not in the oxidase protein sequence itself, but in one of at least two nuclear-encoded proteins that regulate the construction of the cytochrome *c* oxidase complex on the inner membrane of the mitochondrion. The most common of these that lead to Leigh syndrome are mutations in SURF-1 on chromosome 9. SURF-1 serves to insert the heme ring into the cytochrome oxidase complex. A defect in another assembly protein, SCO2, has also been associated with Leigh syndrome. Its likely function is to incorporate the copper ion into the cytochrome *c* oxidase complex. The gene for SCO2 is found on chromosome 17. Mutations in this gene are most common in cases of Leigh syndrome with neonatal onset. Leigh syndrome caused by defects in one of these two nuclear-encoded proteins is inherited as an autosomal recessive disorder. Mutations in mitochondrial DNA (mtDNA) lead to Leigh syndrome in only 10% to 30% of cases.

Most cases of cerebral palsy have antecedents long before parturition. Good Apgar scores, hypotonia, and feeding difficulties can be seen in infants later determined to have cerebral palsy. However, one would not expect to find systemic and/or central nervous system lactic acidosis long after the brain injury.

Herpes encephalitis is unlikely to be symptomatic at birth, because almost all neonatal herpes infections are acquired from an active infection in the birth canal during parturition. Skin vesicles often precede other symptoms and appear around the end of the first week after birth. Seizures and signs of systemic sepsis as well as hepatic involvement are common. The infant in this vignette was born by cesarean section, which provides significant protection from acquiring the virus from lesions in the birth canal; he was symptomatic from the time of birth.

Werdnig-Hoffmann disease (spinal muscular atrophy, type I) is a form of anterior horn cell degeneration presenting in the newborn period in about half of all cases. It is an autosomal recessive disorder. Approximately 98% of cases are caused by the homozygous absence of a region of exons 7 and 8 of the telomeric copy of the SMN gene (SMN1) on chromosome 5. These infants have severe diffuse hypotonia and weakness including the facial muscles, and usually die by 2 years of age. Often proximal muscles are more affected than distal ones early on; deep tendon reflexes may be diminished or absent. Muscle atrophy can be severe. Increased CSF or blood lactate is not associated with Werdnig-Hoffmann disease.

Pompe disease is also known as type II glycogen storage disease, and is caused by a deficiency in 1,4-alpha-glucosidase. The gene is located on chromosome 17. Pompe disease is an autosomal recessive disorder also characterized by striking weakness and hypotonia in early infancy. In Pompe disease, glycogen is deposited in the anterior horn cells and many of the symptoms of early-onset Werdnig-Hoffmann disease are displayed. The heart is usually affected early on as are the skeletal muscles. The tongue is usually large and skeletal muscles show concentric hypertrophy. Lactate is not increased in the CSF or blood.

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American Board of Pediatrics Content Specification(s):

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Recognize the clinical features associated with mitochondrial disorders

Understand the functions of messenger, ribosomal, and transfer RNA

Understand the differential diagnosis, management, and outcomes of neonatal hypotonia

PREVIOUS NEXT

July: Question 3

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11 November 07

12 December 07

Your state screening program uses genetic testing to identify newborns with cystic fibrosis. You receive notification that one of the neonates in your neonatal intensive care unit has two abnormal alleles for the cystic fibrosis transmembrane regulator gene (*CFTR*). The child is healthy, almost ready for discharge from the hospital. The parents want to know what problems their child might have to face.

Of the following, the EARLIEST finding in a neonate with cystic fibrosis such as the neonate in the vignette is:

1	hepatic cirrhosis
2	nasal polyps
3	pancreatic insufficiency
4	pulmonary infection
5	rectal prolapse

You selected 3, the correct answer is 3.

Once meconium ileus is excluded, as in the vignette, most neonates with two abnormal *CFTR* genes will show only pancreatic insufficiency as a symptom of their cystic fibrosis. The other choices are less frequent or appear after the neonatal period.

More than 1,000 known mutations can affect CFTR function. Most of the defects involve the gene producing the 1,480-amino-acid protein, but some involve defects of transcriptional regulation of the gene or of posttranslational processing. The result is a wide range of severity in cystic fibrosis, from only congenital absence of the vas deferens to severe pancreatic exocrine deficiency (Table).

Table. Symptoms of Cystic Fibrosis and CFTR Function (Modified from Stern)

CFTR Function,% of Normal	Manifestation of Cystic Fibrosis
<10	Congenital absence of the vas deferens
<5	Above and demonstrable sweat abnormality
<4.5	Above and progressive pulmonary infection
<1	Above and pancreatic exocrine deficiency, meconium ileus

The pathophysiology of cystic fibrosis involves chloride channel regulation in certain cells. In the sweat glands, the usual processing of sweat in the duct is disrupted before it emerges on the skin surface. The chloride ions in the nascent sweat are not reclaimed from the ductal lumen, and the chloride concentration in the resulting sweat is higher than in patients without cystic fibrosis.

In some exocrine cells of various organs, an abnormality in *CFTR* results in viscid mucous with a low water content. The most accepted model for this process postulates that the abnormal CFTR protein causes a hyperabsorption of sodium ions from the lumen to the interstitium. Water molecules and chloride follow the sodium, leaving only a small quantity of water to hydrate the mucous in the lumen.

In the vas deferens, thickened mucous blocks the lumen in utero, causing involution of the vas deferens and male infertility. In the lung, the tenacious secretions obstruct the distal airways and inhibit eradication of pathogens. Chronic inflammation, progressive fibrosis, and recurrent pneumonia result. Chronic inflammation of the paranasal sinuses causes nasal polyps. Bile duct blockage can lead to cirrhosis. In the pancreas, ductal concretions cause a markedly reduced output of digestive enzymes and bicarbonate. In the fetal intestines, thickened meconium causes the meconium ileus syndrome.

The symptoms of cystic fibrosis exhibited by the neonate appear in order of CFTR severity (Table). The most severe presentation, meconium ileus, manifests at birth (or earlier if abdominal calcifications are seen prenatally) in approximately 15% of patients with cystic fibrosis. Once meconium ileus is excluded, as in the vignette, pancreatic insufficiency will present in 85% of patients with cystic fibrosis as poor growth, both in length and weight.

Sweat chloride testing may not be diagnostic in the neonatal period because of the difficulty in obtaining enough sweat at this age.

Other symptoms do not show up as often in the neonatal period. Respiratory symptoms, such as chronic sinusitis and recurrent pneumonia, occur most often after the neonatal period. Cholestasis may cause a direct hyperbilirubinemia in the neonate, but frank cirrhosis does not appear until hepatic fibrosis has been present for several months. Rectal prolapse, a result of chronic coughing, steatorrhea, and malnutrition, usually presents at 6 months to 3 years of age. An absent vas deferens manifests as male infertility in later life.

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Magnuson DK, Parry RL, Chwals WJ. Selected abdominal gastrointestinal anomalies. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1381-1403

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American Board of Pediatrics Content Specification(s):

Understand the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant

Understand the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

Understand the diagnosis of CF in newborn infants

PREVIOUS NEXT

August: Question 2

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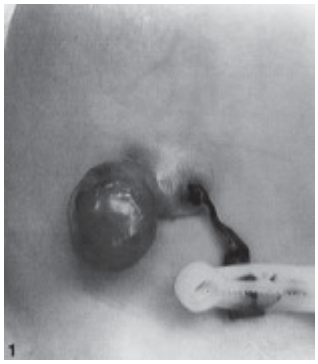
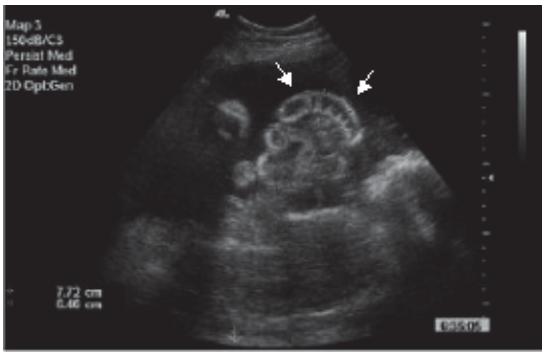
You are asked to counsel the parents of a term infant whose abdomen is depicted in Figure 1.

Figure 1. Periumbilical findings.



Fetal ultrasonography at a gestational age of 20 weeks identified the anomaly depicted in Figure 2.

Figure 2



The anomaly was undetectable on follow-up fetal ultrasonography several weeks later. No other fetal anomalies were detected. The prenatal course was complicated by polyhydramnios and intrauterine growth restriction. Fetal karyotype was 46,XX. Both parents ask about the prognosis.

Of the following, the MOST likely outcome for the infant in this vignette is:

1	cholestasis
2	death during infancy
3	intestinal perforation
4	normal growth and development

5 sepsis

You selected 2, the correct answer is 2.

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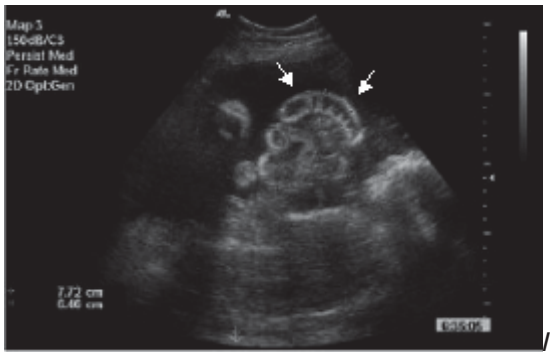
The fetus in this vignette has gastroschisis. Gastroschisis occurs in approximately 1 in 4,000 live births and has no sex predilection. Although the cause is unclear, it is commonly proposed that a vascular accident or developmental defect in the right omphalomesenteric artery leads to loss or malformation of the right lateral fold of the embryo. This theory explains the location of gastroschisis in the right periumbilical abdominal wall.

Gastroschisis is associated with a stillbirth rate of 5% to 12.5%, intrauterine growth restriction (24%-67%), and preterm delivery (average gestational age, 35-36 weeks). Maternal alpha-fetoprotein screening will detect 95% of gastroschisis cases. Fetal ultrasonography shows extra-abdominal intestine that floats freely in the amniotic cavity (Figure 2).

Figure 2



Occasionally, bowel distension and herniation of the stomach and/or bladder may be detected. Differentiation from a ruptured omphalocele can be difficult. The location of the liver outside the abdominal cavity and defects of the spine and limbs suggest the limb-body wall complex. More commonly, a tangled umbilical cord adjacent to the fetal abdomen may be confused with the appearance of gastroschisis; Doppler ultrasonography showing blood flow identifies the tangled loops as the umbilical cord.

Associated anomalies are detected in 7% to 30% of infants with gastroschisis. The most common abnormalities affect the gastrointestinal tract (approximately 25% of cases), however, malrotation is always present. Intestinal atresia, volvulus, perforation, and bowel necrosis may occur.

The infant in this vignette has a “vanishing” gastroschisis with prenatal closure of all or a portion of the abdominal wall defect. In utero intestinal ischemia because of strangulation at a small constricting abdominal opening or volvulus is thought to precede bowel necrosis and subsequent resorption. This phenomenon is rare, but is associated with death in eight of nine reported cases. Of these eight infants, one was stillborn, three died within the first week after birth, and four died of liver failure and/or sepsis at ages 2 to 18 months. The surviving infant in this case series experienced short bowel syndrome and hyperalimentation-associated cholestasis.

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American Board of Pediatrics Content Specification(s):

Understand the embryology, clinical manifestations, and associated abnormalities in gastroschisis

Know the approach to therapy, the complications, and the difficulties providing enteral nutrition in neonates with gastroschisis

PREVIOUS NEXT

August: Question 6

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You agree to have a high school student shadow you on rounds in the neonatal intensive care unit. She is taking advanced placement biology in her senior year and wants to relate the basic molecular biology she is learning to disease processes. One of her many questions concerns transfer RNA (tRNA). She cannot understand how a mutation in a tRNA gene would not stop embryonic development. She wonders if a disease related to such a mutation is known in newborns. You explain that mutations in several mitochondrial genes including tRNA genes have been implicated in clinical syndromes in older people, such as hereditary deafness, Alzheimer disease, and Parkinson disease. You discuss an example of a disorder due to tRNA mutation that presents in newborn infants.

Of the following, the disorder MOST often associated with a mutation of a tRNA gene in newborn infants is:

1	cardiomyopathy
2	diabetes mellitus
3	Leigh syndrome
4	mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)
5	myoclonic epilepsy and red-ragged fibers (MERRF)

You selected 2, the correct answer is 1.

A typical eukaryotic cell contains about 2,000 mitochondria that occupy about one fifth of the cell volume. Mitochondria contain unique genomes and ribosomes that are more typical of bacteria than of eukaryotic cells. They are the engines of aerobic respiration and produce most of the adenosine triphosphate (ie, energy) for cellular metabolism. In addition, they degrade and recycle carbohydrates, proteins, and fats, and produce urea. They also control the concentration of water and other molecules inside the cell.

Mitochondria are a significant source of free radicals in metabolism, producing around 10^7 free radicals per mitochondrion per day. Free radicals are potent mutagens. Moreover, the repair mechanisms of mitochondrial DNA (mtDNA) are less effective than those of nuclear DNA. Consequently, spontaneous mutations of mtDNA occur 10- to 20-fold more frequently than those of nuclear DNA. Tissues with high oxygen consumption (skeletal muscle, heart, and brain) are particularly susceptible to the effects of mtDNA mutations. These mutations tend to accumulate as a person ages.

The quality and severity of a mitochondrial disorder depend on (1) the type and location of the mutation in the mitochondrial genome, and (2) the proportion of mitochondria in a particular

tissue with the mutation (degree of heteroplasmia). Both the quantity and the variety of mtDNA mutations increase with age. If all of the mitochondria in a tissue have a particular mutation, the condition is known as homoplasmia. In addition, many mitochondrial functions are dependent on gene products of mtDNA interacting with those of nuclear DNA, so that somatic mutations can also lead to mitochondrial dysfunctions.

Mitochondrial diseases occur in 1 in 10,000 newborn infants. The mitochondria that provide energy for spermatozoa are shed in the process of fertilization, so that all of the mitochondria inherited by an individual are maternal. Over 100 mitochondrial mutations are known. Information regarding individual mutations can be found in the MITOMAP database. Even though tRNA genes constitute one tenth of mtDNA, two thirds of the mtDNA mutations identified so far occur in tRNA genes. The reason for this is not known.

Cardiomyopathy with clinical onset at birth can be caused by mutations in mitochondrial tRNA genes. Mutations of the mitochondrial tRNA-isoleucine gene and the tRNA-leucine gene have been associated with congenital cardiomyopathy. These infants may also develop neuromuscular disease. The onset of symptoms can be evident at birth or as late as 10 years. Lactic acidosis is common. All such cases have decreased levels of cytochrome *c* oxidase activity and abnormally appearing cardiac muscle. The cardiac myocytes are hypertrophic and diffusely swollen with myofibril disarray. The ultrastructural abnormalities of the mitochondria include hyperplasia and pleomorphism.

Diabetes mellitus (type 2) has been associated with mutations of tRNA-lysine and with other mtDNA mutations. The onset, however, has not been described in newborns.

In most cases of Leigh syndrome (pronounced Lee), the mitochondrial dysfunction is not caused by a mutation in mtDNA, but by an autosomal recessive or X-linked disorder involving a gene product of the nuclear chromosomes. In this syndrome, the energy-generating function of the mitochondrion is affected. Mutations of mtDNA cause 10% to 30% of cases of Leigh syndrome, and are associated rarely with a mutation in mitochondrial tRNA.

Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is a progressive neurodegenerative disorder. Most commonly MELAS has been associated with a mutation in the tRNA-leucine gene, but other mtDNA mutations have also been identified in some cases. The condition presents sporadically or in maternal pedigrees with one of several clinical presentations. Typically, it presents with the features indicated by the name of the disorder, such as encephalomyopathy, lactic acidosis, and strokelike episodes. Other features, such as seizures, diabetes mellitus, hearing loss, short stature, and exercise intolerance can also be seen. The age at onset is usually between 4 and 15 years; the youngest known case was 4 months old.

Myoclonic epilepsy associated with ragged red fibers (MERRF) has been associated most commonly with a mutation in the tRNA-lysine gene. Its onset is in childhood, not in the newborn period. The most characteristic symptom of MERRF syndrome is myoclonic seizures that are usually sudden, brief, jerking spasms that can affect the limbs or the entire body. Ataxia as well as lactic acidosis may be present. Dysarthria, optic atrophy, short stature, hearing loss, dementia, and nystagmus have been described with MERRF.

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American Board of Pediatrics Content Specification(s):

Recognize the clinical features associated with mitochondrial disorders

Demonstrate understanding of maternal inheritance of mitochondrial disorders

Understand the functions of messenger, ribosomal, and transfer RNA

Understand the pathophysiology, including genetics, of an infant with a condition affecting myocardial performance such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

PREVIOUS NEXT

August: Question 1

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11 November 07

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An appropriately grown infant is born at 38 weeks' gestation. Prenatal ultrasonography at 19 weeks' gestation demonstrated a small cystic hygroma, with resolution noted on follow-up ultrasonography. Amniocentesis revealed a 46,XY karyotype. Findings on physical examination of the infant include hypertelorism, low-set ears, redundancy of nuchal skin with a low hairline, pectus excavatum, and bilateral cryptorchidism.

Of the following, echocardiography is MOST likely to demonstrate:

1	aortic coarctation
2	bicuspid aortic valve
3	hypertrophic cardiomyopathy
4	tetralogy of Fallot
5	valvular pulmonic stenosis

You selected 1, the correct answer is 5.

The infant in the vignette exhibits a constellation of phenotypic features consistent with Noonan syndrome (NS). Facial dysmorphism, webbing of the neck, chest deformities, and cryptorchidism are characteristic. In addition, NS is the second most common genetic syndrome associated with congenital heart defects (Down syndrome is most common), with pulmonary stenosis the most frequent lesion. Hypertrophic cardiomyopathy is the second most frequent heart lesion in NS, but may not be present at birth. Tetralogy of Fallot does occur with NS, but at a very low frequency. Many phenotypic characteristics of NS resemble those of Turner syndrome (karyotype 45X), but in NS the karyotype is normal, and both males and females are affected. Aortic coarctation and bicuspid aortic valve represent the most common heart defects occurring with Turner syndrome.

The incidence of NS ranges between 1 in 1,000 and 1 in 2,500 live births, with fetal loss being a common occurrence. Although the mechanism of inheritance appears to be autosomal dominant, up to 60% of cases are the result of de novo mutations. In many cases, the implicated gene has been linked to chromosome 12q. Mutations in *PTPN11*, a gene encoding a ubiquitously expressed protein tyrosine phosphatase, which is important in a variety of developmental pathways, have been demonstrated in up to 60% of cases. Penetrance, though variable, is nearly complete in the presence of the *PTPN11* mutation. Males are affected twice as often as females when there is both an affected parent and a *PTPN11* mutation, suggesting a survival advantage of affected male embryos.

Before the availability of genetic testing for the *PTPN11* mutation, the diagnosis of NS relied on

subjective assessment of the phenotypic features. Prenatally, the presence of a cystic hygroma or nuchal lucency raises suspicion for the diagnosis. Parameters of fetal growth are generally unhelpful, because infants with NS are most often appropriately grown for gestational age. The typical characteristics associated with NS resemble those of Turner syndrome and are listed in the Table.

Table. Characteristics of Noonan Syndrome

1. Facial dysmorphism (100%) Triangular facies Hypertelorism Epicanthal folds Down-slanting palpebral fissures Low-set, posteriorly rotated ears
2. Short neck with webbing, redundancy of skin, or low posterior hairline (30%)
3. Chest deformities Pectus deformities (70%-90%) Shield chest with wide-spaced nipples 4. Cardiac defects (85%) Pulmonary stenosis with or without dysplastic pulmonary valve (50%) Hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction (20%) Atrioventricular canal defects (8%) Aortic coarctation (12%) Atrial septal defect (14%) Tetralogy of Fallot (4%)
5. Cryptorchidism (65%)
6. Bleeding diatheses (20%)
7. Postnatal short stature (50%-60%)
7. Developmental delay (12%) Mild mental retardation (15%-35%)

Expressivity is highly variable and several phenotypic features change with age. For instance, newborns with NS may have less apparent facial dysmorphism, but often demonstrate generalized edema and excess nuchal folds. Over time, the typical facial features may emerge, as well as pectus deformities and short stature. By later adolescence and adulthood, the typical facial features often become less apparent. Genotype does influence cardiac phenotype, with an increased prevalence of pulmonary stenosis among patients with the *PTPN11* mutation, but does not appear to influence other phenotypic features.

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References:

Jones KL. Noonan syndrome. In: *Smith's Recognizable Patterns of Human Malformation*. 6th ed. Philadelphia, Pa: WB Saunders; 2006:124-127

Marino B, Digilio MC, Toscano A, Giannotti A, Dallapiccola B. Congenital heart diseases in children with Noonan syndrome: an expanded cardiac spectrum with high prevalence of atrioventricular canal. *J Pediatr*. 1999;135:703-706

Tartaglia M, Gelb BD. Noonan syndrome and related disorders: genetics and pathogenesis. *Annu Rev Genomics Hum Genet.* 2005;6:45-68

Van der Burgt I, Thoonen G, Roosenboom N, et al. Patterns of cognitive functioning in school-aged children with Noonan syndrome associated with variabitlity in phenotypic expression. *J Pediatr*. 1999;135:707-713

American Board of Pediatrics Content Specification(s):

Recognize the clinical features of the Noonan syndrome

October: Question 6

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11 November 07

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On physical examination of a healthy appearing term infant, heart tones are noted to be best auscultated over the right side of the chest. Chest and abdominal radiographs are obtained (Figure 1 and Figure 2).

Figure 1

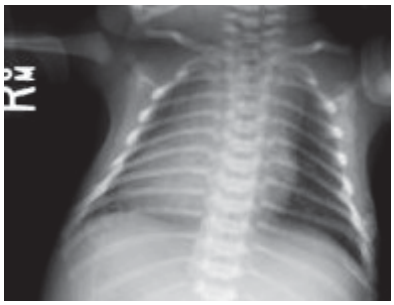
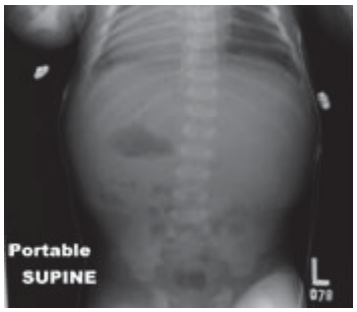


Figure 2



Abdominal ultrasonography confirms a right-sided stomach, and demonstrates a left-sided gallbladder and an asymmetric bilobed liver. Howell-Jolly bodies are not found on examination of the peripheral blood smear, and a damaged red blood cell scan demonstrates a single spleen located in the right upper quadrant of the abdomen.

Of the following, the associated condition MOST likely to be demonstrated in this infant is:

1	cardiac dysrhythmia
2	ciliary dyskinesia
3	impaired immune function
4	intestinal malrotation
5	structural heart defects

You selected 2, the correct answer is 2.

Do you want to add anything to your Learning Plan?

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Specific thoracoabdominal asymmetry of the unpaired organs and vessels develops in 99.9% of individuals. With this arrangement, called *situs solitus*, the cardiac apex, a bilobed lung, the stomach, and the spleen are on the left side of midline, and the vena cava, a trilobed lung, the gallbladder, and the larger liver lobe are on the right side of midline. With the exception of the spleen, which is left-sided at its inception, each unpaired organ originates as a midline structure and lateralizes in later development.

The infant in the vignette has a complete, mirror-image reversal of thoracoabdominal asymmetry called *situs inversus*. Dextrocardia (right-sided cardiac apex and left-sided systemic atrium) is present, along with a right-sided aorta, stomach, and single spleen, and a left-sided trilobed lung, liver, gallbladder, and inferior vena cava. Situs inversus occurs in 0.01% of the population.

Additional structural malformations are uncommon with situs inversus, but occur more often than with situs solitus. However, up to 25% of individuals with situs inversus have ciliary dysfunction and Kartagener syndrome, with the classic triad of situs inversus, bronchiectasis, and chronic sinusitis. The immotile cilia syndrome (primary ciliary dyskinesia) is a causally heterogeneous, autosomal recessive disorder characterized by complete or partial deficiency of ciliary motility owing to structural and functional abnormalities of the protein dynein. In addition to chronic cough, rhinitis and sinusitis, male infertility because of sperm immotility and variable impairment of female infertility characterize the disorder. Situs inversus is present in 50% of patients with the immotile cilia syndrome, while situs solitus is present in the other 50%.

Congenital heart disease occurs in only 3% to 5% of patients with situs inversus, with atrioventricular discordance and transposition of the great vessels the most common abnormalities. Cardiac rhythm disturbances are likewise infrequent. With situs inversus, the single right-sided spleen is functional, and immune dysfunction is not expected. Finally, although the abdominal viscera are reversed in position, with the appendix in the left lower quadrant, malrotation with risk of volvulus is not commonly associated with situs inversus.

When individuals have an apparent combination of situs solitus and situs inversus, with some organs reversed or duplicated, the condition is called *situs ambiguous* or heterotaxy. In contrast to situs inversus, major malformations of one or more of the asymmetric organs commonly occur with this disorderly arrangement. Defects of the heart and great vessels, anomalies of the liver and biliary tract, and malrotation of the bowel are particularly common. In addition, extracardiac midline defects occur in nearly 40% of patients with heterotaxy. Although all mendelian modes of inheritance have been seen with situs ambiguous, the occurrence is usually sporadic. Chromosome abnormalities including 22q11 deletions and teratogens, such as maternal diabetes and retinoic acid, have also been associated with heterotaxy.

The spleen is almost always affected in situs ambiguous, and may be right-sided, absent (asplenia, bilateral right-sidedness, or dextroisomerism), or composed of multiple splenuli (polysplenia, bilateral left-sidedness, or levoisomerism). The term "polyasplenia" has also been used to describe the heterotaxy syndromes. Asplenia has a male predominance, and occurs more frequently than polysplenia (53% versus 42% of patients with heterotaxy). Cardiovascular malformations are frequent with both asplenia (99%) and polysplenia (90%), but are usually conotruncal and more severe with asplenia. The most consistent finding seen with polysplenia is interruption of the inferior vena cava with azygous or hemiazygous continuation. Bilateral left-sidedness (polysplenia) is associated with absence of the normal sinus node (a right-sided structure) and abnormalities of the conduction tissue, with complete heart block found in approximately 20% of these patients. In addition, extrahepatic biliary atresia is uniquely associated with polysplenia.

Impaired immune function is a potential complication of the heterotaxy syndromes. In the spleen, as blood flows past a large bed of macrophages, particulate or soluble antigens are

filtered. In addition, the presence of large numbers of both T and B lymphocytes facilitates initiation and amplification of an antigen-induced immune response. With defective or absent splenic function, morphologic abnormalities of the blood, Howell-Jolly bodies, and siderocytes are present on the peripheral blood smear. With congenital asplenia, severe bacterial infections, particularly with encapsulated organisms, are frequent and antibiotic prophylaxis is recommended. Splenic functions are generally thought to be normal in the presence of polysplenia.

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References:

Aylsworth AS. Clinical aspects of defects in the determination of laterality. *Am J Med Genet*. 2001;101:345-355

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American Board of Pediatrics Content Specification(s):

Realize the association of major congenital anomalies involving the GI tract with those involving other organs

Understand the role of the spleen in normal and abnormal states

PREVIOUS NEXT

October: Question 4

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11 November 07

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A late preterm infant dies after a course of severe respiratory distress, leading you to suspect surfactant protein B deficiency. You learn about an RNA abnormality that is detectable using molecular biological methods, and request a postmortem examination to include a search for this abnormality.

Of the following, the BEST method to detect a specific strand of RNA is:

1	far-western blotting
2	northern blotting
3	Southern blotting
4	southwestern blotting
5	western blotting

You selected 2, the correct answer is 2.

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The testing method used to detect RNA abnormality is northern blotting. To maintain a historical perspective on these techniques, they are described in order of their discovery.

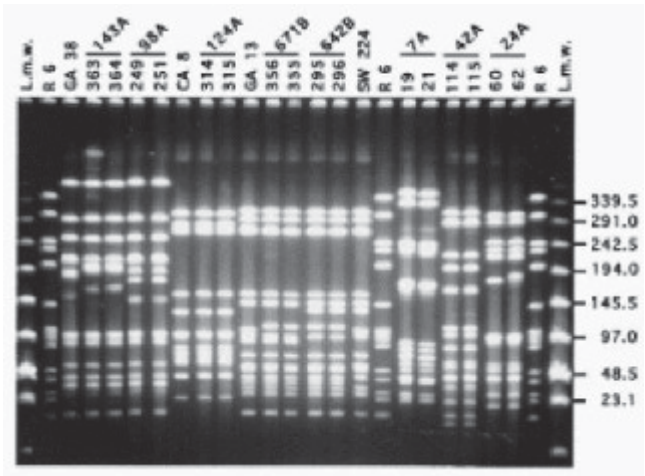
Southern blotting (named for Edwin Southern, so it remains capitalized) detects specific DNA sequences, northern blotting detects specific RNA sequences, western blotting detects specific proteins, southwestern blotting detects specific protein-DNA interactions, and far-western blotting detects specific protein-protein interactions.

Southern blotting, to look for a specific DNA sequence, starts with an aliquot of DNA. The aliquot could be the entire DNA extracted from a tissue sample, or only certain portions of the genome of the tissue. In the past DNA cloning to amplify specific portions was performed using restriction endonucleases, inserting the DNA portion under study into a bacterial plasmid, batch producing bacteria with the special plasmid, and then extracting the plasmid and its special DNA from the batch of bacteria. DNA cloning has been supplanted by polymerase chain reaction as the method of choice to amplify a specific sequence of DNA.

Once the DNA aliquot is in hand, it is treated with restriction endonucleases to produce restriction fragments of the whole DNA. Variations in each individual's DNA haplotype produce these restriction fragments in various lengths and patterns, and termed *restriction fragment length polymorphisms*. These patterns can be made evident by spreading out the DNA fragments using gel electrophoresis; the smaller fragments migrate faster down the gel. Each individual's haplotype will produce a specific pattern of DNA fragments down the gel (Figure 1).

Figure 1: Molecular typing of *Streptococcus pneumoniae* isolates (from Samore and colleagues

[2006])

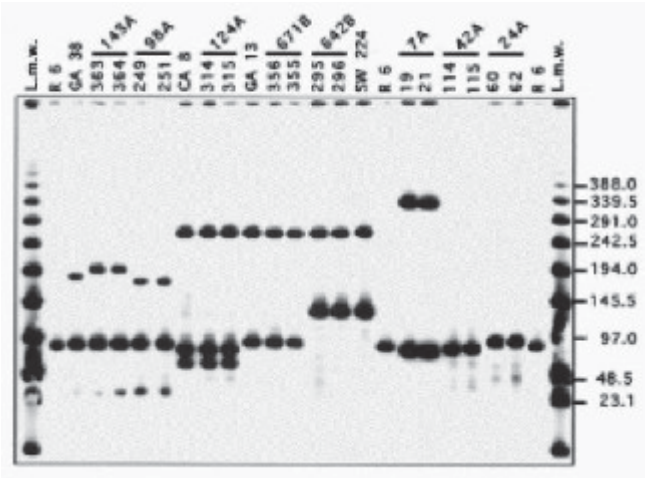


A set of fragments of known lengths is run on the gel at the same time to give a calibration standard.

Because the gel is unstable and the DNA can disperse as soon as the electric field is turned off, the DNA is transferred, or "blotted," onto another medium, usually a sheet of nitrocellulose or polyvinylidene fluoride, where the DNA binds and does not wash off.

The blot with the immobilized DNA is then exposed to a probe solution that includes a known DNA sequence, complementary to the DNA sequence that is sought from the tissue sample. This probe DNA is labeled with a radioactive tracer or a chemiluminescent tag. The probe binds to the specific DNA on the blot, and the bound complex reveals itself on an autoradiograph or optical scanner (Figure 2).

Figure 2: Southern blot hybridization with a specific DNA probe and as revealed on an autoradiograph or optical scanner (from Samore and colleagues [2006])

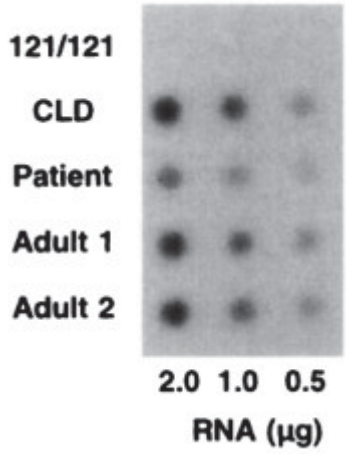


The advantage of this process of electrophoresis, blotting, and probing is that it allows the detection of a miniscule portion of DNA out of the vast 3 billion base-pairs of each human's genome.

The northern blot was developed, not by a "Dr Northern," but by James Alwine and George Stark. RNA is extracted from the sample tissue and subjected to gel electrophoresis, then blotted onto a substrate membrane. The probe can be made of RNA, but because of the difficulties and fastidiousness involved with the handling of RNA, the probe is more often made with complementary DNA. The advantage of this technique over Southern blotting includes the ability to distinguish those parts of the genome that are being expressed from those that are silent, as in tumor-marker analysis. In addition, new mechanisms are coming to light involving

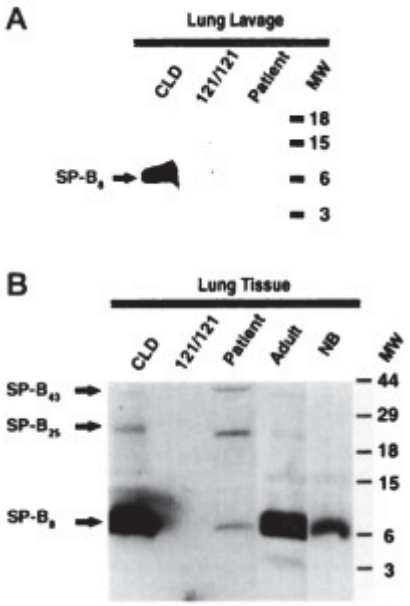
RNA and gene regulation, such as micro (inhibitory) RNA and guide (editing) RNA. Figure 3 shows a variation on northern blotting called dot-blotting, in which the tissue is touched to the substrate membrane directly, without prior gel electrophoresis.

Figure 3: Dot-blot hybridization analysis for SB-P mRNA (from Ballard and colleagues [1995])



Western blotting, also developed by George Stark at Stanford University, is used to detect specific proteins. Samples are extracted from tissues and the denatured proteins are subjected to gel electrophoresis, sorting again by the size of each molecule. The spread-out proteins are blotted onto a stable substrate membrane. Primary antibodies against specific proteins are the probes used to find the specific proteins of interest. The protein-antibody complex is detected using tagged secondary antibodies against the primary antibodies. Clinically, western blotting is useful in diagnosing human immunodeficiency virus infection, Lyme disease, and bovine spongiform encephalopathy. Figure 4 shows a research example of western blotting.

Figure 4: SB-P by Western analysis (from Ballard and colleagues [1995])



Southwestern blotting is similar to western blotting, but the proteins under examination are extracted from the nucleus, and the probe used is made of specific DNA sequences. This tool is valuable in the study of histones and other proteins in the nucleus, but does not have a direct clinical use yet.

Far-western blotting (from Princeton University) is similar to western blotting, except for the use of a nonantibody protein for the probe. Specific protein-protein interactions can be studied, but

again there is no direct clinical use yet.

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References:

Ballard PL, Nogee LM, Beers MF, et al. Partial deficiency of surfactant protein B in an infant with chronic lung disease. *Pediatrics.* 1995;96:1046-1052

Samore MH, Magill MK, Alder SC, et al. High rates of antibiotic resistance in *Streptococcus pneumoniae* from healthy children living in isolated rural communities: association with cephalosporin use and intrafamilial transmission. *Pediatrics.* 2006;108:856-865

Schwartz S. Genetic aspects of perinatal disease and prenatal diagnosis. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:113-140

Soslau G. Recombinant DNA and biotechnology. In: Devlin TM, ed. *Textbook of Biochemistry with Clinical Correlations.* 6th ed. Hoboken, NJ: Wiley-Liss; 2006:246-289

Taeusch HW. Impact of the human genome project on neonatal care. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine, Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:171-185

American Board of Pediatrics Content Specification(s):

Understand concept of DNA and mRNA sequence encoding amino acid structure of proteins

Understand the function and research utility of restriction endonucleases

Understand concept of DNA cloning

Understand the concept and utility of RNA-DNA, RNA-RNA and DNA-DNA hybridization

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November: Question 9

An elderly primiparous woman with no prenatal care has a vaginal delivery of a child with an intact omphalocele. The child appears to be full term. She is grunting, retracting, and cyanotic. No breath sounds can be heard over the right side of the chest, but you hear gurgling sounds. You secure the airway with an endotracheal tube and provide positive pressure ventilation to good effect. A chest radiograph confirms the diaphragmatic hernia. You suspect the child has pentalogy of Cantrell.

Of the following, the finding MOST consistent with the pentalogy of Cantrell is:

1	absence of manubrium
2	coarctation of aorta
3	dysplasia of kidneys
4	exstrophy of bladder
5	open foramen of Bochdalek

You selected 2, the correct answer is 2.

The pentalogy of Cantrell comprises omphalocele, a defect of the lower sternum, a defect in the pericardium, a defect in the anterior diaphragm, and a cardiac defect. A wide variety of cardiac defects have been associated with the pentalogy, and coarctation of aorta is one of those defects. Absence of manubrium, the upper part of the sternum, is not characteristic of the pentalogy. Dysplasia of kidneys is not associated with the pentalogy, but may be associated with other causes of omphalocele. Exstrophy of the bladder can also be associated with omphalocele, but not with the pentalogy. Diaphragmatic hernia associated with the pentalogy involves the anterior foramen of Morgagni, not the posterolateral foramen of Bochdalek.

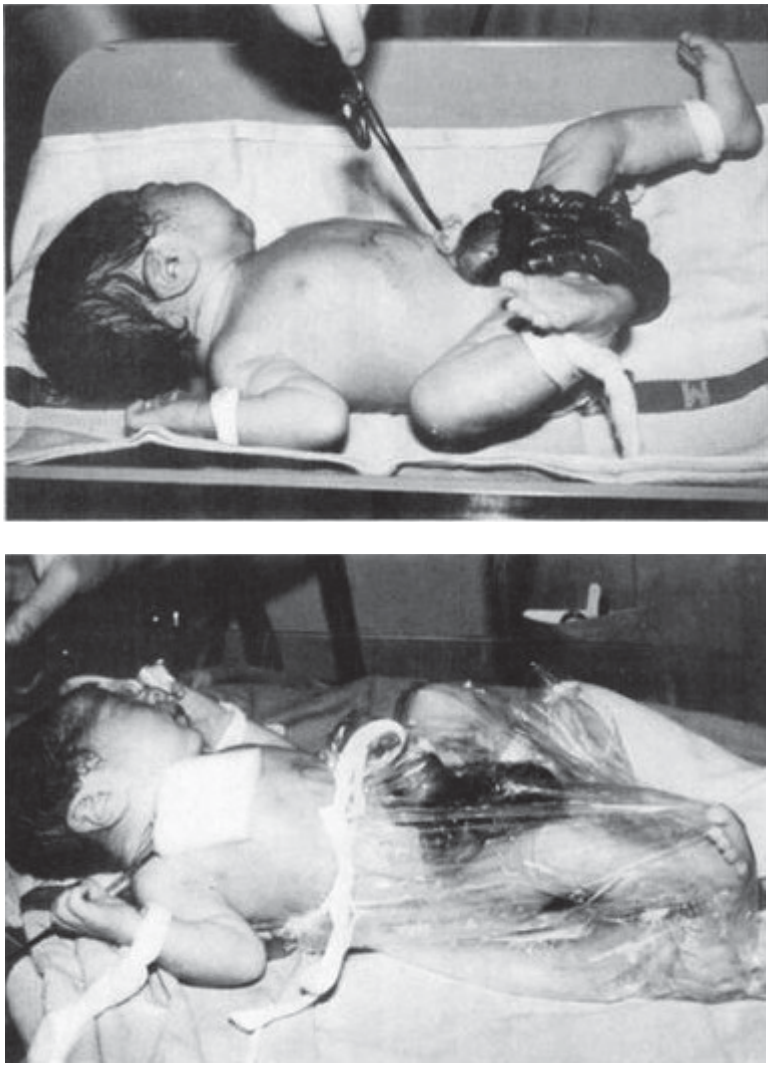
Omphalocele, also known as exomphalos, occurs in 1.5 to 3 cases per 10,000 births. It is associated with advanced maternal age; trisomy of chromosomes 13, 14, 15, 18, and 21 (30% of cases); Beckwith-Wiedemann syndrome (10% of cases); and VACTERL (abnormalities of *v*ertebrae, *a*nus, *c*ardiovascular tree, *t*rachea, *e*sophagus, *r*enal system, and *l*imb buds) syndrome. Associated anomalies are seen in up to 70% of cases, with cardiac defects in up to 50% of cases. The size of the abdominal defect does not correlate with the existence of other anomalies. The overall mortality rate of omphalocele is 80% with heart disease, and it is 10% to 30% without heart disease.

Omphalocele results from the failure of closure of the lateral body folds starting in the fourth week of development. The intestines migrate into the yolk sack in the sixth week and try to return to the abdomen in the 10th week. However, if the lateral body folds have failed to form a

complete abdomen, there is no space for the abdominal return. The intestines then develop with a covering of amnion.

Treatment at birth includes prevention of damage to the membrane from mechanical manipulation or drying (Figure 1).

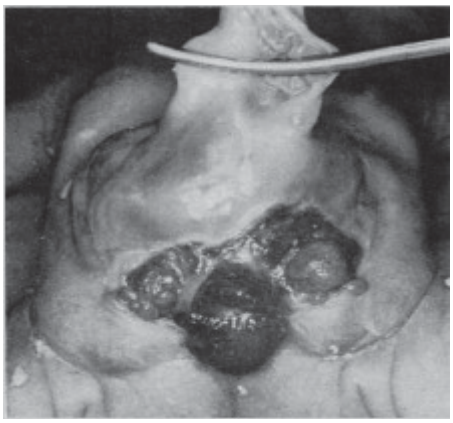
Figure 1: Top, patient at 30 minutes of age. Bottom, bowel bag in use. (From Sheldon [1974].)



If the membrane remains intact through pregnancy and delivery, it can be allowed to slowly epithelialize over the next few weeks to months. With the presence of some lateral abdominal wall, a staged surgical closure can be performed.

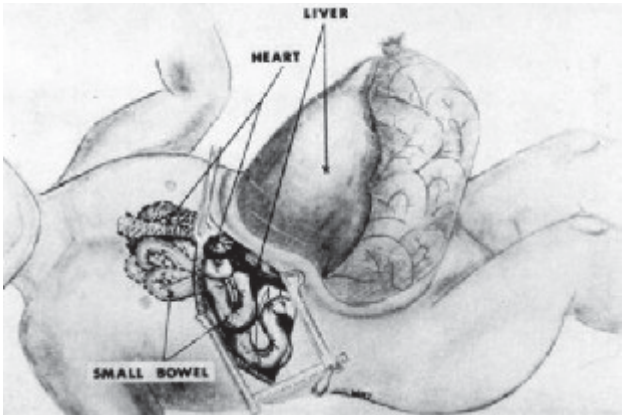
Most often the failure of lateral body fold development centers on the umbilicus in the midabdomen, but the failure can sometimes occur above or below the midabdomen. Failure of lower abdominal closure can associate an omphalocele with bladder exstrophy, cloacal exstrophy, and epispadias (Figure 2).

Figure 2: Intact omphalocele associated with an exstrophy of the cloaca. (From Wesselhoeft and Randolf [1969].)



Failure of upper-abdominal closure results in the pentalogy of Cantrell (Figure 3).

Figure 3: Illustration of surgical findings. Small bowel has herniated through pericardial-diaphragmatic defect into the pericardial cavity (From Toyama [1972].)



All the structures that meet in the upper midabdomen can be affected by incomplete development: the abdominal wall, the pericardium, the lower part of the sternum, the anterior diaphragm, and the heart. Various cardiac defects can be seen, including atrial septal defect, ventricular septal defect, double superior vena cava, tricuspid atresia, coarctation of aorta, tetralogy of Fallot, transposition of the great arteries, and ectopia cordis.

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References:

Berseth CL, Poenaru D. Abdominal wall problems. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1113-1122

Ledbetter DJ. Gastroschisis and omphalocele. *Surg Clin North Am.* 2006;86:249-260

Magnuson DK, Parry RL, Chwals WJ. Selected abdominal gastrointestinal znomalies. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal Perinatal Medicine, Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1381-1403

Sheldon RE. The bowel bag: a sterile, transportable method for warming infants with skin defects. *Pediatrics.* 1974; 53:267-269

Toyama WM. Combined congenital defects of the anterior abdominal wall, sternum, diaphragm, pericardium, and heart; a case report and review of the syndrome. *Pediatrics.* 1972;50:778-792

Wesselhoeft CW, Randolf JG. Treatment of omphalocele based on individual characteristics of the defect. *Pediatrics.* 1969;44:101-108

American Board of Pediatrics Content Specification(s):

Understand the embryology and associated anomalies with omphalocele

Understand the clinical manifestations and the differential diagnosis of omphalocele in neonates

Understand the approach to therapy and complications of omphalocele in neonates

Realize the association of major congenital anomalies involving the GI tract with those involving other organs

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November: Question 6

A pediatrician asks you to examine an infant with dysmorphic features. Prominent features you note in his examination include a beaked nose, broadened thumbs and great toes, maxillary hypoplasia, and cryptorchidism, leading to a diagnosis of Rubinstein-Taybi syndrome. You are asked to counsel the family regarding this condition and the child's future course.

Of the following, the feature MOST consistent with Rubinstein-Taybi syndrome in later life is:

1	antisocial behavior
2	death in early childhood
3	hearing impairment
4	joint contractures
5	mental retardation

You selected 5, the correct answer is 5.

Rubinstein-Taybi syndrome (RTS) was first described in 1963 and has an incidence of 1 in 100,000 to 125,000 births. The Table describes the common clinical manifestations of children with RTS.

Table. Major Clinical Features in Rubinstein-Taybi Syndrome*	
Feature	**Percentage**
Extremities	
Broad great toes	**100%**
Broad thumbs with radial angulation	**87%**
Other broad fingers	**87%**
Developmental Issues	
Speech difficulties	**90%**
Intelligence quotient < 50	**52%**
Facial	
Hypoplastic maxilla with narrow palate	**100%**
Beaked nose with or without nasal septum extending below the alae nasi	**90%**
Down-slanting palpebral fissures	**88%**
Long eyelashes	**87%**
Malpositioned ears with dysplastic helices	**84%**
Heavy eyebrows	**76%**
High-arched eyebrows	**73%**
Other	
Neonatal feeding difficulties	**80%**
Cyrptorchidism	**78% of males**
Hirsutism	**75%**
Postnatal growth deficiency with osseus immaturity	**74%**

*** From Hennekam RC. Rubinstein-Taybi syndrome. *Eur J Hum Genet*. 2006:14:981-985, and Jones KL. *Smith's Recognizable Patterns of Human Malformation*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2006:88-91**

In the neonatal period, the features most typical of RTS are broad great toes (100%), broad thumbs with radial angulation (87%), and other broad fingers (87%).
Infants with RTS also have distinctive facial features, including:

- **Beaked nose with or without nasal septum extending below the alae nasi (90%)**
- **Downward slanting palpebral fissures (88%)**
- **High-arched eyebrows (73%)**
- **Hypoplastic maxilla with narrow palate (100%)**
- **Long eyelashes (87%)**
- **Malpositioned ears with dysplastic helices (84%)**

Although infants may have heavy eyebrows (76%), this feature is usually apparent after the neonatal period and it is not associated with synophris, which is a common clinical manifestation in infants with Cornelia de Lange syndrome. Cryptorchidism occurs in approximately 78% of male infants with RTS. Other physical findings may include the following: eye anomalies (nasolacrimal duct obstruction, ptosis, glaucoma, strabismus, and refractive error), congenital heart defects (patent ductus arteriosus and ventricular or atrial septal defect), joint hypermobility, and skin anomalies (hirsutism, nevus flammeus, and keloid formation). Most infants with RTS have developmental delay in reaching common milestones, including: crawling, 15 months; sitting up, 11 months; walking, 30 months; speaking first word, 25 months; and being toilet trained, 62 months. While most children with RTS can read at 6 years of age or older, most are unable to progress passed a first-grade level. Children with RTS have an intelligence quotient (IQ) in the range of 30 to 79, with half of all affected patients having an IQ less than 50. Despite this cognitive delay, children display excellent social skills. Hearing impairment has not been a consistent feature in RTS. Death during childhood is unusual, and most commonly is related to congenital heart disease.

Respiratory infections (51%) and feeding difficulties (80%) are frequent problems in infancy, and cardiac symptoms may affect one-third of the infants. In later childhood, children with RTS

demonstrate speech difficulties (90%) and a stiff, unsteady gait (85%), prompting speech and physical therapy. Postnatal growth deficiency is common, with adults having an average height of 147 to 153 cm and an average weight of 48 to 55 kg. This is associated with osseus immaturity (74%). Children with RTS may be at higher risk for tumors, mainly brain tumors and leukemia, usually before 15 years of age.

Rubinstein-Taybi syndrome is generally sporadic and the diagnosis can be confirmed with cytogenetic and molecular testing in half of all cases. Some patients may have a submicroscopic deletion involving chromosome band 16p13.3. This site corresponds to the genomic region encoding cyclic adenosine monophosphate response element binding protein (CREB). Other infants may have 1 of 92 possible mutations in the CREB-binding protein (CBP). Mutations in p300, a homolog of CBP, have also been found in patients with RTS.

Parents of a child with RTS should be counseled that there is an empirical recurrence risk of 0.1%. If a person with RTS has a child, the recurrence risk could be as high as 50%. In either situation, reliable prenatal diagnosis is possible if a cytogenetic or molecular abnormality has been detected. Families should be counseled about specific resources, including a support group available at http://www.rubinstein-taybi.org.

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References:

Hennekam RCM. Rubinstein-Taybi syndrome. *Eur J Hum Genet.* 2006;14:981-985

Jones KL. Rubinstein-Taybi syndrome. In: *Smith's Recognizable Patterns of Human Malformation*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2006:88-91

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Wiley S, Swayne S, Rubinstein JH, Lanphear NE, Stevens CA. Rubinstein-Taybi syndrome medical guidelines. *Am J Med Genet.* 2003;119A:101-110

American Board of Pediatrics Content Specification(s):

Recognize the clinical features of syndromes, such as Waardenburg, Treacher Collins, Cornelia de Lange, Mobius, Vater, Rubenstein-Taybi, Beckwith, etc

Recognize the clinical features of the Rubenstein-Taybi syndrome

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December: Question 5

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Teratogens are environmental insults to the fetus occurring after fertilization. In the 1950s, thalidomide was briefly marketed as a sedative and was widely prescribed to pregnant women. During the following years, the incidence of ear deficiencies and limb reduction anomalies, including phocomelia and radial aplasia, increased sharply. Prenatal exposure to thalidomide was linked to these defects, and drug distribution was halted. However, more than 4,000 infants are known to have been affected.

Of the following, the error in morphogenesis resulting in thalidomide-associated phocomelia is BEST categorized as a:

1	deformation
2	disruption
3	dysplasia
4	malformation
5	sequence

You selected 5, the correct answer is 4.

Major congenital anomalies are present in 2% to 3% of live born infants, and up to 15% of infants exhibit minor anomalies or anatomic variants. The term *congenital* refers to the presence of the defect at birth, and does not imply causality. Defects imposing medical and social consequences for the infant, such as cleft palate and neural tube defects, are considered major anomalies, while minor anomalies are structural alterations, such as epicanthal folds and a single palmar crease, that pose no significant health or social burden. Physical differences occurring in 4% or more individuals of a general population are considered normal phenotypic variants.

Inborn errors of morphogenesis can be classified based on the developmental stage during which the alteration occurs, the process causing the change, and the end result. The four categories of morphogenic errors are malformation, deformation, disruption and dysplasia.

Malformations arise from abnormal processes during the initial formation of a structure. This aberrant tissue formation may result in faulty configuration (transposition of the great vessels), incomplete formation (cleft palate) or agenesis (absence of radius). Malformations may be the result of genetic derangements, including chromosome abnormalities (10%) and single gene defects (4%). However, environmental insults, teratogens, may also influence early structural formation. Examples of teratogens include pharmacologic agents, such as thalidomide (as in the vignette), and congenitally acquired viruses, such as rubella. Commonly,

the cause of a malformation is multifactorial, both genetic and environmental (25%), but most often the cause is unknown (40%-45%).

Deformations originate after organogenesis, and arise from unusual and prolonged mechanical forces acting on normal tissue. Although external forces, such as uterine constraint, are usually the cause of deformational anomalies, intrinsic compressive forces, such as edema, may be implicated in some cases. Musculoskeletal tissues are commonly affected, and the result may be a loss of symmetry, altered alignment, abnormal positioning, or distorted configuration. Examples of deformations include tibial bowing and hip dislocation associated with breech presentation, craniostenosis resulting from in utero constraint, and webbing of the neck associated with the involution of a giant cystic hygroma. Deformations typically improve postnatally, but resolution depends on the duration of the abnormal forces, and the extent of subsequent growth.

Disruptions result from the breakdown of normal tissue after formation. The destructive processes include mechanical compressive forces, hemorrhage, thrombosis, and other vascular impairments. Disruptions may manifest as alterations of shape and configuration, division of parts not usually divided, fusion of parts not usually fused, and the loss of previously present parts. Examples of disruptions include a porencephalic cyst secondary to a vascular accident, and limb amputations caused by amniotic bands.

Dysplasia arises from abnormal cellular organization or function, and typically affects a single tissue type. Examples of morphogenic errors resulting from dysplasia include hamartomas, ectodermal dysplasia, and the cartilage abnormalities that result in skeletal dysplasias.

Multiple malformations are present in 0.7% of live births, and a malformation sequence occurs when all of the anomalies can be explained on the basis of a single problem. The oligohydramnios sequence is an example in which musculoskeletal deformations and lung hypoplasia result from the primary problem of amniotic fluid deficiency. The Pierre Robin sequence is another example of a primary defect with secondary effects, in which mandibular maldevelopment leads to micrognathia, cleft palate, and glossoptosis.

Finally, a malformation syndrome occurs in the presence of multiple structural defects that are not explained on the basis of a single initiating defect. However, the pattern of anomalies comprising a syndrome shares a cause, and may result from chromosomal abnormalities, mutant gene disorders, or environmental teratogens.

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References:

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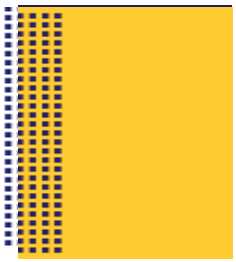
Stevenson RE, Hall JG. Terminology. In: Stevenson RE, Hall JG, Goodman RM, eds. *Human Malformations and Related Anomalies*. New York, NY: Oxford University Press; 1993:21-30

American Board of Pediatrics Content Specification(s):

Differentiate between a malformation, a deformation, and a disruption



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January: Question 9

A 41-week-gestation boy is born to a healthy 28-year-old mother via cesarean section because of breech presentation. His birthweight is 2,850 g (15th to 25th percentile), length 50 cm (50th to 75th percentile), and head circumference 36 cm (>90th percentile). The pregnancy was uncomplicated, with normal amniotic fluid volume noted on ultrasonography. On physical examination he has hypotonia, areas of hypopigmentation, silvery hair, and bilateral cryptorchidism. In addition, he has poor eye movement, depressed facial expression, bilateral mild ptosis, and a high arched palate.

Of the following, the genetic mechanism underlying this child's condition MOST likely results from:

1	aneuploidy
2	chromosomal mosaicism
3	expansion of trinucleotide repeats
4	new mutation
5	uniparental disomy

You selected 5, the correct answer is 5.

The infant described in this vignette has findings consistent with Prader-Willi syndrome (PWS; Table).

Table

Table. Diagnostic Criteria for Prader-Willi Syndrome*

Diagnostic Criteria	% Affected
Major	
Neonatal hypotonia	88
Feeding problems in infancy	79
Characteristic facial features	88
Hypogonadism	51
Minor	
Decreased fetal activity	62
Hypopigmentation	73
Eye abnormalities	68

***Adapted from Holm and colleagues (1993).**

PWS is attributed to genomic imprinting, that is, the expression of the gene depends on the sex of the parent donating the gene. PWS arises when the paternal copy of 15Q11.2-13 is deleted

(70% of cases). Maternal uniparental disomy of the 15 chromosome, resulting from nondysjunction (28% of cases), will also result in PWS. Rare cases involve mutations of the imprinting center. Loss of the maternal copy of 15q11.2-13 results in Angelman syndrome.

Aneuploidy refers to a change in the number of chromosomes; it is the most frequently observed type of cytogenetic abnormality. The two most commonly observed forms of aneuploidy are monosomy and trisomy. Monosomy is the lack of one of a pair of chromosomes, as seen in Turner syndrome. Trisomy is defined as having three chromosomes of a particular type, as seen in Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13).

Chromosomal mosaicism refers to a condition in which an individual has two or more cell populations that differ in the genetic makeup. This situation can affect any type of cell, including blood cells, gametes, and skin. This may lead to a phenotypically normal parent transmitting a mutation to offspring who may express the mutation.

Some regions in the genome have a repeated sequence of DNA, usually of three bases, that can expand from 20 to 30 repeats to more than 100 or even 1,000 repeats. The mechanism leading to an increase in number of repeats is not clear, nor is it clear how the increase leads to disease. Myotonic dystrophy, Huntington disease, and fragile X syndrome are disorders caused by expansion of triplicate repeat sequences.

New mutations may result in different inheritance patterns. Achondroplasia is an example of an autosomal dominant disease in which more than 80% of cases are caused by new mutations. Despite dominant inheritance, a patient with achondroplasia may not have a family history of the disorder and the recurrence risk for siblings is low, but may transmit the disease to future offspring.

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References:

Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The Changing purpose of Prader-Willi syndrome: clinical diagnostic criteria and proposed revised criteria. *Pediatrics.* 2001;108:e92

Holm VA, Cassidy SB, Butler MG, et al. Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics.* 1993;91:398-402

Preece MA, Moore GE. Genomic imprinting, uniparental disomy and foetal growth. *Trends Endocrinol Metab.* 2000;11:270

Lodish H, Scott MP, Matsudaira P, et al. *Molecular Cell Biology*. 5th ed. New York, NY: WH Freeman and Co; 2003.

Scheimann A. Prader-Willi Syndrome. emedicine.com Web site. Accessed July 26, 2007, at www.emedicine.com/ped/topic1880.htm

American Board of Pediatrics Content Specification(s):

Understand how mosaicism modifies clinical presentation

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

Know fetal and placental manifestations of triploidy

Understand the etiology, molecular phenotype, and clinical manifestations of disorders associated with genetic imprinting, such as Prader-Willi syndrome

Recognize the DNA findings, clinical manifestations, and inheritance of expanding genes, such as myotonic dystrophy

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February: Question 7

A term infant presents with low birthweight and microcephaly. Physical examination reveals short palpebral fissures, maxillary hypoplasia, short nose, and a smooth philtrum with a thin upper lip.

Of the following, the risk of a major anomaly in the presence of three or more minor anomalies is CLOSEST to:

1	1%
2	5%
3	10%
4	15%
5	20%

You selected 5, the correct answer is 5.

The infant in the vignette exhibits a pattern of morphologic features consistent with a diagnosis of fetal alcohol syndrome. While major congenital anomalies are recognized in 2% to 3% of liveborn infants, up to 20% of infants exhibit minor anomalies or anatomic variants. The term *congenital* refers to the presence of the defect at birth, and does not imply causality. Defects imposing medical and social consequences for the infant, such as cleft palate and neural tube defects, are considered major anomalies, while structural alterations, such as epicanthal folds and a single palmar crease, that pose no significant health or social burden, are minor anomalies. However, the prevalence of a given feature can vary, based on race, ethnicity, and gender, blurring the distinction between a minor anomaly and a normal phenotypic variant. For example, while uncommon in the Caucasian population, natal teeth are considered a normal variant in the Native American population. As a result, physical differences occurring in 4% or more of a general population are considered normal phenotypic variants. In addition, minor anomalies may be familial, such as isolated ear tags and pits, which may exhibit an autosomal dominant pattern of inheritance. Therefore, family history should also be considered before assigning significance to the presence of a minor malformation.

Major anomalies, such as cleft lip, are easily identified; however, minor anomalies may be subtle and overlooked. Most minor anomalies (70%) affect the face or hands, which are areas of the body with great complexity and variability. Minor anomalies occur with increased frequency in infants born prematurely or with intrauterine growth restriction. Recognizing physical features as minor anomalies is important for the following reasons.

- **Minor anomalies may be markers for occult major malformations, such as sacral hair tufts associated with spinal dysraphism.**
- **Specific patterns of minor anomalies often define genetic syndromes, as with the typical constellation of features involving the face, hands, and feet of individuals with Down syndrome. However, in isolation, these same features carry less significance. For example, 45% of individuals with Down syndrome have single palmar creases, but this feature is found**

unilaterally in 4% and bilaterally in 1% of the general Caucasian population.

- Minor anomalies give consistent clues to the diagnosis of many multianomaly syndromes. For example, fetal alcohol syndrome is suggested by a pattern of minor morphologic features, including short palpebral fissures, maxillary hypoplasia, smooth philtrum with thin and smooth upper lip, altered palmar crease patterns, and small fifth fingernails.
- Finally, the risk of a major anomaly increases as the number of identified minor anomalies increases (Table). In fact, in the presence of three or more minor anomalies, the risk of a major anomaly reaches 20%. Therefore, the identification of multiple minor anomalies should prompt a search for coexistent major malformations.

Table

No. of Minor Anomalies	% of Newborns	Risk for Major Anomaly, %
0	79-84	1
1	15-20	3
2	0.8	10
≥3	0.5	20

References:

Adam M, Hudgins L. The importance of minor anomalies in the evaluation of the newborn. *NeoReviews*. 2003;4:e99-e104

Jones KL. Minor anomalies: clues to more serious problems and to the recognition of malformation syndromes. In: *Smith's Recognizable Patterns of Human Malformation*. 6th ed. Philadelphia, Pa: WB Saunders; 2006:817-834

Stevenson RE, Hall JG. Terminology. In: Stevenson RE, Hall JG, Goodman RM, eds. *Human Malformations and Related Anomalies*. New York, NY: Oxford University Press; 1993:21-30

American Board of Pediatrics Content Specification(s):

Know the frequencies of minor congenital anomalies

Know the frequencies of major congenital anomalies

PREVIOUS NEXT

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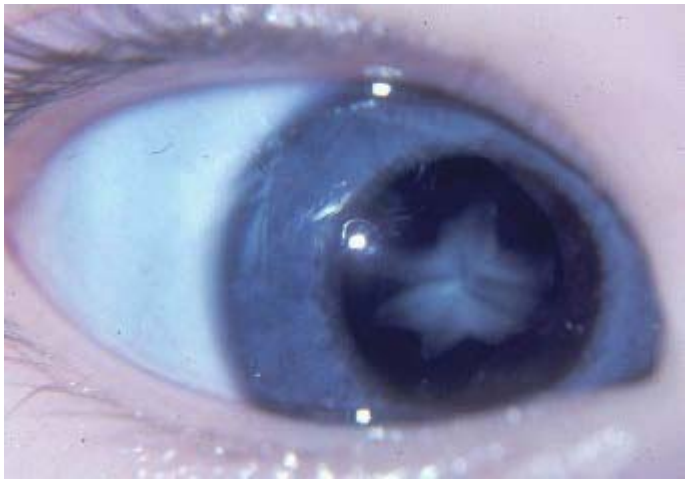
11 November 08

12 December 08

May: Question 9

A male infant is examined at 10 days of age. He was born at 35 weeks' gestation after a pregnancy complicated by mild maternal preeclampsia. His birthweight was 2,300 g, and his length and head circumference also were appropriate for his gestational age. He stayed extra days in the hospital because of mild jaundice, treated briefly with phototherapy. His mother reports that he has been breastfeeding and sleeping well. His current weight is 2,250 g. On physical examination, you are unable to elicit a red reflex bilaterally, and note marked leukocoria (Figure). The remainder of the examination findings are normal.

Figure



Of the following, the diagnosis for this infant is MOST likely to be supported by:

1	erythrocyte enzyme studies
2	history of prematurity
3	karyotype
4	ocular examination of the parents
5	serum 7-dehydrocholesterol concentration

You selected 4, the correct answer is 4.

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(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The red reflex (choroidal light reflex) detects retinal blood vessels appearing as a red glow when viewed through an ophthalmoscope. The presence of a red reflex signifies a lack of obstruction between the external corneal surface and the retina. Leukocoria (white reflex) has many causes, including coloboma, retinoblastoma, and retinal detachment, but is most commonly the result of a cataract. The infant in this vignette has bilateral leukocoria, consistent

with bilateral congenital cataracts.

By definition, a cataract is a nonspecific reaction to a change in lens metabolism leading to lens opacification. The lens, derived from surface ectoderm, grows continuously during life, laying down new lens fibers on its external surface, much like an onion. Processes that alter the glycolytic pathway or epithelial cell mitosis of the avascular lens lead to opacification. The size and shape of a cataract depends on the area of the lens under formation at the time of insult. For example, damage occurring in the early embryonic period leads to opacification in the center of the lens (nuclear cataract), and later periods of damage produce a ringlike opacification (zonular cataract). The visual significance of a cataract depends on the age at onset, location, and morphologic characteristics. Very dense opacifications cause greater visual disturbance, particularly if located in the central axis. Because of associated severe amblyopia and strabismus of the involved eye, unilateral cataracts carry a poorer prognosis for vision than bilateral complete cataracts. Treatment of dense cataracts usually involves lens extraction and subsequent intraocular lens implantation.

Estimates of the prevalence of congenital cataracts range from 1.2 to 6 per 10,000 births, and cataracts are responsible for nearly 10% of all visual loss in children worldwide. Hereditary, inflammatory, and metabolic factors cause most bilateral congenital cataracts. Unilateral cataracts are generally the result of a local ocular phenomenon, including trauma, or a developmental eye abnormality. In addition, cataracts are associated with multiple syndromes, such as Hallermann-Streiff, Pierre Robin, and Rubinstein-Taybi syndromes. However, 60% of unilateral and 40% of bilateral cataracts have no discernible cause.

In developed countries, isolated autosomal dominant (AD) cataracts are most common, and account for 25% of all congenital cataracts. AD cataracts are typically bilateral, of a variety of morphological patterns, and associated with variable expressivity and a high degree of penetrance. Several gene loci have been linked to AD cataracts. Usually there is a clear history of congenital cataracts affecting multiple generations. For all cases of isolated congenital cataracts, as in the infant in this vignette, a thorough family history and ophthalmologic examination of the parents should be done.

Congenital infections, particularly rubella, but also toxoplasmosis, varicella, herpes simplex, and other viruses, account for up to 15% of congenital cataracts. In developing countries, where rates of infection are higher and vaccinations less available, intrauterine infection is the leading cause of congenital cataracts. With congenital rubella syndrome, cataracts occur in 20% of cases, and are usually bilateral. The cataract results from invasion of the lens by the rubella virus, which may remain dormant in the lens material for several years. Microphthalmia, uveitis, and glaucoma are associated ocular findings.

Galactosemia, an inherited deficiency of enzymes for galactose metabolism, is the most common metabolic disorder causing cataracts in infancy. A defect in galactokinase, uridine diphosphate galactose-epimerase, or galactose-1-phosphate uridyltransferase, will result in the conversion of galactose to galactitol in the lens, and a consequent influx of water. This hydration of the lens disrupts the normal packing of the lens fibers, and results in a loss of transparency. Initially, the lens changes appear as a “drop of oil” in the center of the lens. Cataracts associated with galactosemia usually are bilateral, and appear during the first 2 months of age. The removal of galactose from the diet may prevent or reverse initial changes in the lens, but dietary restriction will not completely eliminate the formation of cataracts later in childhood. Classic uridyltransferase deficiency presents early in the newborn period with lethargy, poor feeding, jaundice, hepatomegaly, and in some cases, *Escherichia coli* sepsis. Galactokinase deficiency is associated with cataracts in later childhood and no other manifestations. Erythrocyte enzyme studies and assays of blood galactose are used in the diagnosis of galactosemia. Because the infant in this vignette is well and thriving, it is not likely that galactosemia is the cause of his cataracts.

Prematurity and retinopathy of prematurity have been associated with the development of cataracts. Transient lens opacities have been reported in approximately 3% of low-birthweight infants, who also experienced a high incidence of problems such as respiratory distress, apnea, acidosis, hypothermia, and poor weight gain. The cataracts are bilateral and generally

reversible. Cataracts have also been associated with retinopathy of prematurity, although occurring in only 2% of cases. At 35 weeks' gestation and without illness, it is unlikely that the infant in this vignette has cataracts as a result of prematurity.

Trisomy of chromosomes 13, 18, 21, 10q, and 20p, chromosome translocations, Turner syndrome, and deletion syndromes have all been associated with cataracts. The cataracts are usually bilateral, and occur infrequently. In fact, among infants with trisomy 21, only approximately 1% will develop lens opacification. Because the infant in the vignette has otherwise normal physical examination findings, a karyotypic abnormality is unlikely to be the cause of his cataracts.

Because the lens membrane contains the highest cholesterol content of any known membrane, defects in enzymes of cholesterol metabolism are associated with cataracts. Smith-Lemli-Opitz syndrome, an autosomal recessive deficiency of 7-dehydrocholesterol reductase, results in low cholesterol tissue concentrations, multiple craniofacial and ocular abnormalities, cryptorchidism, developmental delay, growth retardation, and occasionally cataracts. Smith-Lemli-Opitz syndrome can be diagnosed by finding elevated serum 7-dehydrocholesterol concentrations. The infant in this vignette does not exhibit the typical physical anomalies associated with Smith-Lemli-Opitz syndrome, making this an unlikely cause for his cataracts.

References:

Alden ER, Kalina RE, Hodson A. Transient cataracts in low-birth-weight infants. *J Pediatr*. 1973;82:314-318

Arkin M, Azar D, Fraioli A. Infantile cataracts. *Int Ophthalmol Clin*. 1992;32:107-120

Gupta BK, Hamming NA, Miller MT. The eye: diagnosis and evaluation. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 7th ed. St. Louis, Mo: Mosby; 2002:1568-1602

Tesser RA, Hess DB, Buckley EG. Pediatric cataracts and lens anomalies. In: Nelson LB, Olitsky SE, eds. *Harley's Pediatric Ophthalmology*. 5th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2005:255-285

American Board of Pediatrics Content Specification(s):

Recognize the signs of neonatal cataracts

Recognize the conditions associated with neonatal cataracts

PREVIOUS NEXT

January: Question 7

A 14-day-old full-term Caucasian infant who presented with meconium ileus has a positive result to the sweat chloride test for cystic fibrosis (CF). DNA testing reveals the infant to be homozygous for the ΔF508 mutation for CF.

Of the following, the ONLY protein abnormality observed with the homozygous ΔF508 mutation is:

1	abnormal folding
2	absent synthesis
3	decreased ion conductance
4	decreased stability
5	decreased synthesis

You selected 2, the correct answer is 1.

Cystic fibrosis (CF) is the most common life-shortening inherited disease in North America. It is a heterogeneous autosomal recessive disorder that presents as a multisystem disease. It is most common in individuals of northern European descent, with an incidence of approximately 1 in 3,200 live births. Patients with CF have abnormal transport of chloride and sodium across epithelial surfaces in virtually every organ system, but most importantly, in the lungs, pancreas, intestinal mucous glands, liver, reproductive tract, and sweat glands, resulting in thickened, viscous secretions that cause the blockage of ducts and air passages.

The gene for CF is on the long arm of chromosome 7 and spans 250 kb. Its product is a 1,480-amino acid protein—the ***CF transmembrane conductance regulator (CFTR)***—which functions both as a cyclic adenosine monophosphate (cAMP)–regulated chloride channel and as a regulator of other chloride and sodium channels at the cell surface.

The synthesis of the CFTR protein involves transcription of the ***CFTR*** gene into messenger RNA (mRNA), which is translated into protein in the endoplasmic reticulum. The CFTR protein is then glycosylated in the Golgi apparatus and folded into a configuration that allows it to travel through the cytoplasm to the apical surface of airway and mucus gland epithelium. In the apical membrane, normal conductance of chloride and other ions depends on the channel's ability to respond to regulatory molecules.

More than 1,000 disease-associated mutations have been described in the coding sequence, mRNA splice signals, and other regions of the ***CFTR*** gene. These mutations can be classified into six groups on the basis of the mechanism by which they cause disease. The severity of clinical disease varies with the specific genetic mutations present in a patient with CF. Class I to class III mutations are considered "severe," and are associated with pancreatic insufficiency and high sweat chloride values. Class IV mutations are "mild," that is, they are associated with pancreatic sufficiency and intermediate/normal sweat chloride

values.

- Class I—defective protein production: About 5% to 10% of ***CFTR*** defects are the result of nonsense, frameshift, or splice-site mutations, which lead to premature termination of the mRNA and complete absence of CFTR protein (eg, G542X). These mutations are particularly prevalent among persons of Ashkenazi Jewish descent.
- Class II—defective protein processing: These mutations prevent the CFTR protein from trafficking to the correct cellular location. The most common ***CFTR*** mutation, termed **Δ**F508, is categorized as a class II defect. Approximately 50% of individuals with CF who are of northern European ancestry are homozygous for **Δ**F508, and more than 70% carry at least one **Δ**F508 gene. CFTR with the **Δ**F508 mutation lacks a phenylalanine (F) residue at position 508. The defective protein is rapidly recognized as misfolded and is degraded shortly after synthesis, before it can reach its crucial site of action at the cell surface. As seen with the **Δ**F508 mutation presented in the vignette, several mutations—such as N1303K, G85E, and G91R—also lead to a misfolded CFTR protein that is prematurely degraded.
- Class III—defective regulation: These mutations lead to a properly processed, full-length CFTR protein that lacks normal ion-channel activity (eg, G551D).
- Class IV—defective conduction: With class IV mutations, the protein is produced and correctly localized to the cell surface. However, although chloride currents are generated in response to cAMP stimulation, the rate of ion flow and the duration of channel opening are reduced compared with normal CFTR function (eg, A455E mutation).
- Class V: These mutations result in reduced numbers of CFTR transcripts.
- Class VI: These mutations result in defective CFTR stability at the cell surface.

Knowledge of the ***CFTR*** gene has provided opportunities to develop treatments tailored specifically for CF. These potential treatments include ***CFTR*** gene replacement, suppression of nonsense mutations (eg, gentamicin), restoration of folding and function of mutant CFTR channels (eg, curcurmin, a nontoxic compound and the major constituent of the spice turmeric), activation of alternative chloride channels, inhibition of sodium absorption, and other ionic and osmotic manipulations to normalize fluid and bicarbonate levels on epithelial surfaces.

References:

Boat TF, Acton JD. Cystic fibrosis. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. ***Textbook of Pediatrics.*** Philadelphia, Pa: Elsevier-Saunders; 2007:1803-1817

Boucher RC. Cystic fibrosis. In: Fauci AS, Kasper DL, Longo DL, et al, eds. ***Harrison's Principles of Internal Medicine.*** New York, NY: McGraw-Hill; 2008

Orenstein DM. Cystic fibrosis. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister GE, Siegel NJ, eds. ***Rudolph's Pediatrics.*** New York, NY: McGraw-Hill; 2003

Proesmans M, Vermeulen F, De Boeck K. What's new in cystic fibrosis? from treating symptoms to correction of the basic defect [published online ahead of print April 4, 2008]. ***Eur J Pediatr***

Riordan JR. CFTR function and prospects for therapy [published online ahead of print February 27, 2008]. ***Annu Rev Biochem***

Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. ***N Engl J Med.*** 2005;352(19):1992-2001

Wieczorek G, Zielenkiewicz P. DeltaF508 mutation increases conformational flexibility of CFTR protein [published online ahead of print January 28, 2008]. ***J Cyst Fibros***

American Board of Pediatrics Content Specification(s):

Understand concept of protein folding and conformation related to function

Understand the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

Understand the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant

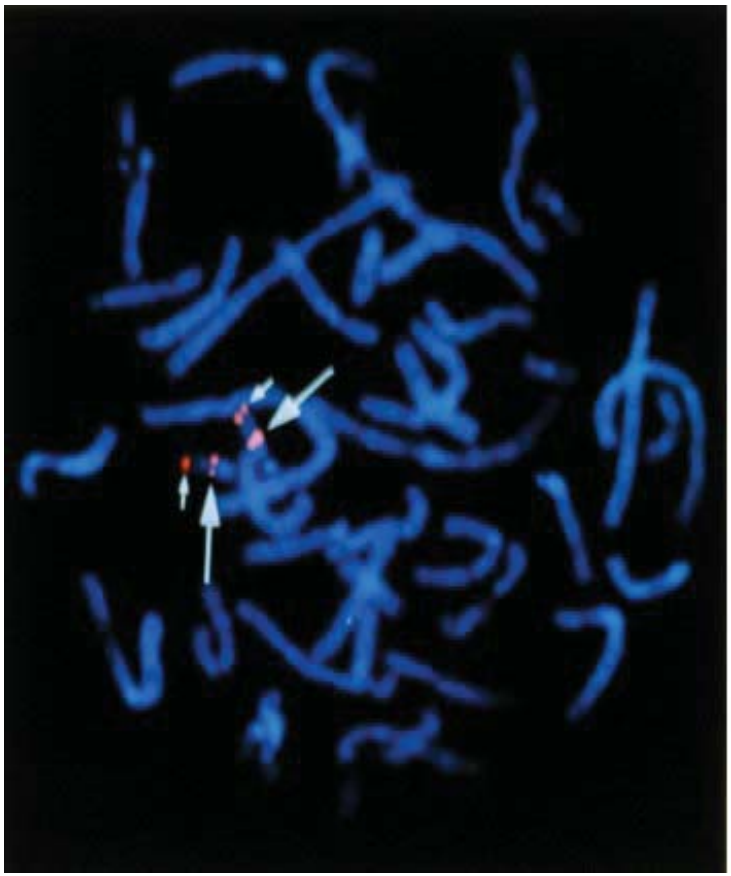
Understand the diagnosis of cystic fibrosis in newborn infants

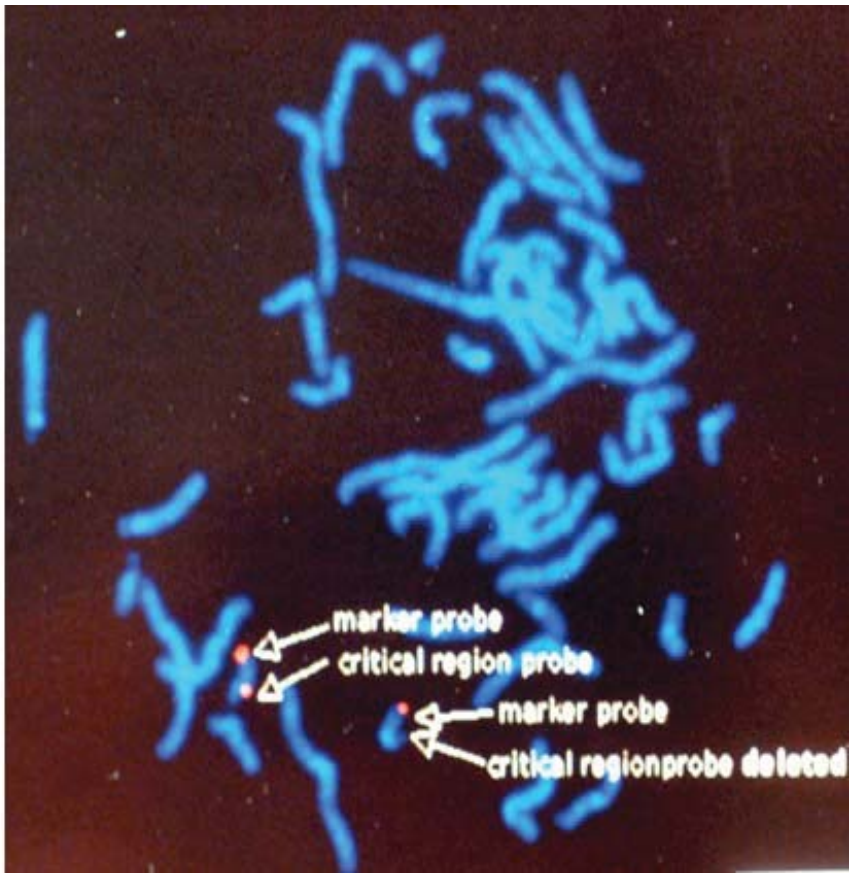
PREVIOUS NEXT

February: Question 6

A male African American newborn infant is delivered at 36 weeks' gestation by a 25-year-old primiparous woman. The pregnancy was complicated by antenatal diagnosis of interrupted aortic arch type B and truncus arteriosus. The cardiac diagnosis is confirmed on postnatal echocardiography. The patient is receiving continuous infusion of alprostadil. The infant has early neonatal hypocalcemia and is treated with calcium supplements. Immunologic testing reveals decreased CD3 T-cell numbers and decreased immunoglobulin (Ig) A and elevated IgE levels. Fluorescence in situ hybridization (FISH) for chromosome 22q11.2 is positive for hemizygous microdeletion (Figure). You are discussing the recurrence risk of the disease in family members of this patient.

Figure: Fluorescence in situ hybridization (FISH) of a patient with hemizygous deletion of chromosome 22q11.2 (right) compared with a normal inidividual (left). The FISH on the right shows that one copy of chromosome 22 has only one fluorescent signal (the marker probe) compared with the normal case which has two signals on each chromosome (control probe and the probe specific to 22q11.2) (adapted from Shprintzen [2008]).





Of the following, the MOST accurate statement regarding the genetics of the 22q11.2 deletion syndrome is that the:

1	female offspring of the patient will be carriers of the microdeletion
2	offspring of the patient will have a 50% chance of inheritance
3	patient's father is a carrier of the microdeletion
4	patient's mother is a carrier of the microdeletion
5	syndrome is not inherited and is sporadic

You selected 1, the correct answer is 2.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Hemizygous deletion of chromosome 22q11.2 is common, affecting nearly 1 in 3,000 to 1 in 7,000 children. It ranks second only to trisomy 21 among the common genetic causes of syndromic congenital heart disease. Four clinical syndromes associated with hemizygous deletion of chromosome 22q11.2 are:

- ***DiGeorge*** (cardiac anomalies, hypoparathyroidism, immunodeficiency): 35% to 90% of patients have the hemizygous deletion
- ***Velocardiofacial*** (pharyngeal dysfunction, cardiac anomaly, dysmorphic facies): 80% to 100% of patients have the hemizygous deletion
- ***CHARGE*** (***c***oloboma, ***h***eart defect, ***a***tresia choanae, ***r***etardation of growth, ***g***enitourinary problems, ***e***ar anomalies): 58% to 71% of patients are associated with mutations of ***CHD7*** gene on chromosome 8
- ***CATCH 22*** (***c***ardiac, ***a***bnormal facies, ***t***hymic hypoplasia, ***c***left palate, and ***h***ypocalcemia resulting from 22q11 deletion)

Contemporary diagnosis of the 22q11.2 deletion and related syndromes is based on a fluorescent in situ hybridization (FISH) study of chromosome 22q11 which is accurate 100% of the time.

In 90% of cases, the disorder occurs as the result of a new mutation, and in 10% the disorder is inherited from a parent in an autosomal dominant fashion. This indicates that 22q11.2 is a highly mutable region of the human genome and that the area is prone to rearrangement. Rarely, the syndrome may be caused by other chromosomal abnormalities (deletion of chromosome 10p13) or maternal environmental factors (such as alcohol, retinoids). Genetic counseling is crucial in families with an affected parent because the penetrance is 100%, recurrence risk is 50%, and offspring are often more severely affected.

Thus the correct response regarding the genetics of 22q11.2 deletion syndrome is that offspring of the patient have a 50% chance of inheritance because this is an autosomal dominant disorder. In autosomal dominant disorders, each affected patient has an affected parent, assuming that no new mutations have occurred. This is in contrast to autosomal recessive disorders in which both parents of an index patient are heterozygous carriers of the mutation. The mother of an affected male patient may be a heterozygous carrier in X-linked disorders. Carrier state in female offspring of an affected male patient is a hallmark of X-linked disorders.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Primary defects of cellular immunity. In: ***Textbook of Pediatrics.*** Philadelphia, Pa: Elsevier Saunders; 2007

Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. ***Lancet.*** 2007;370(9596):1443-1452

Shprintzen RJ. Velo-cardio-facial syndrome: 30 years of study. ***Dev Disabil Res Rev.*** 2008;14(1):3-10

Sullivan KE. The clinical, immunological, and molecular spectrum of chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. ***Curr Opin Allergy Clin Immunol.*** 2004;4(6):505-512

Tegay D. CHARGE syndrome. eMedicine.com Web site. Accessed August 21, 2008, at: **www.emedicine.com/ped/TOPIC367.htm**

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology including genetics of a cyanotic neonate

Understand the pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion

Understand the pathophysiology, including genetics, of a neonate with a mixed cardiac lesion

Recognize the karyotype and clinical manifestations associated with the common deletion syndromes

Recognize specific patterns of mendelian inheritance

Demonstrate understanding of inheritance patterns and recurrence risks for autosomal dominant disorders

Understand the indications and limitations of molecular cytogenetic studies (eg, FISH), specifically in the diagnosis of aneuploidy and microdeletion

Understand the DiGeorge anomaly

PREVIOUS NEXT

March: Question 4

You are asked to see a 4-week-old female infant admitted for projectile vomiting. Except for evidence of mild dehydration and the presence of a small perisagittal, midabdominal mass, her examination findings are normal. Family history indicates that her only maternal aunt and one of the aunt's sons had been diagnosed with pyloric stenosis. A pyloromyotomy is performed. Her family history intrigues you to study the inheritance pattern.

On review of the literature, the following characteristics of pyloric stenosis are discovered:

- The incidence is 1 to 5 per 1,000 live births in the general population
- Five males are affected for each female overall
- Recurrence risk for first-degree relatives, compared with the risk for the general population, is greater for relatives of female patients (Table)

Risk of Pyloric Stenosis in First-Degree Relatives*		
	Male Relative	Female Relative
Male proband	10-fold	25-fold
Female proband	35-fold	80-fold

* Risk in first-degree relatives of patients with pyloric stenosis compared with the general population (males, 0.005; females, 0.0001).

Of the following, the inheritance pattern MOST consistent with these observations is:

1	autosomal dominant
2	autosomal recessive
3	multifactorial
4	X-linked dominant
5	X-linked recessive

You selected 4, the correct answer is 3.

Although every condition that runs in families is not necessarily genetic, genetic factors may contribute to environmental influences that lead to familial experience with disease. Many infectious diseases affecting families are largely the result of purely environmental influences (ie, familial but not genetic), whereas some genetic conditions, such as many of the chromosomal disorders, arise spontaneously (ie, genetic but not familial). Conditions recurring in families which do not conform to mendelian inheritance patterns may result from multifactorial inheritance, involving interplay among multiple genetic and/or environmental influences. Multifactorial inheritance is often associated with conditions with a population frequency higher than 1%. The genetic component may be influenced by variable penetrance of individual genes or by interplay among two or more genes. Relevant environmental factors

may be intrauterine, or they may involve extrauterine influences such as aging, diet, or chemical exposure.

An important concept involving multifactorial inheritance involves the proximity of the relationship among family members. Risk is proportional to the number of genes in common with the affected relative. Identical twins have complete sharing of their genes; any lack of concordance among them involves environmental differences. First-degree relatives are defined as those sharing 50% of their genes, such as an individual's parents, siblings, or children. Second-degree relatives share 25% of their genes, as seen among aunts, uncles, nieces, nephews, and grandparents. Third-degree relatives, such as first cousins, share 12.5% of their genes. Because of this drop-off in shared genes, the risk of having a familial condition decreases dramatically as the degree of relationship with the affected relative increases. Contrast this with an autosomal dominant condition, in which risk is directly proportional to the degree of relationship.

A second important concept in multifactorial inheritance is that of the threshold effect. For example, closure of the palate involves genes controlling the growth rate of the head (tending to separate the palatal anlage), growth of the tongue (with potential to separate palatal shelves), and growth of the palatal arches (toward each other). If a genetic variant causes delay in palatal arch closure, whether the patient will ultimately have a cleft palate is determined by the degree to which that delay allows for palatal closure before the **"**threshold,**"** the critical stage when the rates of head or tongue growth intrude upon palatal closure. To have the defect, all three genes interact. Because closer relatives of an affected individual share more genes, they would be more likely to share the combination of genetic effects leading to the cleft than would more remote relatives.

Pyloric stenosis (PS) is of interest because the threshold varies by sex: the observation that the male incidence is five times higher (1/200 males vs 1/1,000 females) suggests that the threshold for females requires more defective genes than is required for PS among males. Because affected females will therefore have more abnormal genes to pass on, their relatives will show a higher risk than that seen in the general population (Table). Conditions having greater risk among relatives of affected individuals from the lower incidence sex are typically multifactorially inherited. Other multifactorially inherited conditions with a sex-related variance in incidence include open neural tube defect (five times more prevalent among females) and congenital dysplasia of the hip (nine times more common among females).

Some conditions require the interaction of an abnormal gene with an environmental trigger, which may be in either the intrauterine or the postnatal environment. Confirmed examples are few, but include the relationships between the genetic predisposition for neural tube defect with environmental folate or the relationship of heart disease with exercise.

Several observations may make a condition's recurrence pattern consistent with multifactorial inheritance:

- Most affected individuals have normal parents.
- Studies of conditions shown to have a population frequency higher than 1%, including allergy, cleft lip and palate, handedness, or neural tube defects, suggest interplay among genetic factors (which may be single genes, but more often polygenic) and environmental modifiers.
- Inheritance in a family is less than that predicted by monogenic models, but greater than expected from chance (the general population).
- Consanguinity increases the risk for an affected child, but only two-fold compared with unrelated individuals. Consanguinity in autosomal recessive conditions yields a much greater risk increase.
- The recurrence risk increases with the disease severity among affected children. For mendelian characteristics, the risk for recurrence is independent of the severity seen in affected individuals. In multifactorial inheritance, a more severe effect correlates with a greater amount of (abnormal) genetic material to pass on, thus disease severity correlates with risk of recurrence.

The recurrence risk is greater when more siblings are affected, because involvement of multiple affected children suggests that the parents' genetic contributions are closer to the threshold required for clinical disease. In mendelian-inherited conditions, regardless of past experience, the recurrence risk is determined by the type of inheritance pattern.

- Penetrance (the likelihood of seeing a given genotype expressed phenotypically) is a part of the inheritance pattern in a family, ie, more severely affected probands have more severely affected relatives, suggesting that multigenetic or environmental modifier(s) have an effect.
- Relatives of affected individuals may show increased risk for conditions in related diagnostic categories, eg, an individual with one autoimmune disease may have relatives with different autoimmune diseases.
- Because the probabilities of being affected are different among males and females, when affected, members of the least likely sex have a greater chance of having affected offspring.

Among infants at or after 20 weeks' gestation with congenital malformations, multifactorial inheritance comprises the largest identifiable fraction of underlying causes (22.8% of cases), followed by familial (14.4%), chromosomal (10.1%); single gene, teratogen, and uterine factors (each contributing <5%). The cause for congenital anomalies could not be determined in 43.1% of cases, making **"**unknown**"** the most prevalent situation underlying congenital malformations.

Multifactorial inheritance is seen with adult height, handedness, and intelligence, as well as with multiple clinical conditions including neural tube defects, congenital heart disease, cleft lip/palate, congenital hip dysplasia, atopy, diabetes, cancer, club foot, and PS (as in this vignette).

The familial recurrence risk described does not correlate well with any of the mendelian inheritance patterns and the pattern of inheritance is not a good fit for the options given.

Autosomal dominant inherited conditions often arise spontaneously from unaffected parents with a negative family history for the condition. Most have complete penetrance, thus affected individuals can expect to pass the trait to one half of their offspring. The pattern described in this vignette is not consistent with this pattern because neither parent is affected and other relatives are affected.

Autosomal recessive conditions arise when both parents are heterozygous for the condition. Affected parents rarely have an affected child, as was noted for the aunt and cousin of this affected female infant.

X-linked dominant inheritance fits the pattern described for the aunt/cousin combination of this vignette, but is not consistent for the proband patient, whose mother is unaffected.

X-linked recessive conditions appear among male offspring of unaffected mothers who carry both the recessive gene and its dominant (normal) allele.

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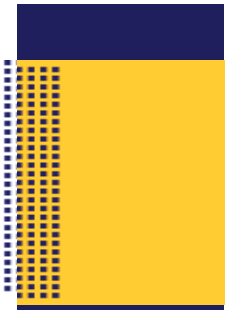

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American Board of Pediatrics Content Specification(s):

Differentiate between multifactorial and Mendelian inheritance

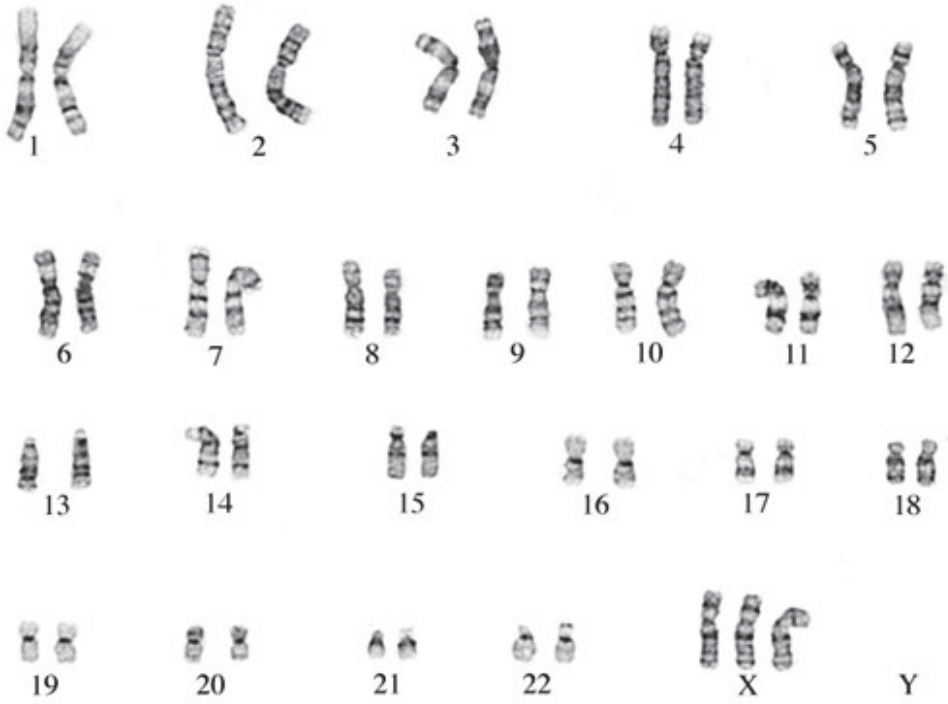
Know the recurrence risks and factors of multifactorial disorders

PREVIOUS NEXT

April: Question 4

A 38-year-old pregnant woman undergoes amniocentesis for advanced maternal age. The karyotype of the fetus is shown in Figure 1.

Figure 1



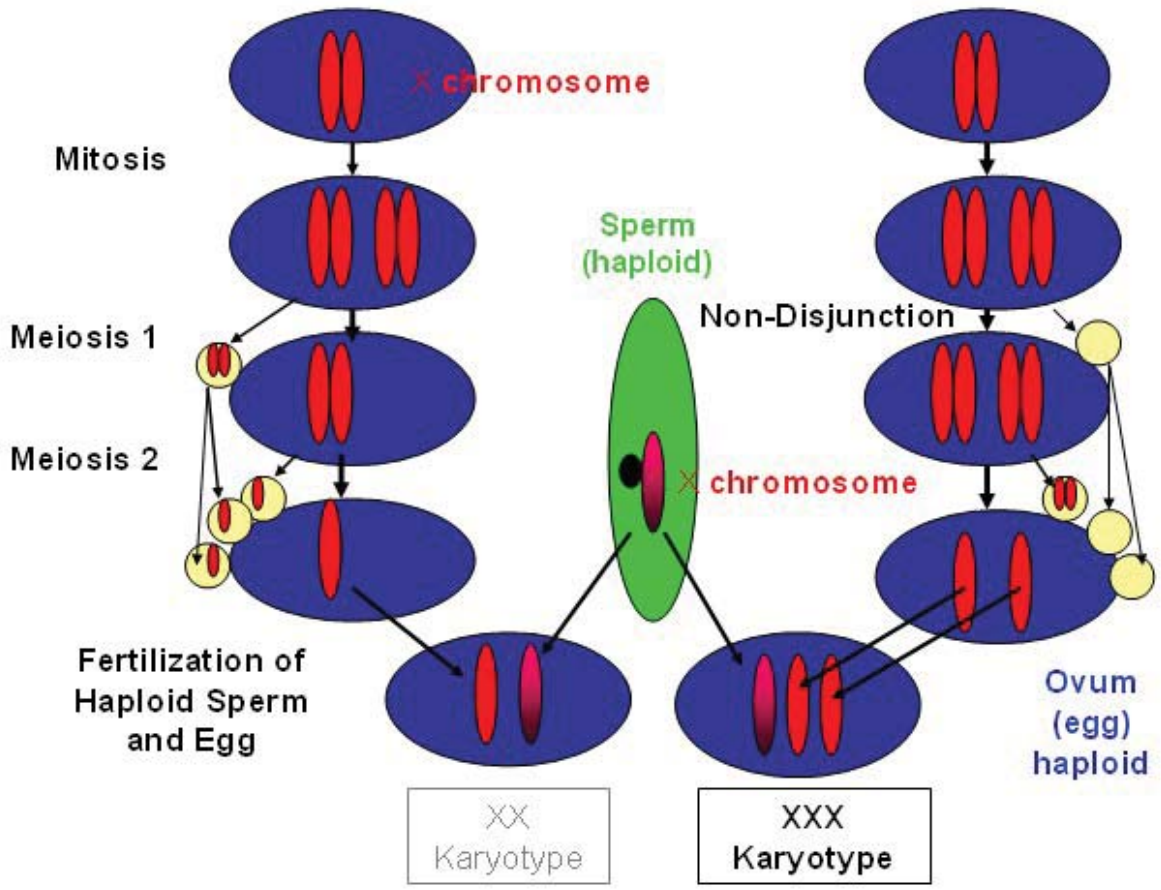
Of the following, the outcome MOST likely in such a fetus is:

1	facial dysmorphism
2	fetal death
3	learning disability
4	macrocephaly
5	short stature

You selected 4, the correct answer is 3.

The XXX syndrome, as indicated by the karyotype in the fetus in this vignette, is common among women, with an estimated incidence of 1 in 1,000 female live births. The XXX syndrome results from nondisjunction during meiosis I when one gamete ends with an extra X chromosome (Figure 2).

Figure 2: Oogenesis, nondisjunction, and fertilization: XXX syndrome



Ninety percent of cases of XXX syndrome are of maternal origin and associated with advanced maternal age.

Most women with XXX syndrome function well and are self sufficient. Although the intelligence is normal in most affected women, the intelligence quotients are generally lower than in unaffected siblings by 10 to 15 points. Speech and language deficits, motor coordination delays (such as delayed walking, clumsiness, and awkwardness), psychosocial disorders (such as depression, conduct disorders, undersocialization, and psychosomatism), and learning disabilities are frequent. These deficits, however, are generally mild.

The phenotype with XXX syndrome is variable and subtle. Minor birth defects, if detected in affected neonates, may include hypertelorism, wide spaced nipples, brachycephaly, mild microcephaly, epicanthal folds, upslanting palpebral fissures, ear abnormalities, and clinodactyly. A small percentage of cases have abnormalities of the urogenital tract, brain, skeleton, heart, and craniofacial structures. Birthweight may be slightly lower than in infants with normal karyotypes. Characteristic facial features and macrocephaly are not usually present.

Fetal death is not more frequent in fetuses with XXX syndrome than in the general population. Nuchal translucency may be present on fetal ultrasonography during the first trimester, but fetal anatomy most often is normal.

During adolescence, tall stature becomes apparent. Social, behavioral, and psychological disorders may also become evident. Women with XXX syndrome are frequently described as shy, quiet, dull, or without zest. This affect is partially explained by the presence of delays in expressive language and cognition. Sexual development and function is normal, although late menarche, amenorrhea, ovarian failure, and sterility with streak gonads have been reported. Offspring of women with XXX syndrome are usually normal. Individuals with the XXX genotype and mosaicism have been reported. The phenotype in such individuals is milder than that of the XXX syndrome.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

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American Board of Pediatrics Content Specification(s):

Understand the implications of a prenatal diagnosis of sex chromosome aneuploidy for the long term developmental outcome of an infant

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuploidy

PREVIOUS NEXT

May: Question 2

After examining a male newborn infant with dysmorphic features, you request a genetics consultation to confirm your preliminary diagnosis of Treacher Collins syndrome.

Of the following, the clinical features that are MOST likely to be observed in this infant are:

1	beaked nose, broad thumbs and great toes, cryptorchidism, hypoplastic maxilla
2	colobomas, downslanting eyelids, dysmorphic ears, malar hypoplasia
3	deafness, hemifacial microsomia, preauricular skin tags, vertebral anomalies
4	deafness, lateral displacement of medial canthi, partial albinism, synophrys
5	downturned angles of mouth, micromelia, synophrys, thin upper lip

You selected 5, the correct answer is 2.

Treacher Collins syndrome (TCS), also known as mandibulofacial dysostosis, occurs in 1 in 25,000 to 50,000 live births. Infants with TCS have specific symmetric facial features (**http://www.emedicine.com/ped/TOPIC1364.Htm**) including the following:

- Downslanting palpebral fissures (89% of cases)
- Malar hypoplasia with or without a cleft in the zygomatic bone (81%)
- Mandibular hypoplasia (78%)
- Dysmorphic ears (77%)
- Lower lid coloboma (69%)
- Partial to total absence of lower eyelashes (53%)

Infants with TCS may also have conductive deafness (40%), visual loss (37%), external ear canal defects (36%), and/or cleft palate (28%). Some individuals with TCS may have scalp hair that extends onto their lateral cheek (26%). Mental retardation has been observed in 5% of patients with TCS. Based on these descriptions, the clinical features of colobomas, downslanting eyelids, dysmorphic ears, and malar hypoplasia best describe an infant with TCS.

Children with TCS should be monitored closely for several potential complications. Because infants with TCS may have a narrow airway, they may develop respiratory problems, sometimes requiring a tongue-lip adhesion, mandibular distraction, or a temporary tracheostomy. Early recognition of deafness and potential correction with hearing aids or surgery are important to maximize the child's speech development. It is critical to obtain an ophthalmologic screening in children with TCS; amblyopia is the most common cause of visual loss in affected

individuals. Surgical correction of the facial abnormalities is initiated after a large amount of facial growth has occurred, typically with multiple procedures beginning after 7 years of age.

Treacher Collins syndrome is an autosomal dominant disorder with a variable degree of penetrance. Mutations in the gene ***TCOF1***, located on chromosome 5, lead to morphogenetic problems of the first and second branchial arches followed by maldevelopment of the cartilage, bone, and connective tissue in the craniofacial region. Radiographic images of a hypoplastic zygomatic arch are usually diagnostic of TCS, particularly because this finding is observed in even mildly affected individuals.

The clinical features of beaked nose, broad thumbs and great toes, cryptorchidism, and hypoplastic maxilla are commonly found in infants with a diagnosis of Rubinstein-Taybi syndrome (RTS). In the neonatal period, the most typical features of RTS are broad great toes (100%), broad thumbs with radial angulation (87%), or other broad fingers (87%). Infants with RTS also have distinctive facial features including:

- Hypoplastic maxilla with narrow palate (100% of cases)
- Beaked nose with or without nasal septum extending below the alae nasi (90%)
- Downslanting palpebral fissures (88%)
- Long eyelashes (87%)
- Malpositioned ears with dysplastic helices (84%)
- High-arched eyebrows (73%)

While infants may have heavy eyebrows (76%), this feature is usually apparent after the neonatal period and it is not usually associated with synophrys. Cryptorchidism occurs in approximately 78% of male infants with RTS.

The clinical features of deafness, hemifacial microsomia, preauricular skin tags, and vertebral anomalies are commonly found in infants with a diagnosis of Goldenhar syndrome, also known as oculo-auriculo-vertebral dysplasia or hemifacial microsomia. The phenotypical findings are variable because of heterogeneous causes. Similar to TCS, Goldenhar syndrome is attributable to abnormal development of the first and second branchial arches, but the clinical manifestations in these two syndromes are distinct. The most obvious difference between these two syndromes is that Goldenhar syndrome is associated with asymmetric facial features. Characteristic features of individuals with Goldenhar syndrome include preauricular skin tags (90%), hemifacial microsomia (77%), vertebral anomalies such as hemivertebrae or hypoplasia (70%), and microtia (52%). Children with Goldenhar syndrome may also have ocular abnormalities, including epibulbar dermoid, upper lid notch, strabismus, and/or microphthalmia. In addition, affected children may also have malar, maxillary, or mandibular hypoplasia; middle ear anomalies with variable deafness; decreased parotid gland secretion; and/or tongue anomalies. Cardiac disease (such as ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, or coarctation of aorta) and renal defects (such as ectopic or fused kidneys, renal agenesis, ureteral duplication, or multicystic dysplastic kidneys) can occasionally be found in affected children.

The clinical features of deafness, lateral displacement of medial canthi, partial albinism, and synophrys are commonly found in infants with a diagnosis of Waardenburg syndrome. This syndrome is categorized into four types:

- Type I (autosomal dominant, mutation in ***PAX3*** gene): Lateral displacement of the medial canthi, deafness (25%), pigmentary abnormalities
- Type II (autosomal dominant): Normal placement of the medial canthi, deafness (50%), pigmentary abnormalities
- Type III (autosomal dominant): Upper limb defects (such as bone and muscle hypoplasia, flexion contractures, and syndactyly), oculoauditory, and pigmentary abnormalities
-

Type IV (autosomal dominant or recessive): Hirschsprung disease and features of type II

Congenital sensorineural deafness is the result of a defect in the organ of Corti; this hearing loss is usually nonprogressive and profound. Affected individuals with Waardenburg syndrome usually have pigmentary abnormalities, usually evident by a white forelock, which may be present at birth, and/or isochromic blue eyes with hypochromic irides. This partial albinism can also be expressed as hypopigmented ocular fundi, white eyelashes, premature graying, and/or hypopigmented skin lesions. Affected individuals may have a medial flare of bushy eyebrows, which may meet in the midline.

The clinical features of downturned angles of mouth (94% of cases), micromelia (93%), synophrys (98%), and thin upper lip (94%) are commonly found in infants with a diagnosis of Cornelia de Lange syndrome. Growth deficiency is evident prenatally and failure to thrive persists, often associated with feeding difficulties. Other clinical features associated with Cornelia de Lange syndrome include long and curly eyelashes (99%), microbrachycephaly (93%), syndactyly of toes (86%), micrognathia (84%), anteverted nares with depressed nasal bridge (83%), hirsutism (78%), fifth finger clinodactyly (74%), and undescended testes (73%). Cardiac or gastrointestinal defects, hearing loss, mental retardation, and/or behavioral abnormalities can also be observed in these children.

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Wiley S, Swayne S, Rubinstein JH, Lanphear NE, Stevens CA. Rubinstein-Taybi syndrome medical guidelines. ***Am J Med Genet.*** 2003;119A:101-110

American Board of Pediatrics Content Specification(s):

Recognize the clinical features of the Treacher Collins syndrome

Recognize the clinical features of syndromes, such as Waardenburg, Treacher Collins, Cornelia de Lange, Mobius, Vater, Rubenstein-Taybi, Beckwith, etc

Recognize the clinical features of the Rubenstein-Taybi syndrome

Recognize dysmorphic syndromes associated with hearing loss, such as Waardenburg and Goldenhar syndromes

Recognize the clinical features of the Waardenburg syndrome

PREVIOUS NEXT

November: Question 10

A 36-year-old primigravida presents for prenatal care at 16 weeks' gestation. Because of her age, she is concerned that her infant will have Down syndrome. You discuss aneuploidy screening tests, including nuchal translucency (NT) measurement and serum maternal analytes: α-fetoprotein (AFP), pregnancy-associated plasma protein A (PAPP-A), human chorionic gonadotropin (hCG), unconjugated estriol (uE_3), and inhibin A.

Of the following, the combination of screening tests with the HIGHEST sensitivity for predicting Down syndrome in the fetus of this woman is:

1	AFP, hCG, and uE_3
2	AFP, hCG, uE_3, and inhibin A
3	NT alone
4	NT, AFP, hCG, uE_3, and inhibin A
5	NT, PAPP-A, and hCG

You selected 4, the correct answer is 2.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Prenatal screening for fetal aneuploidy, particularly Down syndrome, has evolved from the use of maternal age, to algorithms integrating first- and second-trimester tests using ultrasonography and biochemical markers. Chorionic villus sampling and amniocentesis are diagnostic, but carry inherent procedure-related risks. Therefore, the need exists for noninvasive screening tests to modify maternal age-related risk and identify high-risk patients. The optimal screening test will have a low false-positive rate (1 − specificity) and a high detection rate (sensitivity) for the disorder. A detection rate of at least 75% and a false-positive rate of less than 5% are desirable.

Maternal serum analyte concentrations change with gestation and differences exist among laboratories and assays. To achieve comparable values, results for serum markers are expressed as multiples of the median (MoM). The absolute value of the assayed analyte is divided by the gestation-specific median value of the marker in the laboratory. By definition, 1.0 MoM is the central value for the unaffected population of singleton pregnancies. For example, an MoM value of 0.5 represents one half the population median, whereas an MoM value of 2.0 represents twice the population median. In addition, screening tests may be reported as screen positive or screen negative based on fixed cutoff values.

Maternal serum marker screening for Down syndrome was introduced in 1984, with the reported association between low maternal serum alpha-fetoprotein (AFP) and Down syndrome. In the 1990s, detection rates improved with the addition of total or free human chorionic gonadotropin (hCG) and unconjugated estriol (uE_3). When this triple marker protocol is used to modify maternal age–related Down syndrome risk (decreased concentrations of

maternal serum AFP and uE_3, and increased hCG concentrations), the detection rate for Down syndrome approaches 70%, with an acceptable false-positive rate of approximately 5%. Adding maternal inhibin A concentration (increased in Down syndrome) to the triple screen constitutes the quadruple screen, and improves the detection rate for Down syndrome to approximately 80%. However, inhibin A, uE_3, and AFP are only useful markers in the second trimester.

Nuchal translucency (NT) refers to a fluid collection at the back of the fetal neck and lower cranium, which can be visualized on ultrasonography. An association between NT measurements greater than the 95th percentile for crown-rump length and the risk of Down syndrome was reported in the 1990s, with a detection rate ranging from 69% to 75%, and a false-positive rate of 5% to 8%. However, the detection rate for Down syndrome using NT alone is lower than that of the quadruple screen. Furthermore, NT measurement is only valid from 10-4/7 to 13-6/7 weeks of gestation, with the optimal time for assessment at 12 to 13 weeks. Additional first-trimester ultrasonographic markers, such as nonvisualized nasal bone, have potential as markers for aneuploidy, but their use has not yet been standardized.

When applied together, the maternal serum markers, pregnancy-associated plasma protein A (PAPP-A) and hCG, carry a detection rate for Down syndrome of only 61% (PAPP-A concentrations are decreased and hCG concentrations are increased). However, the combined use of PAPP-A, hCG, and NT improves the detection rate for Down syndrome to 83%, while maintaining a false-positive rate of 5%. PAPP-A is only a useful screen for aneuploidy when measured in the first trimester.

Independently using first- and second-trimester screening tests improves detection rates for Down syndrome (up to 98%), but the false-positive rates are additive. This results in a potential increase in unnecessary invasive procedures. Alternatively, an **"**integrated**"** approach to screening, using both first- and second-trimester tests, but with results reported only after all screening is completed, provides the highest sensitivity (94%-96%) with an acceptable false-positive rate (5%). Because results from integrated screening are not reported until the second trimester, algorithms for sequential screening have been proposed. With this strategy, patients identified at high risk for fetal aneuploidy based on first-trimester screening might opt for an early invasive procedure.

Considering the available array of biochemical markers and ultrasonography, all women, regardless of age, should be offered noninvasive aneuploidy screening before 20 weeks of gestation. The Table summarizes first- and second-trimester screening tests currently available. Patients presenting early in pregnancy should be offered screening that combines either integrated or sequential first- and second-trimester testing. For the woman in the vignette, with her pregnancy already in the second trimester, optimal screening for Down syndrome is limited to the quadruple screen (AFP, hCG, uE_3, and inhibin A).

Table: Prenatal Screening Options for Down Syndrome and Associated Modified Age-related Risk*

Screening Option	Markers	Trimester	DR (%)	FPR (%)	PPV
Maternal age	Maternal age	1st and 2nd	44	16	1:218
1st trimester combined	NT, hCG, PAPP-A	1st	83	5.0	1:27
Triple screen	AFP, uE_3, hCG	2nd	71	7.2	1:59
Quadruple screen	AFP, uE_3, hCG, inhibin A	2nd	77	5.2	1:50
Integrated	NT, PAPP-A, AFP, uE_3, hCG, inhibin A	1st and 2nd	87	1.9	1:10
Serum integrated	PAPP-A, AFP, uE_3, hCG, inhibin A	1st and 2nd	85	4.4	1:26

AFP = alpha-fetoprotein; DR = detection rate; FRP = false-positive rate; hCG = total or free human chorionic gonadotropin; NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A; PPV = positive predictive value; uE_3: unconjugated estriol.

* Adapted from Summers (2007).

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

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Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. ***N Engl J Med***. 2005;353:2001-2011

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Summers AM, Langlois S, Wyatt P, Wilson RD, Society of Obstetricians and Gynaecologists of Canada. Prenatal screening for fetal aneuploidy. ***J Obstet Gynaecol Can. 2007;187:146-161***

American Board of Pediatrics Content Specification(s):

Understand the significance of abnormal maternal values on a second trimester multiscreen or alpha-fetoprotein test

PREVIOUS NEXT

November: Question 6

A male infant born at 24 weeks' gestation with a birthweight of 650 g is being discharged from the hospital at 36 weeks' postmenstrual age with a discharge weight of 2,340 g. He has normal physical examination findings and interacts well with his parents. His mother, a local director of the March of Dimes, asks you to speak to her staff about the causes of mental retardation.

Of the following, the MOST common cause of severe mental retardation in the United States is:

1	Down syndrome
2	fetal alcohol syndrome
3	fragile X syndrome
4	iodine deficiency
5	low birthweight

You selected 5, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The myriad known causes of mental retardation are often grouped into prenatal, perinatal, and postnatal causes (Table). Discussions about which cause is more common than others are usually qualified by the degree of mental retardation (mild or severe) and the baseline population (developed countries or worldwide) under consideration. The three most identifiable causes of severe mental retardation in the United States are fetal alcohol syndrome, fragile X syndrome, and Down syndrome. Of these, Down syndrome is the most prevalent. Iodine deficiency is not a major cause of mental retardation in the developed world. Low birthweight is recognized as a risk factor for mental retardation, not a cause for it.

Table: Categories of Causes of Mental Retardation and Their Relative Proportions*

Prenatal (60%-80%)	Perinatal (8%-12%)	Postnatal (10%)
Chromosomal disorders	Infections	Infections
Genetic syndromes	Stroke	Toxins
Infections	Asphyxia	Injury
Toxins	Nutritional deprivation	Central nervous system malformations

* Adapted from Sherr and Shevell (2006), and Kinsbourne and Wood (2006).

Mild mental retardation, with an intelligence quotient (IQ) between 50 to 55 and approximately 70, has a prevalence of 1.1% to 2.2% in the United States. It accounts for more than 85% of all cases of mental retardation. An identifiable cause is found in 13% to 30% of children with mild mental retardation. Heritable factors and environmental influences are both believed to contribute to mild mental retardation. Early intervention and educational programs may be of considerable benefit to this group of children.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Severe mental retardation, with an IQ less than 35 to 40, has a US prevalence of 0.3%. A cause is identified in 70% to 80% of children with severe mental retardation. Chromosomal or genetic syndromes account for 40% to 50% of cases, with developmental brain abnormalities and inborn errors of metabolism accounting for an additional 9% each.

Down syndrome, 1 in 800 live births, accounts for 4% to 7% of cases of mental retardation in developed countries and up to 40% of cases of severe mental retardation. IQ scores tend to decline for the first decade and then stabilize in adolescence. Adults with Down syndrome are at an increased risk for Alzheimer disease, with an estimated 25% of those older than age 35 years exhibiting the signs and symptoms of Alzheimer's type dementia.

Fetal alcohol syndrome (FAS), with a prevalence of 1 in 500 to 3,000 live births, is the most preventable cause of mental retardation in developed countries. FAS is diagnosed in 10% of cases of mild mental retardation. Although FAS and fetal alcohol effects may be more prevalent overall than Down syndrome, they account for only 1% of cases of severe mental retardation.

Fragile X syndrome is the most common inherited cause of mental retardation. It affects 1 in 1,500 to 4,000 live male births and 1 in 2,500 to 6,000 live female births. Signs of fragile X syndrome, including large ears, large head circumference, long narrow face, highly arched palate, and macroorchidism, are usually not seen at birth. The wide spectrum of impairment seen in this syndrome, from learning defects to severe mental retardation, is often complicated by behavioral problems or autism.

Iodine deficiency is the leading worldwide cause of preventable mental retardation, both mild and severe. Up to 2 billion people are at risk for iodine deficiency disease, of which 3 million are estimated to have severe mental retardation and hypothyroidism (cretinism). The hypothyroidism of the fetus induced by the mother's iodine deficiency makes the resulting hypothyroidism of the infant more severe than that seen in developed countries, where fetal hypothyroidism is usually tempered by transplacental passage of some maternal thyroid hormones. The mandatory iodizing of salt, a strategy successful in developed countries, still faces significant hurdles in the rest of the world.

The most common causes of mental retardation in the United States that are treatable at birth are hypothyroidism (1 in 4,000 live births) and phenylketonuria (1 in 15,000 live births). Trials of dietary cholesterol supplements for the Smith-Lemli-Opitz syndrome (1 in 20,000-40,000 live births) are promising.

Low birthweight (<2,500 g) occurs in 1 in 12 live births in the United States and 1 in 7 live births worldwide. Of itself, low birthweight is not considered a cause of mental retardation, but is a risk factor. Other risk factors include consanguinity, poverty, maternal illiteracy, and male sex. The risk for mental retardation in low-birthweight infants is two to four times the risk for normal birthweight infants, with a higher risk ratio for severe mental retardation.

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Task Force on DSM-IV. Disorders usually first diagnosed in infancy, childhood, or adolescence. In: First MB, ed. ***Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)***. Washington, DC: American Psychiatric Association; 2000:39-134

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American Board of Pediatrics Content Specification(s):

Know the common causes of mental retardation

Know the clinical features of fragile X syndrome

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Know the developmental consequences of maternal substance abuse, such as cocaine, heroin, alcohol, and tobacco, on the fetus, infant, and child

PREVIOUS NEXT

December: Question 5

The infant in the Figure has a 3-year-old sister with micrognathia, deafness, and retinal detachment. The ophthalomogic examination of this infant demonstrates abnormal architecture of the vitreous gel.

Figure

Of the following, the MOST likely diagnosis in this infant is:

1	Marfan syndrome
2	Nager syndrome
3	Stickler syndrome
4	Treacher Collins syndrome
5	velocardiofacial syndrome

You selected 2, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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The infant in this vignette presents with micrognathia, glossoptosis, and cleft palate (Robin sequence). Robin sequence may occur in isolation or as an element of a number of syndromes. Of the syndromes listed, Stickler syndrome commonly presents with Robin sequence; associated symptoms include ophthalmologic abnormalities, deafness, and joint laxity, and subsequent arthritis.

Stickler syndrome, also referred to as hereditary arthro-ophthalmopathy, is an autosomal dominant inherited syndrome with an incidence of approximately 1 in 10,000 live births. Most affected patients have

mutations in one of the following three collagen genes: ***COL2A1***, ***COL11A1***, and ***COL11A2***. These genes code for type II and type XI collagens that are expressed primarily in cartilage, the vitreous of the eye, the middle and inner ear, and nucleus pulposus. Affected neonates typically have a flat midface with a depressed nasal bridge, telecanthus, epicanthal folds, short nose, anteverted nares, and Robin sequence. Robin sequence results from primary mandibular maldevelopment occurring before 9 weeks of gestation with secondary features of micrognathia, cleft palate, and glossoptosis. Severe micrognathia may compromise the upper airway, necessitating tracheostomy in the newborn period. Neonatal eye findings include high myopia that is nonprogressive; abnormal architecture of the vitreous gel is pathognomonic of this disorder. A predisposition to retinal tears and detachment as well as premature cataracts is observed. Joint hypermobility is present in infancy and decreases with age. Mitral valve prolapse may occur. Patients typically have radiographic findings of spondyloepiphyseal dysplasia. Osteoarthritis is common, as are complications of femoral head abnormalities (Legg-Perthes disease, slipped epiphysis). Both sensorineural and conductive hearing losses are frequent.

Marfan syndrome (MFS) is an autosomal dominant disorder that has an estimated incidence of 1 in 5,000 persons. Its most prominent features are skeletal, cardiovascular, and ocular. Most cases of MFS result from mutations in the fibrillin-1 gene (***FBN1***) on chromosome 15. The fibrillin-1 gene encodes the glycoprotein fibrillin, a major constituent of microfibrils, which comprise the structural components of the suspensory ligament of the lens and which serve as substrates for elastin in the aorta and other connective tissues. Classic MFS is generally asymptomatic in the newborn and may be difficult to diagnose early. Affected neonates may have hypermobility of the large joints and mild contractures of the fingers and elbows. Infants with classic MFS are unlikely to demonstrate cardiac features. The typical facial appearance includes down-slanted palpebral fissures, malar flattening, a prominent nose, ear proptosis, and a high arched palate. Occasionally, ectopia lentis can present in the newborn period and should prompt further consideration of MFS. The neonatal Marfan syndrome (nMFS) is much rarer and clinically more severe than classic MFS. Infants with nMFS demonstrate senile-appearing facies, crumpled ears, redundant skin, arachnodactyly, pectus deformities, and flexion contractures. Severe cardiac valve regurgitation and dilation of the proximal aorta are common and the prognosis is directly correlated with the severity of the cardiac involvement. Micrognathia and Robin sequence are not associated with classic or neonatal MFS.

Nager syndrome (acrofacial dysostosis syndrome) is a rare disorder. Both autosomal recessive and autosomal dominant inheritance have been reported, although most cases arise sporadically. Patients with Nager syndrome often present at birth because of respiratory problems from Robin sequence. The mandibulofacial dysostosis is characterized mainly by severe micrognathia and malar hypoplasia; cleft palate is always present. The palatal cleft is wide and the palate is shortened in the anteroposterior dimension. These craniofacial features are similar to those of Treacher Collins syndrome, but unlike Treacher Collins syndrome, Nager syndrome is not associated with colobomas. The limb deformities in the Nager syndrome consist of absence of the radius, radioulnar synostosis, and hypoplasia or absence of the thumbs. Affected children have short stature and normal intelligence, but may have delays in speech and language development from hearing impairment. Abnormal architecture of the vitreous gel and retinal detachment have not been reported with Nager syndrome.

Treacher Collins syndrome, also called mandibulofacial dysostosis, is an autosomal dominant disorder with variable penetrance occurring in 1 in 25,000 to 50,000 live births. Bilateral abnormal development of the first and second brachial arches is the result of mutations in the gene ***TCOF1***, which encodes the protein treacle and is located on chromosome 5 (5q31.3-q33.3). Craniofacial tissues such as cartilage, bone, and connective tissues develop abnormally as a direct result of neural crest cell dysfunction. Affected neonates present with malar hypoplasia, zygomatic clefts, downslanting palpebral fissures, and colobomas of the eyelids. Neonates may present with respiratory compromise secondary to midfacial hypoplasia, because the very shallow nasopharynx and small nose are inadequate for nasal respiration. Many affected children have retrognathia and glossoptosis, which can restrict their airways further. Cleft lip and palate and choanal atresia may occur. External ear abnormalities are common and profound sensorineural hearing loss is almost universal. Abnormal architecture of the vitreous gel has not been reported with this disorder.

Velocardiofacial syndrome (VCFS), also known as Shprintzen syndrome, is an autosomal dominant disorder caused by a deletion in chromosome 22q11. The deletion occurs in approximately 1 in 4,000 live births and can be detected by means of fluorescent in situ hybridization. VCFS has overlapping features of the DiGeorge sequence (DS) and the conotruncal anomaly face syndrome. The gene ***TBX1*** may be responsible for the cardiac

defects seen with DS and VCFS. Most infants with VCFS present with hypotonia and heart defects. Transient neonatal hypocalcemia occurs in 20% of cases. Congenital heart defects occur in 85% of cases; the most common are ventricular septal defect, right-sided aortic arch, and tetralogy of Fallot. Facial features include retrognathia, a long vertical face with a prominent nose, and microcephaly. Clefts of the secondary palate are common; velopharyngeal incompetence results in speech impediment. VCFS has not been associated with abnormalities in the vitreous gel of the eye.

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American Board of Pediatrics Content Specification(s):

Know the associations and clinical manifestations of macroglossia and hypoplastic mandible

Recognize the clinical features and know how to manage craniofacial anomalies

PREVIOUS NEXT

January

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **2** Correct Answers: **1**

Question 1

You see an infant with an unusual facial appearance that is not typical of any of the described dysmorphic syndromes. Observation of family picture albums reveals infant pictures of older family members with similar features. Of note, all grew to adulthood, and other than having similar facial features, they have no matching health problems. You consider the genetic possibilities underlying this phenomenon and consider the variations in gene structure that could underlie this change.

Of the following, in the human genome, the MOST common modification in gene structure is:

- **A.** deletion
- **B.** duplication
- **C.** insert
- **D.** nucleotide variation
- **E.** wild type

Correct

Of the 25,000 genes comprising the human genome, gene sequencing among different people is identical 99% of the time. Although this is obviously a high concordance, the potential for considerable variation remains high because the human genome has 3.3 billion base pairs. There are estimated to be 12 million potential variations between any two persons' genomes. The most frequent or unmodified base pair sequence of a given segment of DNA or gene is termed the wild, or common, allele. Infrequently occurring differences in DNA structure, defined as being found in less than 1% of the population, are termed mutations. Differences occurring more frequently (>1%) are termed *polymorphisms*.

The most frequent type of polymorphism results from changes in single base pairs (nucleotide variation) and is known as single-nucleotide polymorphism (SNP). In the human genome, over 12 million SNPs have been catalogued. An SNP may occur anywhere along the DNA helix. If the SNP affects the amino acid coding portion of a gene, the resultant protein may be absent or dysfunctional. A change in noncoding segments of DNA may affect other aspects of transcription, such as the promoter or enhancer, or there may be no demonstrable adverse effect.

Single-nucleotide polymorphisms are relatively easy to detect, but the true relationship of a particular SNP to a disease state or condition is more difficult to ascertain. If the goal is to

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use the presence/absence of an SNP as a marker of risk, the identified SNP among patients could be either truly a part of the gene associated with the condition in question or located nearby (closely linked) on the chromosome. On the other hand, if the goals are to use gene function(s) to understand the biology of a condition and/or to devise a new treatment, finding abnormalities directly affecting the gene controlling the condition in question is more essential and difficult.

Polymorphisms of DNA that are less common than SNPs include deletions or insertions of DNA segments into or from the wild DNA allele. Another variant of polymorphism involves duplication of segments of DNA, often repeating several times (tandem repeats). As with SNPs, some of these variants may occur in active genes or in DNA affecting gene expression and thus be associated with a phenotype or with a disease; other variants may be silent.

For the case in the vignette, because no genetic marker has been previously identified, a case control study of affected individuals' DNA could be conducted to identify SNPs or other polymorphisms associated with affected individuals and absent from the DNA of unaffected family members. This process is called linkage analysis. If such an association were found, the hypothesis that this variant truly is related to the facial features would then require confirmatory studies. Whether these studies should be done can only be determined from the impact of the condition on affected individuals and the ability of the genetic knowledge to further desired health outcomes.

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Attia J, Ioannidis JPA, Thakkinstian A, et al. How to use an article about genetic association: C, what are the results and will they help me in caring for my patients? *JAMA*. 2009;301:304-308

American Board of Pediatrics Content Specification(s):

05_Genetics_Dysmorphism: Know how linkage studies are used clinically

05_Genetics_Dysmorphism: Know the meaning of the terms point mutation, polymorphism, and haplotype

05_Genetics_Dysmorphism: Know basic functional units of a gene, including intron, exon, promoter, enhancer, and polyadenylation sequence

Continue

April

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **1** Correct Answers: **0**

Question 1

A full-term female infant with a late prenatal diagnosis of tetralogy of Fallot is admitted to the neonatal intensive care unit. Her examination reveals the following dysmorphic craniofacial features: cleft palate; prominent nose with squared nasal root and narrow alar base; narrow palpebral fissures; abundant scalp hair; vertical maxillary excess with a long face; and a retruded mandible with chin deficiency. The infant's initial serum ionized calcium is 2.4 mg/dL (0.6 mmol/L).

Of the following, genetic testing for this infant is MOST likely to discover a:

- **A.** deletion
- **B.** duplication
- **C.** monosomy
- **D.** single gene mutation
- **E.** trisomy

Incorrect:

Correct Answer: A

The infant in this vignette most likely has DiGeorge syndrome (DGS), also known as velocardiofacial, CATCH 22 (*c*ardiac defects, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, and *h*ypocalcemia), Shprintzen, or conotruncal anomaly face syndrome. In 1981, the deletion associated with DGS was identified on chromosome 22 at q11.2. Three megabases of DNA are lost from this site in 80% to 90% of people affected with DGS. This deletion corresponds to an insufficiency of approximately 40 contiguous genes, many of which have not been well characterized. The next most common omission arises proximal to this deletion; this smaller defect removes 25 genes.

DiGeorge syndrome is an autosomal dominant disorder and is the most common chromosomal deletion syndrome in humans, occurring in 1 in 4,000 live births. The pattern of organ malformations involving the heart, thymus gland, and parathyroid gland coincides with an abnormal migration of neural crest cells leading to abnormal development of the fourth branchial arch and third and fourth pharyngeal pouches.

Eighty-five percent of affected individuals have conotruncal defects,

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including tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, or perimembranous ventricular septal defects. Characteristic craniofacial findings in this disorder include the following: secondary cleft palate; prominent nose with squared nasal root and narrow alar base; narrow palpebral fissures; abundant scalp hair; deficient malar area; vertical maxillary excess with a long face; retruded mandible with chin deficiency; minor auricular anomalies; and microcephaly (http://timesonline.typepad.com/photos/uncategorized/p8170066_1.jpg [accessed May 20, 2009]). Affected individuals may have slender and hyperextensible hands and fingers. Patients with DGS may have aplasia or hypoplasia of the thymus leading to abnormal T-cell function. Transient neonatal hypocalcemia resulting from primary hypoparathyroidism may occur in 70% to 80% of infants with DGS. Up to 90% of individuals affected with DGS have developmental delay and low intelligence quotient. Later in life, these individuals are at greater risk for mild to moderate learning problems, attention deficit disorder, autism spectrum disorder, and bipolar disorder.

Ninety percent of the chromosomal deletions associated with DGS arise de novo. Indeed, most affected individuals do not have a family history of this disorder. Only 7% of parents with affected infants have been found to carry the deletion. Parents who carry the deletion may not appear symptomatic as a result of variable expression. Thus, parental testing of this syndrome is critical to assess the recurrence risk in future pregnancies; while the commonly occurring de novo mutations carry a very low recurrence risk, identification of a parental deletion ensures a 50% risk of this disorder in future pregnancies because of the autosomal dominant nature of the deletion.

The variable clinical phenotype of individuals affected with DGS, even among affected members of the same family, highlights the variable expressivity of this disorder. Indeed, this syndrome has been previously described using five distinct names, emphasizing the variable clinical constellations of DGS. Some patients with DGS have mild learning disabilities and subtle craniofacial malformations, while others die in the neonatal period as a result of thymic aplasia and major cardiovascular abnormalities. The diversity of this syndrome is most likely related to the heterozygous microdeletion of approximately 25 to 40 genes on chromosome 22. In addition, environmental factors may also play a role in the diverse phenotype. As a result of variable clinical manifestations, DGS is probably underdiagnosed.

Interestingly, the size of the missing DNA is not related to the extent or the severity of DGS. Rather, the deletion of multiple crucial genes spanning the deleted region correlates with disease expression. Thus, a small deletion of critical genes will lead to a more severe phenotype compared with the milder clinical manifestations of individuals who have a larger deletion of less significant genes. Similar phenotypes may occur in affected individuals with nonoverlapping deletions, emphasizing the complex molecular mechanisms underlying this syndrome.

Prenatal and postnatal chromosomal diagnosis of DGS requires a request for fluorescence in situ hybridization (FISH) of the targeted 22q11.2 site. Although FISH testing for this specific deletion can identify most patients with DGS, 7% of affected individuals with clinical features of DGS will have a negative FISH result. While a small percentage of these individuals may have a deletion affecting the short arm of chromosome 10, a chromosomal abnormality is not currently detectable in the remaining group. However, because the phenotype is consistent, these individuals are still considered to have DGS.

Of all the genes that are lost in the DiGeorge deletion, T-box transcription factor (*Tbx1*) is most responsible for the cardiovascular, craniofacial, thymic, thyroid, and parathyroid manifestations of the syndrome. Indeed, affected individuals with karyotypically normal DGS have been found to have mutations of this gene. The protein for the *Tbx1* gene has an extremely dose-sensitive effect; deleterious DGS-like effects are observed with either quantitative or qualitative changes above as well as below its usual limit. Several other genes within the deleted region, such as *COMT*, *CDC45L, HIRA*, and *UFD1L*, may also contribute to the DiGeorge phenotype. DiGeorge phenotype is not associated with chromosomal duplications, monosomies, trisomies, or single gene mutations.

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American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the pathophysiology (including genetics) of a neonate with a right-sided cardiac lesion

09_Immunology: Recognize the clinical features and know the evaluation and management of disorders associated with T-cell dysfunction, including DiGeorge sequence and HIV infection

17_EENT_mouth_neck: Know the clinical and diagnostic features of the DiGeorge sequence (velocardiofacial syndrome, 22q11 deletion)

Continue

June

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **8** Correct Answers: **3**

Question 8

A local pediatrician asks you to “check out a baby” in the newborn nursery. He has been called by the nurses because the infant had a single umbilical artery. The infant was delivered at 38 weeks’ gestation at a birthweight of 3,200 g. The woman’s prenatal course and family history were normal. Gestational age was confirmed on ultrasonography at 10 weeks and repeat ultrasonography findings at 24 weeks’ were normal. No abnormalities are detected on physical examination. You ask the resident to consider the association of congenital anomalies with a single umbilical artery and value of added testing.

Of the following, isolated single umbilical artery HAS BEEN shown to be associated with:

- **A.** Afro-Caribbean heritage
- **B.** cardiovascular anomalies
- **C.** macrosomy
- **D.** occult renal anomalies
- **E.** post-term birth

Incorrect:

Correct Answer: D

Single umbilical artery (SUA) often has been described in association with adverse perinatal outcomes, with morbidity or mortality in individual patients attributed to chromosomal or structural abnormalities. SUA occurs with persistence of the original artery of the embryonic body stalk, atrophy of a previously normal umbilical artery, or agenesis of one of the umbilical arteries.

The incidence of SUA is higher in infants of white women than in infants of African-American, Afro-Caribbean, or Japanese heritage. Infants of multiple gestations have higher risks also. Maternal diabetes also increases the risk. When a SUA is discovered prenatally, significant fetal anomalies are reported in about 20% of cases, and include cardiovascular, gastrointestinal, renal anomalies—alone or in combination. Chromosomal abnormalities affect 20% of cases, with trisomy 18 being the most frequent. Perinatal mortality ranges from 5% to 20%, with two thirds of the deaths occurring in utero. Neonatal mortality is highly correlated with the presence of multiple anomalies. Because of these aforementioned factors, the finding of SUA in a fetus is a call to action, which includes a

Feedback

detailed anatomic survey; fetal echocardiography; fetal karyotyping; and serial evaluation of fetal growth, even in the absence of structural or chromosomal abnormalities.

Of what significance is the finding of an isolated single umbilical artery in an otherwise normal-appearing infant? Of the factors listed, only occult renal anomalies is associated with isolated SUA.

In surveys of records of infants having isolated SUA, significant associations include the following:

- gestational age is lower (39 vs 40 weeks; $P<.001$),
- mean birthweight is lower (3,160 vs 3402 g; $P<.001$),
- prematurity is more common (15% vs 7.4%) as is extreme prematurity (3.9% vs 1.2%; $P=.019$)
- intrauterine growth restriction is more prevalent (5.4% vs 1.9%; $P<.001$)

When infants having chromosomal or multisystem anomalies are excluded, occult multisystem anomalies have not been reported in association with SUA.

Recent surveys of the literature and case studies have addressed the relationship between isolated SUA and occult or significant renal anomalies. The existing data are confusing and a bit conflicting. In a metaanalysis of 37 studies of SUA over a 40-year period, only seven studies contained data regarding isolated SUA. The investigators found significant renal or urinary abnormalities in 8% of cases, with the most common abnormality, vesicoureteral reflux (VUR) of grade 2 or higher, in 2.9% of cases. Although controls were not available in the studies in the metaanalysis, investigators made estimates from the reported incidence of renal anomalies in the general population and concluded that silent renal anomalies of any severity may be sixfold higher and severe malformations up to be threefold higher among infants with isolated SUA. Because VUR comprised the majority of the severe cases, and because VUR and associated urinary tract infection may precede reflux nephropathy, the authors of the metaanalysis recommended that infants having isolated SUA undergo renal ultrasonography and a micturating cystourethrogram. Renal ultrasonography alone has been associated with a positive predictive value of only 32.5% for suggesting VUR. Follow-up recommendations include having a low threshold for diagnosis of urinary tract infection in these patients.

In another analysis, isolated SUA was found in 129 of 33,067 sequential newborns at a single institution, an incidence of about four cases per 1,000 live births. The data confirmed the association with prematurity and fetal growth restriction. Of the 122 infants who underwent renal ultrasonography, two had clinically significant renal anomalies (absent kidney; unilateral hypodysplastic kidney with grade 2 VUR) and three had minor, transient abnormalities. The authors of the study also compared their data with data from the general population. Their data also found that occult renal anomalies occured more often among infants with isolated SUA (4.1% vs 0.9%; $P=.005$), but no significant differences were found in the prevalence of clinically significant renal anomalies (1.6% vs 0.4%, $P=.74$), albeit the trend suggests the need for more data. The authors concluded that although the overall incidence of renal abnormality may be higher in association with SUA, the risk for significant abnormality is no greater than that in the general population. They believe that the incidence of significant renal anomalies in infants with isolated SUA does not warrant routine postnatal renal imaging. Their conclusion was supported in a second study of 52 cases of isolated SUA over 8 years at a single hospital in Europe. Although 10% of the infants were found to have abnormalities on renal ultrasonography, none was clinically significant and the authors do not recommend routine screening.

Prenatal ultrasonography may play a role in decision making about renal studies in cases of SUA. If the mother had undergone sophisticated ultrasonography, including examination of fetal anatomy, especially if the SUA had been detected and the renal system was well visualized; further imaging may be avoided, as suggested in the vignette. Of note, if screening is desired, delay until the second month after birth may allow transient findings to resolve.

Although there is no consensus regarding screening for renal anomalies in infants having isolated SUA, screening has regularly revealed an increased prevalence of minor renal anomalies. Prenatal screening may play a role in making individual case decisions.

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American Board of Pediatrics Content Specification(s):

07_Water_Salt_Renal: Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants

13_Skin: Know how to evaluate and manage disorders of the umbilical cord, including granulomas, persistent omphalomesenteric duct remnant, and patent urachus

Continue

July

Question 9

A 3-week-old male infant, born at 33 weeks' gestation with a normal head circumference and a birthweight at the 25th percentile for gestational age, has had persistent conjugated hyperbilirubemia and poor weight gain. His total serum bilirubin concentration is 5.2 mg/dL (88.9 µmol/L) with a conjugated fraction of 2.1 mg/dL (35.9 µmol/L). During the past week he has gained less than 10 g/kg per day while receiving 150 mL/kg per day of fortified expressed breast milk. His stools are pale yellow. Physical examination reveals icteric sclera, a broad forehead, deeply set eyes, and a systolic heart murmur at the left upper sternal border, which radiates to the axilla and back. The liver is palpable at the right costal margin. He has a healthy sibling, but his father (**Figure 1**) has had a liver transplantation.

Figure 1: Photographs of neonate's father as an older adolescent. Note the broad forehead, deep set eyes, and pointed chin. (From Spinner [2007].)

Of the following, the infant is MOST likely to have additional findings of:

- **A.** abnormal vertebrae
- **B.** cataracts
- **C.** hepatic cysts
- **D.** intracranial calcifications
- **E.** renal cysts

Incorrect:

Correct Answer: A

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The infant in this vignette is most likely to have Alagille syndrome, as suggested by

persistent cholestasis, poor weight gain, typical facial features, and family history of liver disease. Neonatal cholestasis is characterized by an accumulation of components of bile, most commonly conjugated bilirubin, in the bloodstream. A conjugated bilirubin concentration higher than 2 mg/dL (>34 µmol/L) or a conjugated bilirubin/total bilirubin ratio higher than 15% are measures commonly used to define neonatal cholestasis. Cholestasis results from decreased bile flow and/or excretion. The cholestasis in Alagille syndrome is the result of intrahepatic bile duct hypoplasia.

There are many ways to categorize the myriad causes of neonatal cholestasis. A simple practical method is to divide the disorders anatomically into three main categories **(Table)** that reflect the primary site of the disease:

- extrahepatic bile ducts
- intrahepatic bile ducts
- hepatocytes

Table: Neonatal Cholestatic Disorders*

Extrahepatic bile ducts • Biliary atresia • Choledochal cyst and choledochocele • Biliary hypoplasia • Choledocholithiasis • Bile duct perforation • Neonatal sclerosing cholangitis
Intrahepatic bile ducts • Syndromic paucity (Alagille syndrome, mutation in *JAG1*) • Nonsyndromic paucity • Hypothyroidism • Panhypopituitarism • Bile duct dysgenesis • Congenital hepatic fibrosis • Ductal plate malformation • Polycystic kidney disease • Caroli disease • Hepatic cysts • Cystic fibrosis • Langerhans cell histiocytosis • Hyper-IgM syndrome
Hepatocytes • Sepsis-associated cholestasis • Neonatal hepatitis • Viral infections • Toxoplasmosis • Syphilis • Progressive familial intrahepatic cholestasis syndromes • Bile acid synthetic defects • Urea cycle defects • Tyrosinemia • Fatty acid oxidation disorders • Mitochondrial enzymopathies • Peroxisomal disorders (Zellweger syndrome) • Carbohydrate disorders

- Lipid storage disorders
- α_1-Antitrypsin deficiency
- Neonatal hemochromatosis
- Total parenteral nutrition-associated cholestasis

* Adapted from Karpen (2002).

Intrahepatic and extrahepatic bile ducts are lined by columnar epithelium that is derived from two embryologically distinct sources. The intrahepatic bile ducts arise from hepatoblasts in the liver parenchyma, whereas the extrahepatic bile ducts arise from invaginations of the embryonic foregut. This distinction may help to explain how certain biliary diseases reside exclusively in the intrahepatic or extrahepatic domain.

Paucity of intrahepatic bile ducts can be divided into syndromic and nonsyndromic forms. Alagille syndrome, the syndromic form, is an autosomal dominant disorder with variable penetrance. It is a multiorgan disorder that consists of:

- bile duct paucity
- posterior embryotoxon
- vertebral anomalies (butterfly vertebrae)
- cardiovascular abnormalities
- triangular facies (frontal bossing, deep-set eyes, narrow pointed chin)

Patients with Alagille syndrome present with poor weight gain, cholestasis, and peripheral pulmonic stenosis. In a series of 92 patients with Alagille syndrome, cholestasis was reported in 96% of cases, peripheral pulmonic stenosis in 90%, and a characteristic facies, noted in the father of this infant, in 96%. Posterior embryotoxon (**Figures 2** and **3**) occurred in 78% of cases. Osseous abnormalities can include shortening of the distal phalanges and vertebral arch defects (eg, hemivertebrae, butterfly vertebrae [**Figure 4**], and decreased interpedicular distance).

Figure 2: Photograph of posterior embyrotoxon which presents as a sharply defined concentric white line (see arrows) or opacity anterior to the limbus at edge of iris. The line is due to a thickened or hypertrophied Schwalbe ring. (From Dhir [2008].)

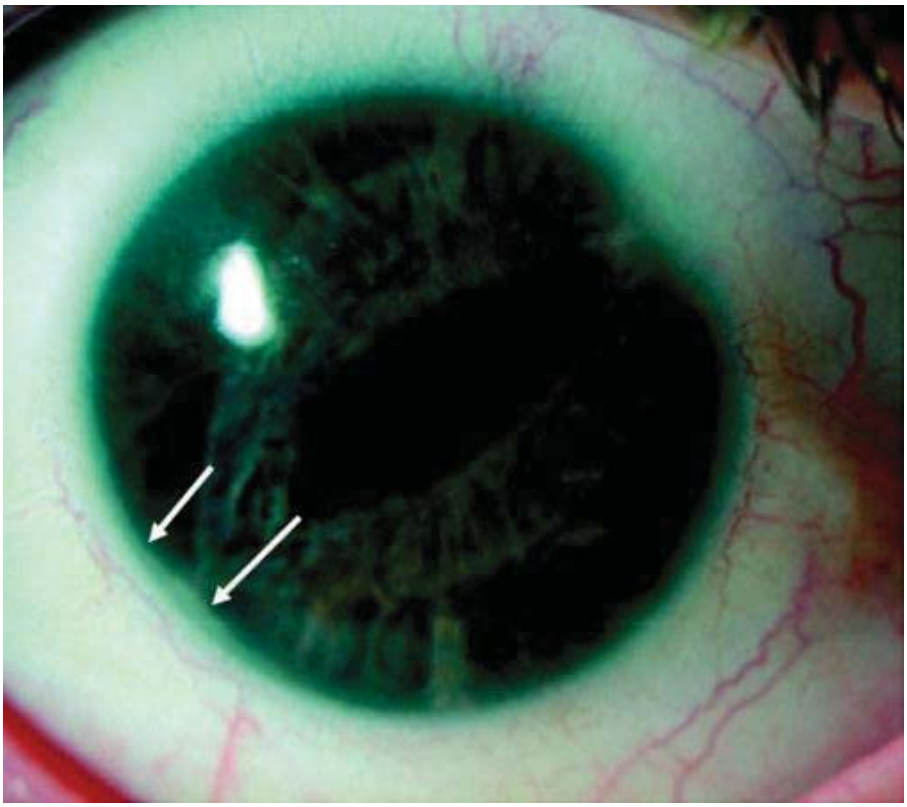

Figure 3: Slit-lamp examination of the eye shown in Figure 2. Sharply defined white line (see arrows) can be seen at the edge of the iris. (From Dhir [2008].)

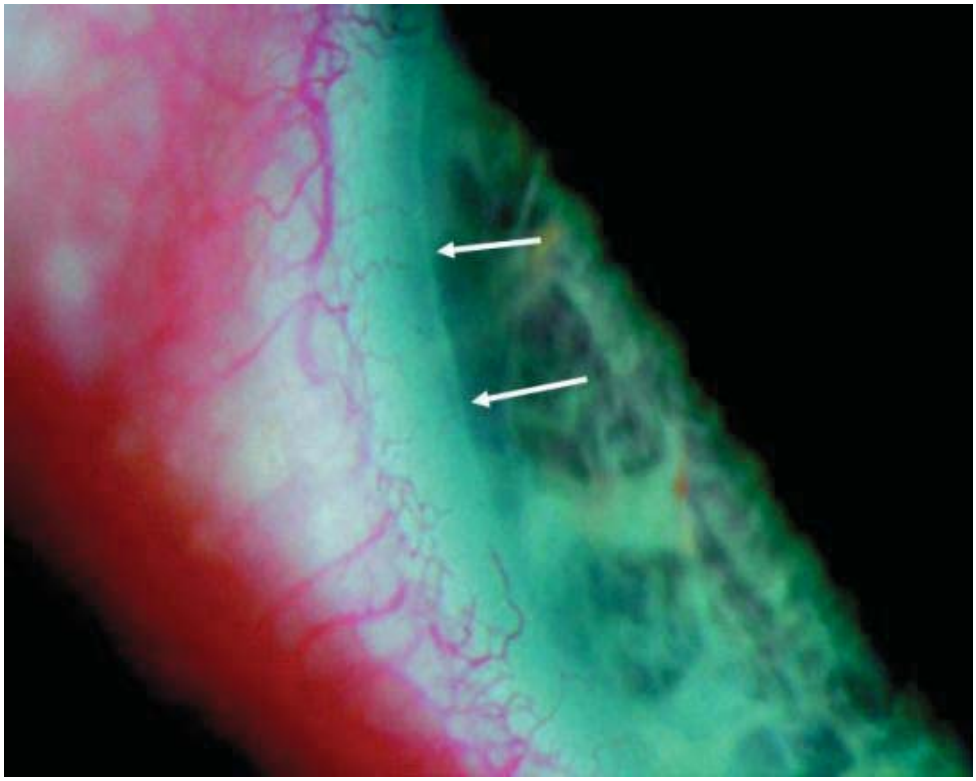

Figure 4: Radiograph of a butterfly vertebrae in older child with Alagille syndrome. (Radiograph courtesy of Robert Wells, MD, Pediatric Diagnostic Imaging.)

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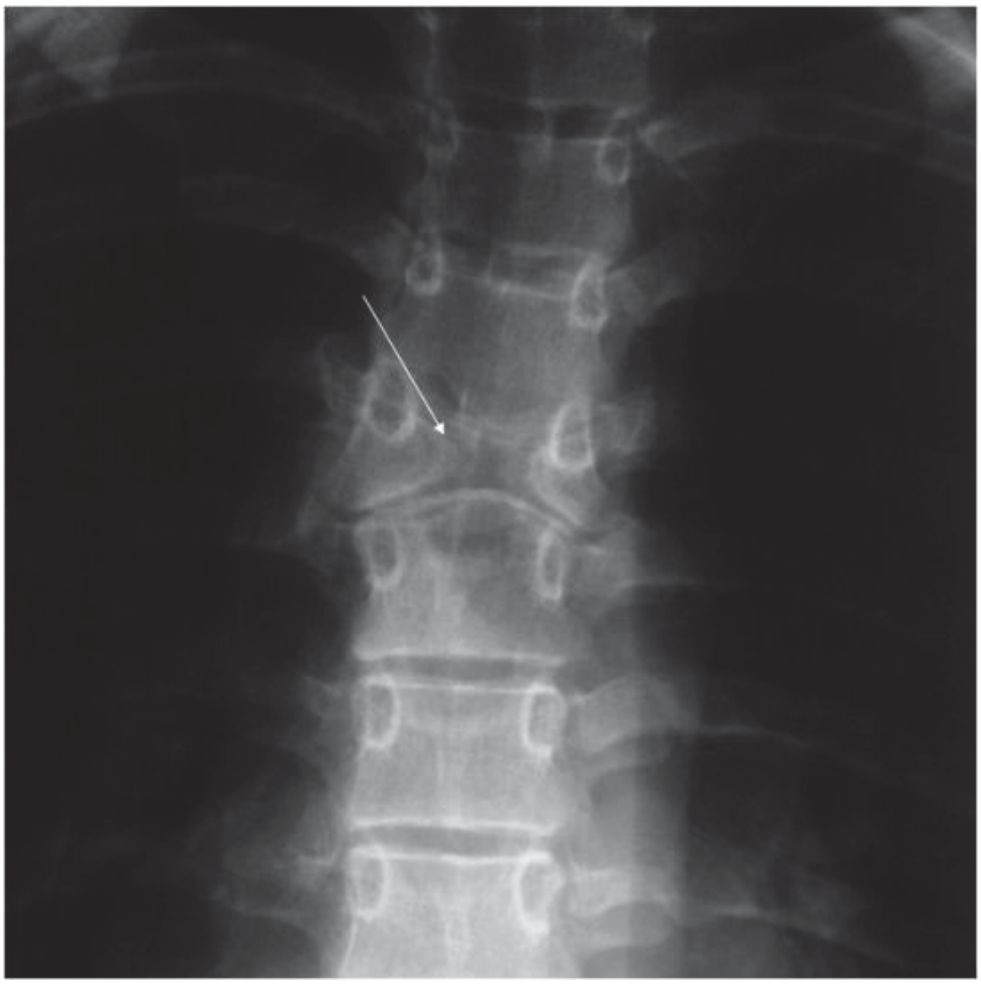

Hepatomegaly is not always present, and ultrasonographic findings of the abdomen are usually unremarkable. Laboratory analysis reveals an elevated serum bilirubin concentration, approximately 50% of which is conjugated. Serum alkaline phosphatase and gamma glutamyl transpeptidase may be extremely elevated, whereas serum aminotransferase concentrations are mildly to moderately increased.

The hallmark of Alagille syndrome is a decreased ratio of interlobular portal bile ducts to portal tracts (<0.5:1). Histologic features during the first months after birth may be similar to those of neonatal hepatitis. Ballooning hepatocytes, portal inflammation, and giant cell transformation may be present. Often the number of interlobular bile ducts is not diminished on initial biopsies, and bile duct proliferation may be present. However, paucity of interlobular bile ducts is usually apparent after 3 months of age. Extrahepatic bile ducts are open, but often narrowed or hypoplastic.

The mechanisms involved in the pathogenesis of bile duct paucity in Alagille syndrome are not established. A mutation in the *JAG1* gene has been identified in approximately 70% of affected patients. *JAG1* encodes Jagged1, a ligand in the notch signaling pathway that is involved in cell fate determination during development. The strong *JAG1* expression during human embryogenesis in the vascular system and in other mesenchymal and epithelial tissues implicates abnormal angiogenesis in the pathogenesis of Alagille syndrome. Although a vascular basis for the anomalies in Alagille syndrome seems likely, the exact mechanism leading to bile duct paucity remains unknown.

The clinical course of Alagille syndrome is marked by varying severity of cholestasis, often worsened by intercurrent viral infections. Long-term prognosis depends on severity of liver disease and associated malformations. In a series of 168 patients with Alagille syndrome, survival rates with a native liver were 51% and 38% at 10 and 20 years of age, respectively. Liver transplantation increases the 10- and 20-year survival rates to 68% and 62%, respectively.

Galactosemia as well as a number of other inborn errors of metabolism or storage disorders can impair bile formation or flow (Table) at the level of the hepatocyte. Symptomatic

galactosemia (classic galactosemia) is caused by complete or near complete deficiency of galactose-1-phosphate uridyl transferase. Without the transferase enzyme, neonates are unable to metabolize galactose-1-phosphate, which subsequently accumulates to cause injury to the kidney, liver, and brain. Classic galactosemia is an autosomal recessive disorder that can cause bilateral nuclear cataracts. Neonates with classic galactosemia do not have dysmorphic facial features, and the infant in this vignette did not have a course that would be compatible with complete deficiency of galactose-1-phosphate uridyl transferase activity.

Viral, bacterial, and parasitic infections (Table) may cause cholestasis through sepsis-associated cytokines. Neonates with severe symptomatic congenital cytomegalovirus (CMV) infections may present with hepatosplenomegaly, elevated hepatic enzymes, and cholestasis. Intrauterine growth restriction, chorioretinitis, microcephaly, and periventricular calcifications also may be present. CMV is not familial and has not been associated with peripheral pulmonic stenosis; the neonate in this vignette had no other stigmata of congenital CMV infection.

Hepatic and renal cysts are seen in patients with Caroli syndrome, an autosomal recessive disorder that can impair bile flow and result in neonatal cholestasis. Congenital intrahepatic ductal dilation and features of hepatic fibrosis result in repeated episodes of acute cholangitis that cause conjugated hyperbilirubinemia and leukocytosis. Patients with Caroli syndrome may also have autosomal recessive polycystic kidney disease. Caroli syndrome is not associated with dysmorphic facial features or peripheral pulmonic stenosis.

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Feedback

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American Board of Pediatrics Content Specification(s):

11_Gastroenterology: Know the pathogenesis and clinical features, differential diagnosis, and treatment of intrahepatic biliary hypoplasia

11_Gastroenterology: Know the etiology, clinical manifestations, and differential diagnosis of metabolic and familial causes of cholestasis in the neonate

11_Gastroenterology: Know the laboratory and imaging features and management of metabolic and familial causes of cholestasis in the neonate

Continue

January

Question View: 0

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **6** Correct Answers: **2**

Question: 6

A 3,060-g male infant is born at 36 weeks' gestation following a pregnancy complicated by gestational diabetes. He is noted to have asymmetric crying facies and dysmorphic facial features (**Figures 1** and **2**). A cardiac murmur is auscultated and a chest radiograph is obtained (**Figure 3**). An epibulbar dermoid is noted on examination of the right eye.

Figure 1

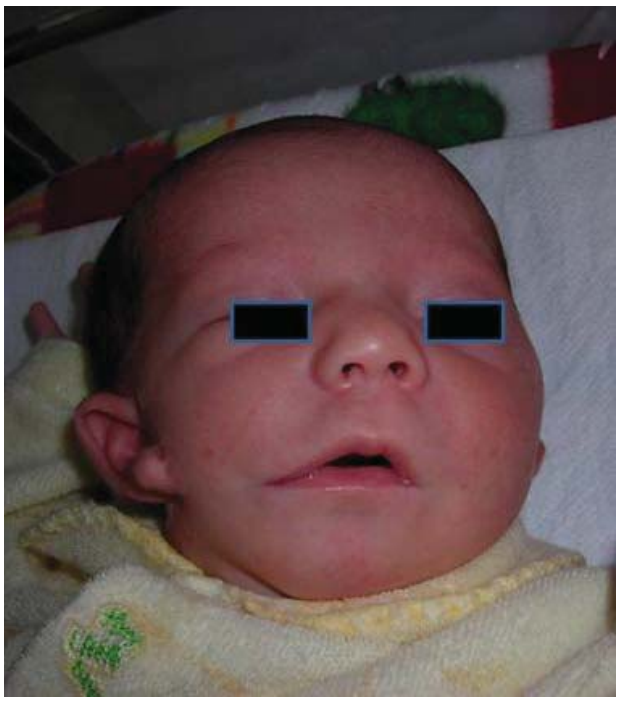


Figure 2

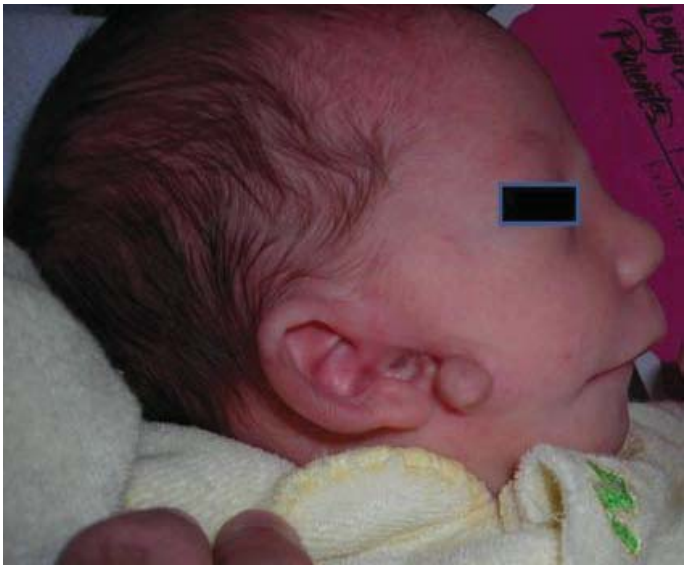
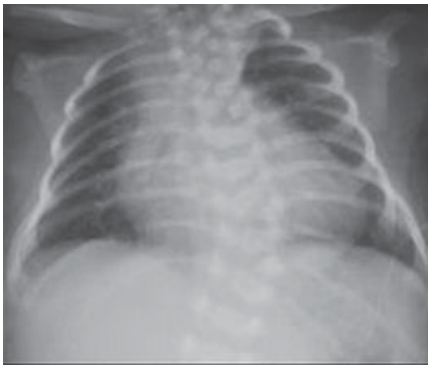


Figure 3



Of the following, the MOST likely diagnosis for this infant is:

- **A.** branchio-oto-renal syndrome
- **B.** Goldenhar syndrome
- **C.** hemifacial microsomia
- **D.** Marshall syndrome
- **E.** Townes-Brocks syndrome

Incorrect

Correct Answer: B

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The infant in the vignette has congenital anomalies consistent with Goldenhar syndrome. First described in 1952, Goldenhar syndrome represents a severe form of the oculo-auriculo-vertebral spectrum (OAVS), which is characterized by epibulbar dermoids, microtia, preauricular tags, facial underdevelopment, and vertebral anomalies. Phenotypic expression of OAVS is highly variable. Problems in morphogenesis of the first and second branchial arches, specifically perturbation of neural-crest cell migration and differentiation, lead to the predominant features. Most cases of OAVS are sporadic, but close inspection has revealed minor features in up to 45% of a proband's relatives, and cases of autosomal dominant inheritance with variable expression have been reported. Based on findings from mouse studies, potential candidate genes in the region of chromosome 6q may influence the occurrence of OAVS. In addition, a higher incidence of OAVS is seen among infants of diabetic mothers, including those with gestational diabetes. The frequency of occurrence is estimated at 1 in 5,600 births with a male-to-female ratio of 3:2.

Hemifacial microsomia, characterized by unilateral facial hypoplasia, ispsilateral ear anomalies, preauricular tags, mandibular hypoplasia, and hyperteleorism, represents a mild manifestation of OAVS. When

Feedback

accompanied by ocular and vertebral anomalies, this pattern of anomalies is referred to as *Goldenhar syndrome*. Abnormalities in Goldenhar syndrome are unilateral in 70% of cases. Additional facial abnormalities include macrostomia, a lateral cleftlike extension of the corner of the mouth (Figure 1). Hypoplasia of the depressor anguli oris muscle results in asymmetric lower facial movement, particularly pronounced during crying (referred to as asymmetric crying facies). Accessory preauricular tags commonly occur in a line from the tragus to the corner of the mouth, and middle ear anomalies occur with variable degrees of deafness. Ocular findings include epibulbar dermoid, upper lid notch, and microphthalmia. Cleft lip and palate are occasional findings. Hemi- and hypoplastic vertebrae (Figure 3) involve the cervical spine more often than the thoracic spine. Cardiac, renal, skeletal, and central nervous system abnormalities also occur. In addition, pulmonary hypoplasia has been reported in association with Goldenhar syndrome.

Branchio-oto-renal syndrome (Melnick-Fraser syndrome) is characterized by branchial arch anomalies (preauricular pits and branchial cleft cysts), auricular or external auditory canal abnormalities, hearing loss, and renal or urinary tract defects. Hemifacial microsomia, epibulbar dermoid, and vertebral anomalies have not been described with this syndrome. The inheritance pattern of branchio-oto-renal syndrome is autosomal dominant with variable expression. Mutations in the human homolog of the Drosophila eyes absent gene, *EYA1*, localized to chromosome 8, are found in most cases. Branchio-oto-renal syndrome is responsible for 2% of profound deafness in children.

Marshall syndrome is an autosomal dominant disorder characterized by cataracts, sensorineural deafness, and an extremely short nose with a flat nasal bridge. Implicated mutations are the gene encoding for the α1 chain of type XI collagen, *COL11A1*, found on chromosome 1. Branchial arch and vertebral anomalies are not characteristic of Marshall syndrome.

Townes-Brocks syndrome is an autosomal dominant syndrome caused by mutations in the *SALL1* gene on chromosome 16. Townes-Brocks syndrome shares features with Goldenhar syndrome and may have a common genetic cause. Craniofacial abnormalities, including ear anomalies, preauricular tags, hemifacial microsomia, and sensorineural hearing loss, are common to both, but anal, renal, and limb anomalies are characteristic of Townes-Brocks syndrome.

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American Board of Pediatrics Content Specification(s)

Genetics/Dysmorphism: Recognize the clinical features and know how to diagnose and manage craniofacial anomalies

Genetics/Dysmorphism: Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome)

Genetics/Dysmorphism: Know the syndromes associated with abnormalities of the eye including craniofacial abnormalities, coloboma, abnormalities of the orbit, the eyebrows, the eyelids, the eyelashes, the cornea, the iris, and the retina

Genetics/Dysmorphism: Recognize the association of abnormalities of the ear and congenital syndromes

March

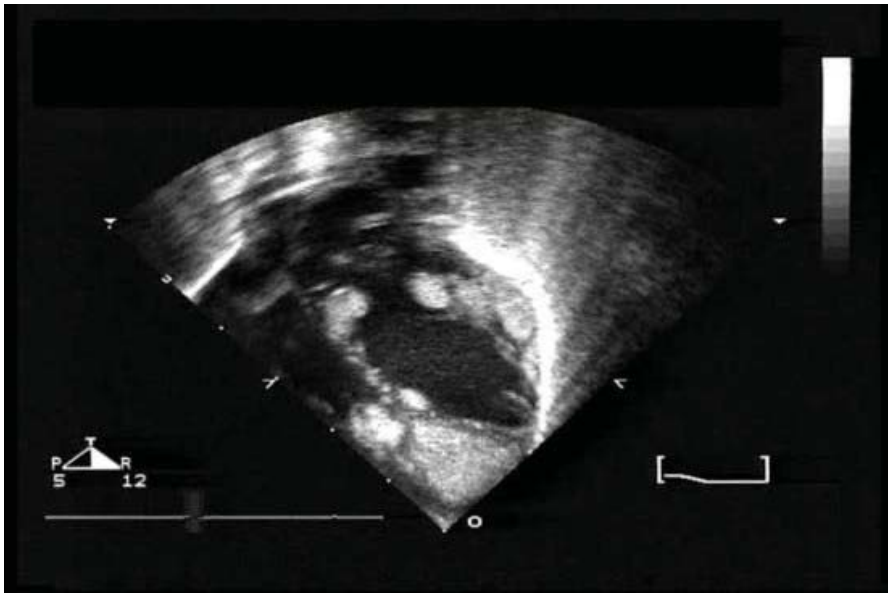
Question View: 0

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **7** Correct Answers: **0**

Question: 7

A 1,500-g infant is born at 33 weeks' gestation by cesarean section secondary to fetal heart rate decelerations. The pregnancy was complicated by a fetal tachyarrhythmia noted at 28 weeks' gestation, which resolved spontaneously. Prenatal ultrasonography demonstrated hypertrophy and a small mass in the left ventricular outflow tract of the heart. After delivery, echocardiography demonstrated multiple tumors in the walls of the left and right ventricles, the interventricular septum, and the left ventricular outflow tract (**Figure 1**).

Figure 1: Echocardiogram demonstrating multiple rhabdomyomas



Of the following, the MOST likely additional clinical finding in this infant is/are:

- **A.** café au lait spots
- **B.** hypopigmented macules
- **C.** Lisch nodules
- **D.** nevus sebaceous
- **E.** port-wine nevus

Incorrect

Correct Answer: B

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The infant in the vignette has multiple cardiac rhabdomyomas. Primary cardiac tumors are rare in the newborn, and though teratomas, myxomas, and fibromas may be seen, rhabdomyomas predominate. Up to 80% of newborns with cardiac rhabdomyomas will have tuberous sclerosis complex (TSC), and up to 60% of individuals with TSC will manifest cardiac rhabdomyomas. In fact, the cardiac rhabdomyoma is the earliest detectable hamartoma in TSC, and may be diagnosed in fetal life as early as 22 weeks' gestation. Therefore, the infant in the vignette likely has TSC.

Tuberous sclerosis complex is a dominantly inherited disorder, characterized by the formation of multiple hamartomas. Although phenotypic expression is variable, penetrance is 100%, and the spontaneous new mutation rate may be as high as 80%. TSC is caused by one of two gene deletions. TSC1 involves a deletion on the long arm of chromosome 9 (9q34; protein product hamartin) and TSC2 has a deletion on the short arm of chromosome 16 (16p13.3; protein product tuberin) and only 48 base pairs of DNA from the gene for adult-onset polycystic kidney disease, *PKD1*). Both genes are tumor suppressor genes, whose function is to regulate cell growth and differentiation. No differences in phenotype are noted with deletion of *TSC1* or *TSC2*, except when a contiguous deletion affects both *TSC2* and *PKD1*.

In 1998, revised diagnostic criteria for TSC classified signs into major and minor features (**Table**). No single sign is present in all affected individuals, and the diagnosis of TSC relies upon two or more distinct types of lesions, rather than multiple lesions in the same organ system.

Table: Revised Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features
• facial angiofibromas or forehead plaque
• nontraumatic ungula or periungual fibroma
• hypomelanotic macules (three or more)
• shagreen patch (connective tissue nevus)
• multiple retinal nodular hamartomas
• cortical tuber
• subependymal nodule
• subependymal giant cell astrocytoma
• cardiac rhabdomyoma, single or multiple
• lymphangiomyomatosis
• renal angiomyolipoma
Minor Features
• multiple, randomly distributed pits in dental enamel
• hamartomatous rectal polyps
• bone cysts
• cerebral white matter radial migration lines
• gingival fibromas
• nonrenal hamartoma
• retinal achromic patch
• “confetti” skin lesions
• multiple renal cysts
Definite Tuberous Sclerosis Complex:
Either two major features or one major feature plus two minor features
Probable Tuberous Sclerosis Complex:
One major plus one minor feature
Possible Tuberous Sclerosis Complex:
Either one major feature or two or more minor features

From Roach ES, et al. Tuberous Sclerosis Complex Consensus Conference: revised clinical diagnostic criteria. *J Child Neurol.* 1998;13:624-628.

Cutaneous lesions occur in nearly all individuals with TSC. Ash leaf–shaped hypopigmented macules (**Figure 2**) occur in 90% of affected individuals, and may be present at birth or develop during the first 2 years. Shagreen patches (collagenomas) are raised firm plaques located on the forehead or sacrum, and may also be present in the newborn (**Figure 3**). Café au lait spots (**Figure 4**) are noted in some patients with TSC, but occur less frequently than hypopigmented lesions. The brain lesions of TSC include cortical or subcortical white matter tubers composed of abnormal giant astrocytes (70% of cases) and subependymal glial nodules (90% of cases). Seizures reflecting underlying cortical dysplasia occur in up to 80% of cases, and often begin in infancy. Renal involvement includes angiomyolipomas (75% of cases) and more rarely, features of autosomal polycystic kidney disease. Asymptomatic retinal hamartomas, achromic patches (75% of cases), and lymphangiomyomatoses of the lung (1% to 6% of cases) may develop as well. Facial angiofibromas (adenoma sebaceum) and periungual fibromas develop later in childhood.

Figure 2: Hypopigmented macule (ash leaf spot)

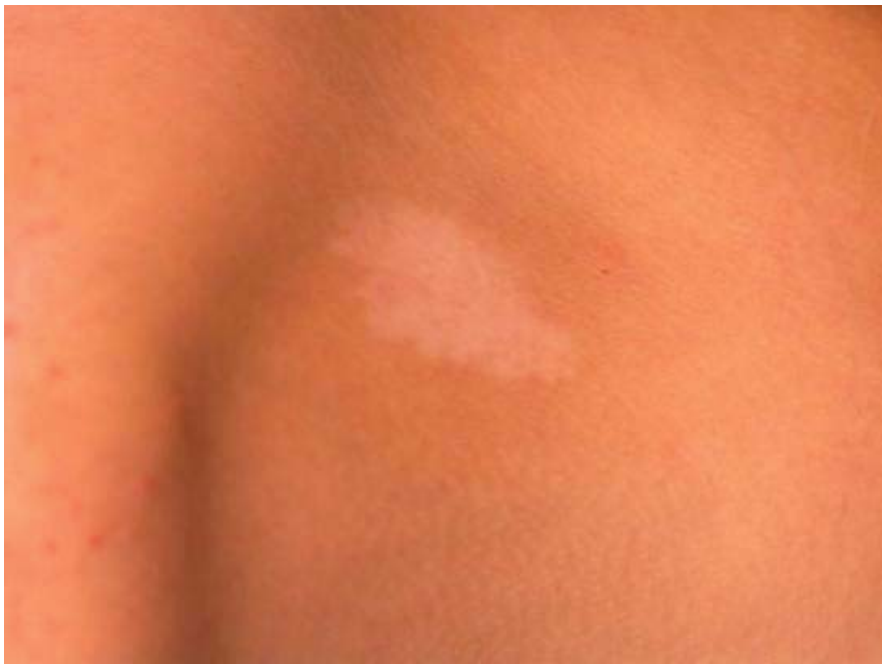

Figure 3: Shagreen patch (Smith ML. Neurocutaneous syndromes. In: Textbook of Pediatric Care. Elk Grove Village, Ill: American Academy of Pediatrics; 2008:chap 298(Fig 298-8). Available at: *Pediatric Care Online* [subscription only]. Updated August 26, 2008).

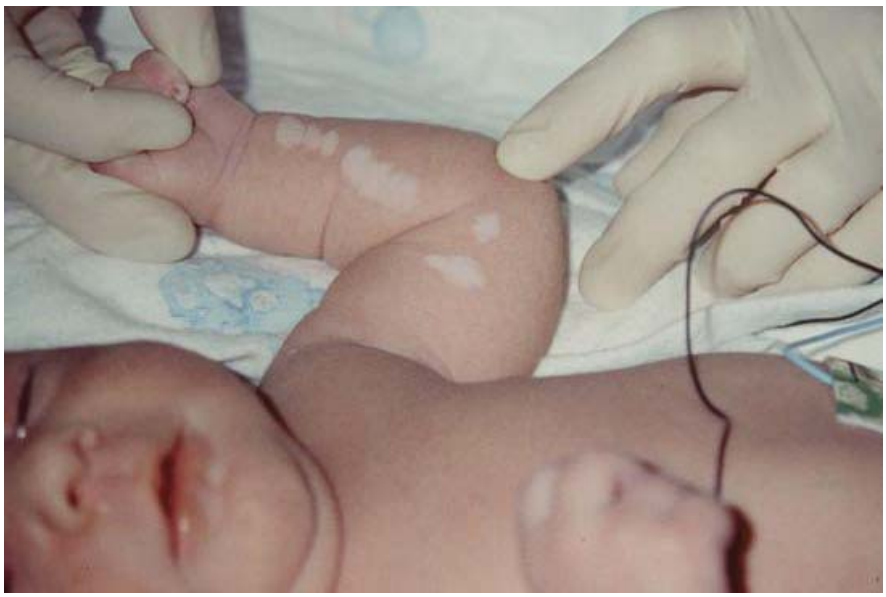

Figure 4: Café au lait macules

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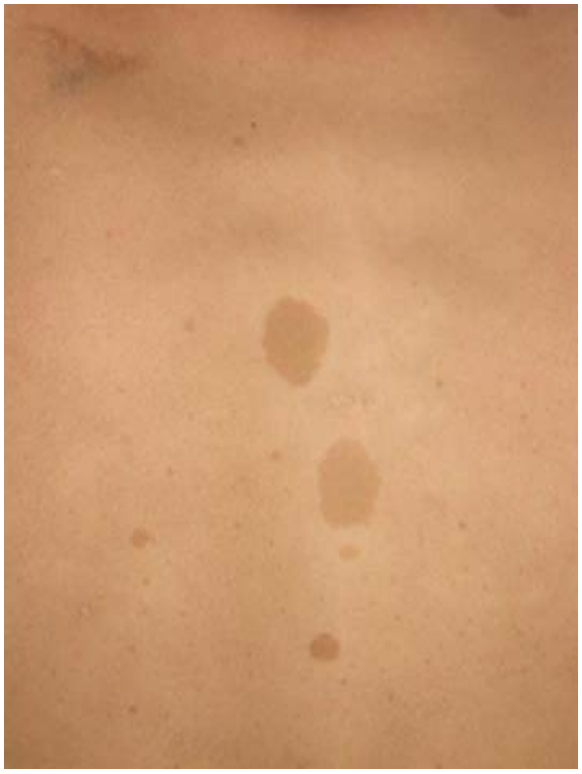
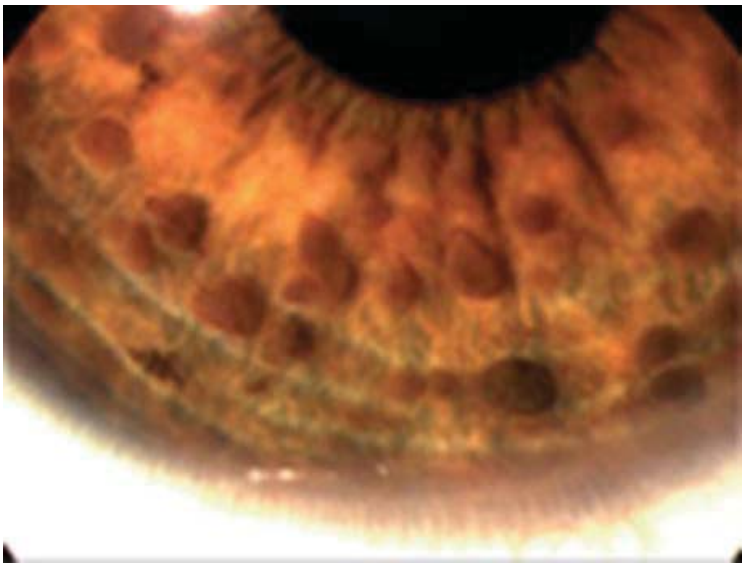


Café au lait spots are discrete uniformly hyperpigmented skin patches resulting from the presence of giant melanosomes and increased melanin content (Figure 4). Although solitary café au lait spots are common in the general population, multiple spots are the hallmark of neurofibromatosis type 1 (NF1). This neurocutaneous disorder involves abnormal development of neural crest cells and tumors of the nervous system. Café au lait spots may be present in the newborn with NF1, but the lesions tend to be fewer, smaller, and lighter than lesions found in older children. Axillary, inguinal, or inframammary freckling present at birth and in association with café au lait spots indicates a diagnosis of NF1. Neurofibromas may develop on any nerve, and may be present at birth, but cutaneous neurofibromas usually do not develop until preadolescence.

Lisch nodules are asymptomatic yellowish-brown melanocytic hamartomas on the iris, and are the most common clinical feature of NF1 (**Figure 5**). Lisch nodules are not present at birth, but develop after puberty in 90% of affected individuals. Neurofibromatosis is the only disorder known to be associated with Lisch nodules.

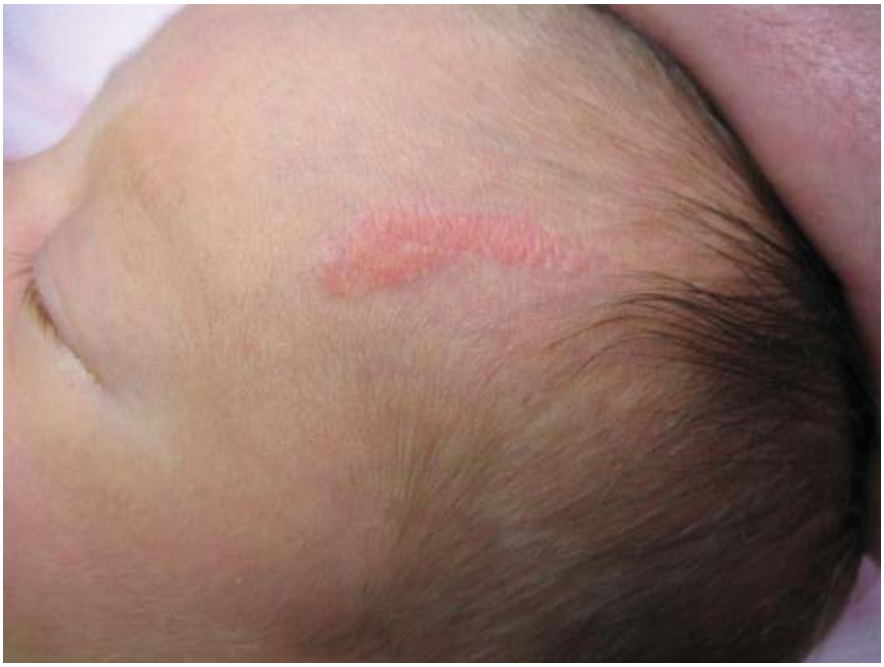
Figure 5: Lisch nodules. (Reprinted with permission from Nature Publishing Group. http://www.nature.com/eye/journal/v19/n3/full/6701478a.html. Accessed November 17, 2010)



The nevus sebaceus is a hamartoma of appendageal structures seen in 0.3% of newborns (**Figure 6**). The typical lesion is a yellow-pink or yellow-orange plaque with a pebbly or velvety surface located on the scalp

or face, where pilosebaceous and apocrine structures are prominent. Lesion size varies from 1 to several centimeters and can be round, oval, or linear in shape. The nevus sebaceus is usually an isolated lesion, but rarely is associated with other developmental abnormalities in the epidermal nevus syndrome. Because the nevus sebaceus has a propensity to develop neoplastic growths, elective excision during childhood or adolescence often is recommended.

Figure 6: Nevus sebaceous



The port-wine stain (nevus flammeus) is a congenital malformation of dilated capillarylike vessels occurring in up to 0.5% of newborns (**Figure 7**). A facial port-wine nevus in the distribution of the first branch of the trigeminal nerve (cranial nerve V1) and an ipsilateral leptomeningeal angioma characterize Sturge-Weber syndrome (also known as encephalofacial or encephalotrigeminal angiomatosis). Seizures, hemiparesis, mental retardation, and ophthalmologic manifestations are associated but not requisite neurologic manifestations of this disorder. The origin of this congenital defect is unclear, and likely involves dysmorphogenesis of the cephalic neuroectoderm. Only 5% to 8% of individuals with a port-wine stain in the location of the trigeminal nerve will have the Sturge-Weber syndrome.

Figure 7: Port wine nevus (Krowchuk DL. Rash. In: Textbook of Pediatric Care. Elk Grove Village, Ill: American Academy of Pediatrics; 2008:chap 213(Fig 213-2). Available at: *Pediatric Care Online* [subscription only]. Updated August 26, 2008).

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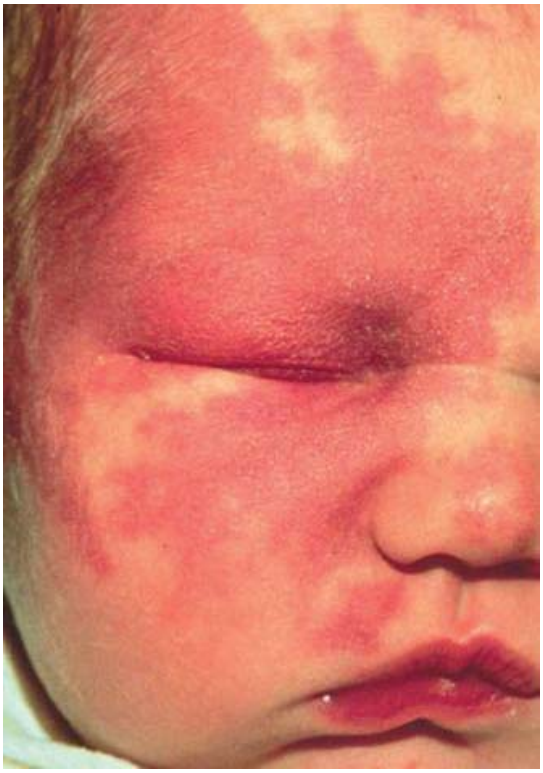

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American Board of Pediatrics Content Specification(s)

Skin disorders: Know how to diagnose and manage port wine stain and know the association with Sturge-Weber syndrome

Skin disorders: Know the differential diagnosis and syndromes associated with hyperpigmented lesions, including cafe au lait spots, giant hairy nevus, incontinentia pigmenti, and pigmented nevi

Skin disorders: Know the differential diagnosis and syndromes associated with hypopigmented lesions, including ash leaf macules, white forelock, and albinism

Neurology: Know the clinical features, diagnosis, management and outcome of neuromuscular disorders including neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, etc.

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Table: Conditions Associated With Broad Thumbs and Toes

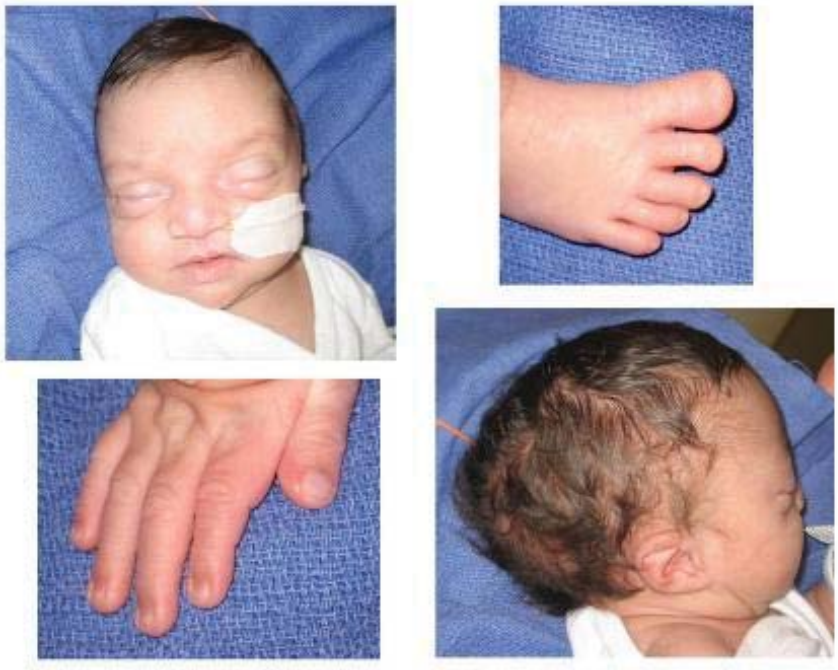
Condition	Thumbs	Toes	Incidence (/1,000 live births)
Pfeiffer	Broad	Broad	1:100,000
Rubinstein-Taybi	Broad, radially angulated	Broad, radially angulated	1:125,000
Greig	Preaxial and/or postaxial polydactyly Broad thumbs on occasion	Preaxial and/or postaxial polydactyly Broad toes on occasion	rare
FG syndrome type 1	Broad	Broad	rare
Cleidocranial dysplasia	Broad	Not affected	rare
Simpson Golabi Behmel	Broad	Not affected	rare
Teunissen Cremers	Broad	Broad	rare
Larsen	Broad	Not affected	rare
Leipert	Broad	Not affected	rare

Au

Question: 2

A full-term female newborn is admitted for tachypnea that resolves within 2 hours. Physical examination reveals a number of abnormal features (**Figure**). The infant's father also has broad thumbs and great toes.

Figure



Of the following, the MOST likely syndrome in the newborn in the vignette is:

✗	**A.**	Apert
○	**B.**	Crouzon
○	**C.**	Greig
○	**D.**	Pfeiffer
○	**E.**	Rubenstein Taybi

Incorrect

Correct Answer: D

Pfeiffer syndrome is an autosomal dominant condition characterized by broad thumbs and great toes, midface hypoplasia, and variable degrees of craniosynostosis (most frequently bicoronal). It occurs in 1 in 100,000 live births (**Table**). Although not seen in this infant, syndactyly of fingers and toes, radiohumeral synostosis of the elbows, hydrocephalus, and imperforate anus are found frequently in Pfeiffer syndrome. Most cases are sporadic but pedigrees occur, as in the case

in the vignette. Three subtypes have been described:

- Type 1. This is the classic phenotype characterized by symmetric bicoronal craniosynostosis, variable syndactyly, broad thumbs, and widened great toes. Patients with the type 1 phenotype survive to adulthood; they have normal intelligence; and the inheritance is in an autosomal dominant pattern.
- Type 2. This phenotype is characterized by multiple suture craniosynostosis (cloverleaf skull deformity), severe exorbitism, elbow ankylosis, broad thumbs and great toes, and visceral involvement including central nervous system complications (hydrocephalus). Poor neurodevelopment and early death are anticipated in patients with this phenotype; inheritance follows a sporadic pattern.
- Type 3. This phenotype shows characteristics similar to those of type 2 but without the cloverleaf skull deformity. Severe exorbitism and brain abnormalities that cause long-term neurodevelopmental disabilities are present. Early death is common; inheritance follows a sporadic pattern.

Diagnosis of Pfeiffer syndrome, like that of most craniosynostosis syndromes except Muenke syndrome and *FGFR2*-related isolated coronal synostosis, is diagnosed based on clinical findings. Molecular genetic testing for heterozygous mutations of the fibroblast growth factor receptors 1, 2, and 3 are useful in uncertain cases or for prenatal diagnosis.

Apert syndrome, or acrocephalosyndactyly type I, is an autosomal dominant disorder. It occurs in 1 in 160,000 live births. Although patients with this syndrome do not have broad thumbs and toes, fusion of the thumb and great toe with other digits may give an appearance of being broad. Characteristic findings include bicoronal craniosynostosis and midface hypoplasia; exorbitism, hypertelorism, low-set ears, downslanting eyes, cleft or high arched palate, and flat nose with bulbous tip also are frequently present. The presence of syndactyly with fusion of bone and soft tissues of the fingers (mitten hand) and toes (sock feet) distinguishes Apert syndrome from similar syndromes. Notably, compared with other syndromes, Apert syndrome is more often complicated by anomalies of other organ systems, especially the brain (corpus callosum and limbic structure malformations, gyral abnormalities, hypoplastic white matter, and heterotopias of gray matter), heart, and kidneys. Ten percent of patients experience progressive hydrocephalus because of brain constraint produced by multiple suture craniosynostosis. Intelligence and survival can be normal but the presence of hydrocephalus and brain malformations has an important effect on these outcomes.

Crouzon syndrome, or craniofacial dysostosis type I, is an autosomal dominant condition that occurs more frequently than other craniosynostosis syndromes, 1 in 25,000 live births. Characteristic features include tall, flat forehead because of bicoronal synostosis, proptosis, and midface hypoplasia. The degree of abnormality in these findings is often mild, especially compared with Apert syndrome, and may be subtle enough not to be identified as abnormal. The hands and feet of infants with Crouzon syndrome are normal. Intelligence and life expectancy are also normal.

Greig cephalopolysyndactyly syndrome is a rare autosomal dominant condition caused by mutation in the *GLI3* gene on chromosome 7. Characteristic features include pre- and postaxial polydactyly of hands and feet, syndactyly, macrocephaly, and hypertelorism. Broad thumbs and great toes may also be present. Mild cases can have normal growth, development, and survival. Severe cases exhibit hydrocephalus, seizures, and cognitive disability. Diagnosis, as in the craniosynostosis syndromes, is established on clinical findings and family history. Molecular genetic testing is available.

Rubinstein Taybi syndrome, or broad thumbs–hallux syndrome, is an autosomal dominant condition with a frequency of 1 in 125,000 live births. Broad, often radially angulated, thumbs and/or great toes are prominent characteristics. Other features include distinct facies with the columella extending below the nares, high arched

eyebrows, downslanting palpebral fissures, and high arched palate. Involvement of other organ systems may be evident during the perinatal period. Coloboma, cataracts, congenital heart defects (one third of cases), renal abnormalities, high arched palate, micrognathia, hypotonia, and cryptorchidism are relatively common findings. With time, laryngomalacia, "grimacing" smile, short stature, hearing loss, sleep apnea, gastroesophageal reflux, constipation, orthopedic problems, and moderate to severe cognitive disability (IQ 25-79) become apparent. Diagnosis is based on clinical findings supplemented with fluorescence in situ hybridization, sequence analysis, and deletion/duplication analysis for the cyclic adenosine monophosphate response element-binding (CREB) protein (50% to 60% of cases) and/or *EP300* (3% of cases) genes on chromosome 16.

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American Board of Pediatrics Content Specification(s)

Genetics/Dysmorphism: Recognize the clinical features and know how to diagnose and manage craniofacial anomalies

Genetics/Dysmorphism: Recognize the clinical features and know how to diagnose and manage congenital anomalies of the upper extremities, such as syndactyly, polydactyly, absent clavicles, absent radius, Sprengel deformity, limb reduction

Genetics/Dysmorphism: Recognize the clinical features and know how to diagnose and

manage congenital anomalies of the lower extremities, such as metatarsus adductus, talipes equinovarus, syndactyly, polydactyly, limb reduction

Genetics/Dysmorphism: Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome)

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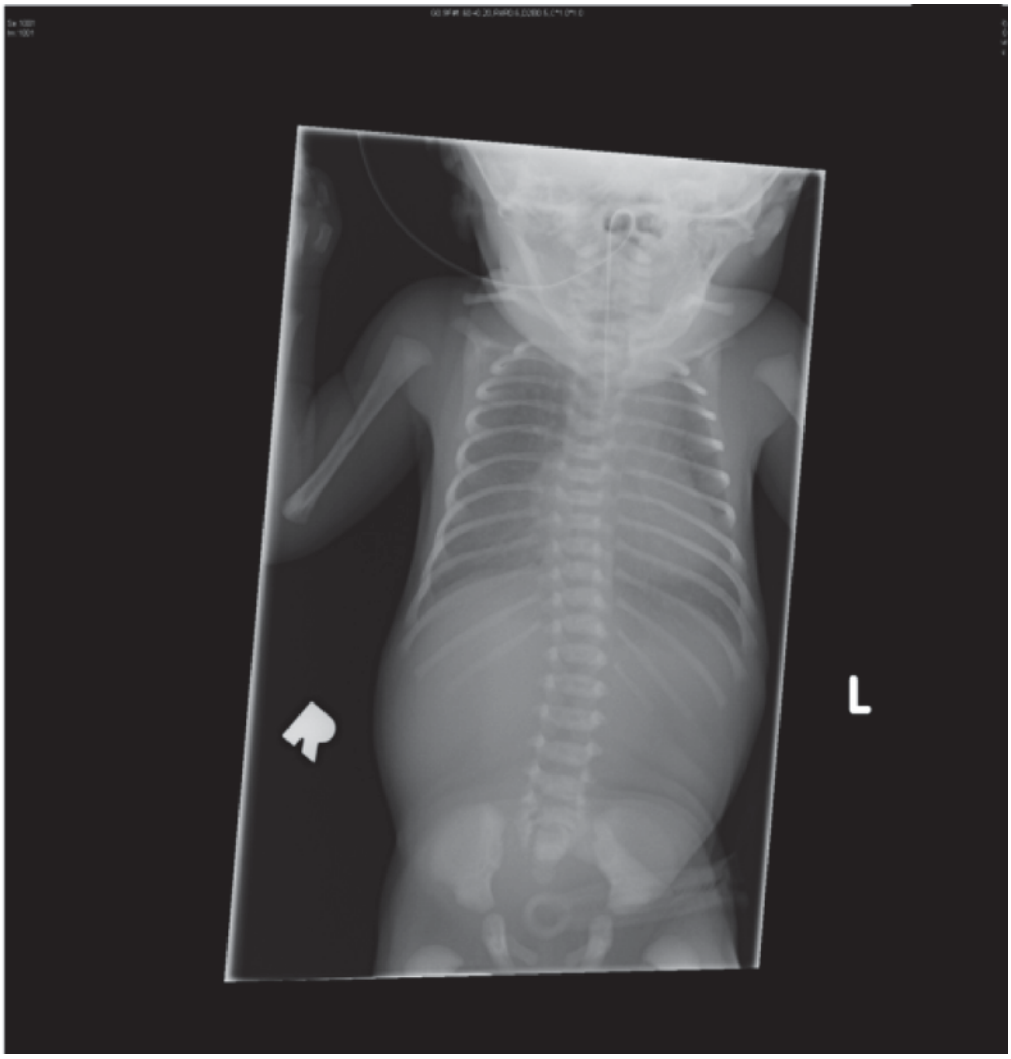
Question View: All (10)

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **9**

Question: 2

A 32-year old woman delivers a male infant at 34 weeks' gestation following preterm labor. Serial fetal ultrasonography showed normal fetal anatomy except for polyhydramnios and an absent stomach. Immediately after birth, the infant has apnea and requires 2 minutes of positive-pressure ventilation. After resumption of spontaneous respirations, the nurse places a nasogastric tube and obtains the radiograph shown in **Figure 1**.

Figure 1



Of the following, the MOST likely syndrome found in this infant is:

○	**A.**	Beckwith-Wiedemann
✓	**B.**	CHARGE
○	**C.**	DiGeorge
○	**D.**	Fryns
○	**E.**	Treacher-Collins

Correct

The combination of an absent fetal stomach and polyhydramnios, as found in the infant in this vignette, is observed in fetuses with an esophageal atresia, diaphragmatic hernia, situs inversus, and musculoskeletal or neurologic abnormalities. The postnatal radiographic findings (**Figure 2**) of a nasogastric tube that stops in the proximal esophagus and lack of air in the gastrointestinal tract despite positive pressure ventilation, suggest that the infant has an esophageal atresia (EA). Because the bowel pattern is gasless, a distal tracheoesophageal fistula (TEF) is unlikely. The infant has either an isolated EA (type A, Gross classification) or an

EA with a proximal TEF (type B, Gross classification) (**Figure 3**). Furthermore, he has 13 ribs on the left side of the thoracic cage.

More than 50% of infants with an EA have additional congenital anomalies. Cardiac malformations are the most common, occurring in about 25% to 30% of affected infants, and are associated with a higher mortality and morbidity. Additional organ systems that are commonly affected include the following: anorectal (14%), genitourinary (14%), gastrointestinal (13%), vertebral/skeletal (10%), respiratory (6%), and other (11%). Although these anomalies are thought to occur sporadically, clinical data suggest that there may be some underlying genetic cause for the transmission of EA/TEF. Indeed, there have been reports of siblings with EA, including one family with three affected children.

About 15% to 20% of patients with CHARGE syndrome have EA/TEF. Individuals with this syndrome may have the following anomalies: *c*oloboma, *h*eart disease, choanal *a*tresia, growth and/or mental *r*etardation, *g*enitourinary defects and/or hypogonadism, and *e*ar anomalies and deafness. In 1998, the disorder was redefined to include four major criteria, known as the 4 Cs (*c*hoanal atresia, *c*oloboma, *c*haracteristic ears, and *c*ranial nerve anomalies), and minor identifiers, one of which is EA/TEF. Individuals with all four major criteria or three major and three minor criteria are highly likely to have CHARGE syndrome. The reported incidence ranges from 0.1 to 1.2 per 10,000 live births. A mutation in the chromodomain helicase DNA-binding (*CHD7*) gene has been identified in more than 75% of affected individuals. Because the infant in this vignette has an EA, CHARGE syndrome should be considered in the differential diagnosis.

Several other syndromes have been described in infants with EA/TEF. Approximately 10% to 30% of infants affected with EA/TEF have anomalies that cluster to form the VACTERL association, which occurs in approximately 1.6 per 10,000 live births. This acronym describes a combination of anomalies including *v*ertebral, *a*norectal, *c*ardiac, *t*racheo*e*sophageal, *r*enal or *r*adial, and *l*imb abnormalities. Of the VACTERL components, EA/TEF is commonly linked with vertebral and cardiac anomalies. At present, the minimum number of defects that must be present to describe an infant with the VACTERL association is not defined, and the pathogenesis is unknown.

Chromosomal abnormalities, including trisomies 13, 18, and 21 occur in approximately 4% of infants with EA. Infants with EA/TEF may also have Apert syndrome (irregular craniosynostosis, midfacial hypoplasia, syndactyly, broad distal phalanx of thumb and big toe), Pfeiffer syndrome (brachycephaly, mild syndactyly, broad thumbs, and toes), Feingold syndrome (intestinal atresias, microcephaly, congenital heart defects, and limb abnormalities), or Pallister-Hall syndrome (bifid epiglottis, hypothalamic hamartoblastoma, postaxial polydactyly, anal atresia, and occasionally laryngeal clefts). Less commonly, patients with Fanconi anemia (anemia, abnormal skin pigmentation, microphthalmia, microcephaly, congenital heart defects, limb and renal defects, and susceptibility to cancer) and Opitz G syndrome (midline abnormalities with mental retardation and agenesis of the corpus callosum) have also been diagnosed with EA/TEF.

The overgrowth disorder known as Beckwith-Wiedemann syndrome is characterized by macrosomia, macroglossia, organomegaly, omphalocele, and ear creases. It is estimated to occur in 1 in 13,700 live births. Affected individuals have a predisposition to the development of embryonal tumors. Beckwith-Wiedemann syndrome is a disorder attributable to multiple abnormal mechanisms affecting the genes in the 11p15 chromosome region. Prenatal ultrasonography typically shows an umbilical-cord insertion into the membrane covering the abdominal wall defect. Polyhydramnios is also associated with Beckwith-Wiedemann syndrome. The postnatal lateral radiograph will demonstrate intestinal contents external from the abdominal cavity and contained within the omphalocele. Sometimes gastrointestinal air is limited as a result of associated ascites.

DiGeorge syndrome, also known as velocardiofacial, CATCH 22, Shprintzen, or conotruncal anomaly face syndrome, is the most common chromosomal deletion syndrome in humans, occurring in 1 in 3,000 to 4,000 live births. This syndrome is attributable to an abnormal migration of neural crest cells leading to abnormal development of the fourth branchial arch and third and fourth pharyngeal pouches. This developmental abnormality leads to absence or hypoplasia of the thymus, cardiac abnormalities, and hypocalcemia. Characteristic craniofacial findings in this disorder include the following: secondary cleft palate; prominent nose with squared nasal root and narrow alar base; narrow palpebral fissures; abundant scalp hair; deficient malar area; vertical maxillary excess with a long face; retruded mandible with chin deficiency; minor auricular anomalies; and microcephaly. Although EA/TEF is not typically found in infants with DiGeorge syndrome, a few case reports have described infants with DiGeorge and CHARGE syndrome who had an EA/TEF.

Individuals with Fryns syndrome have congenital diaphragmatic hernia, primary or secondary pulmonary hypoplasia, craniofacial anomalies, distal limb hypoplasia, and central nervous system malformations. An EA/TEF is not typically found in affected individuals. Fryns syndrome is thought to be the most common syndrome associated with congenital diaphragmatic hernia and is estimated to occur in 7 of 100,000 live births. Similar to the infant in the vignette, fetuses affected with Fryns syndrome typically exhibit polyhydramnios; often the fetal stomach is small or not visualized. Postnatal radiographs show gastrointestinal gas in the lung field with the herniated bowel. In contrast to the radiograph of the infant in the vignette, the postnatal radiograph in infants with Fryns syndrome demonstrates bowel gas within the affected lung with a normal distal intestinal gas pattern.

Treacher-Collins syndrome, also known as mandibulofacial dysostosis, occurs in 1 in 25,000 to 50,000 live births. Affected individuals have malar hypoplasia, downslanting palpebral fissures, lower eyelid defects, and external ear malformations. Mutations in the gene *TCOF1*, located on chromosome 5, lead to morphogenetic problems of the first and second branchial arches followed by maldevelopment of the cartilage, bone, and connective tissue within the craniofacial region. Radiographic images showing a hypoplastic zygomatic arch are usually diagnostic of Treacher-Collins syndrome. While some affected fetuses will have polyhydramnios and a small fetal stomach, affected infants will have normal abdominal radiographic findings.

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American Board of Pediatrics Content Specification(s)

Gastroenterology: Know the various types and diagnostic features of tracheoesophageal fistulae and esophageal atresias

Genetics/Dysmorphism: Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome)

Genetics/Dysmorphism: Recognize the karyotype and clinical manifestations associated with the common deletion syndromes

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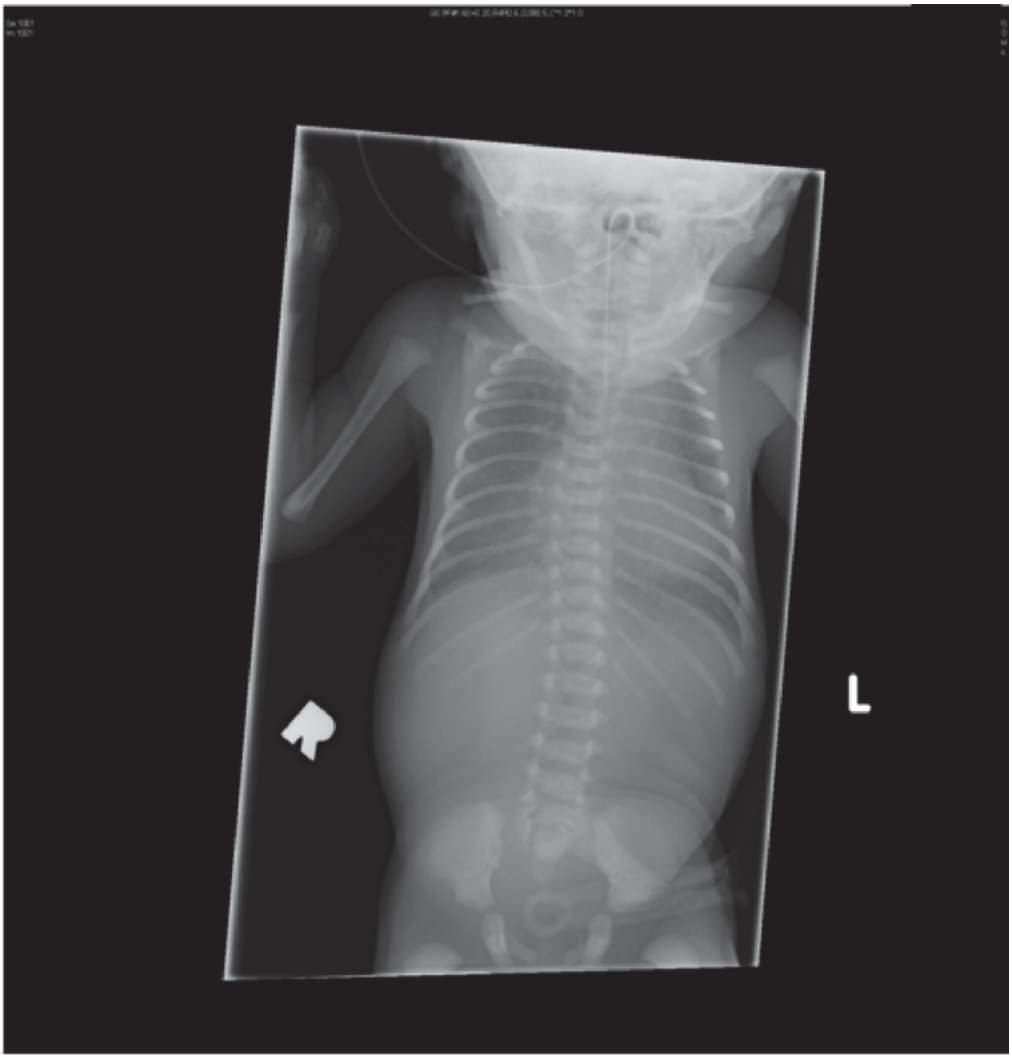
Figure 2: This radiograph shows a nasogastric tube that ends within the proximal esophagus. The lack of gas in the gastrointestinal system suggests that the infant has an esophageal atresia without a distal tracheoesophageal fistula. Note the 12 paired ribs and a solitary left 13th rib. The lungs show a mild diffuse reticulogranular pattern consistent with surfactant deficiency.



November

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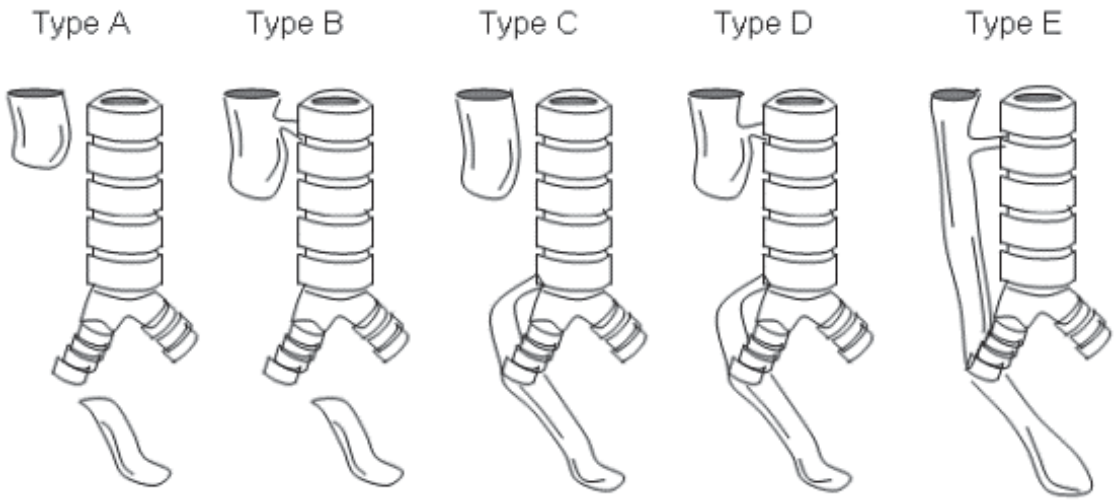
Figure 3: The five types of esophageal atresia are categorized as type A through type E, as per the Gross classification



November

Question View: All (10)

Page 2 of 11

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **9**

Question: 2

A 32-year old woman delivers a male infant at 34 weeks' gestation following preterm labor. Serial fetal ultrasonography showed normal fetal anatomy except for polyhydramnios and an absent stomach. Immediately after birth, the infant has apnea and requires 2 minutes of positive-pressure ventilation. After resumption of spontaneous respirations, the nurse places a nasogastric tube and obtains the radiograph shown in **Figure 1**.

Figure 1

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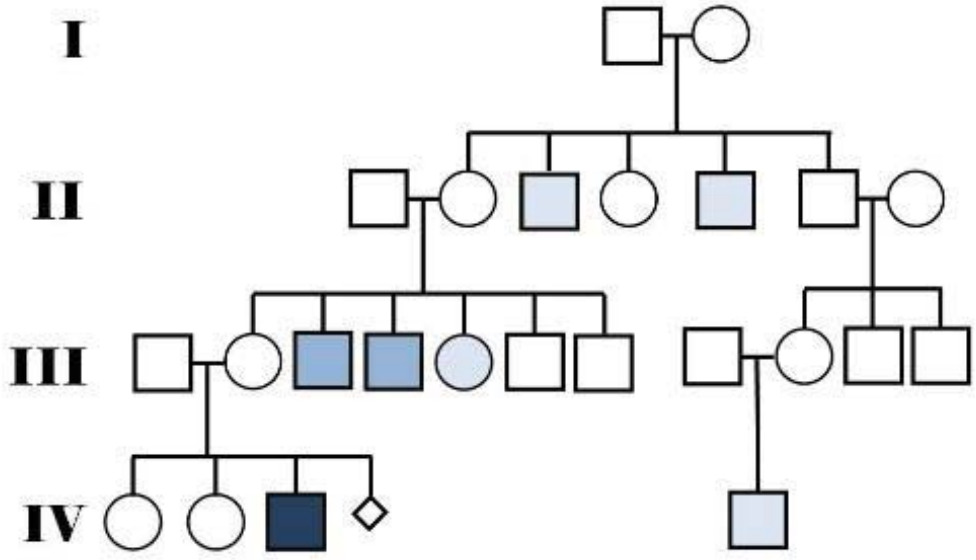
ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **9**

Question: 9

A 29-year-old woman is pregnant with her fourth child. Her first two children are healthy girls. Her third child is a 3-year-old boy who was recently evaluated for developmental delay. He has learned few words, has some features of autism, and is hyperactive. He also flaps his hands frequently. His growth has been slow (fifth percentile for length and weight) except for his head (75th percentile). He has a long face and prominent ears. Test results for fragile X syndrome were positive. She brought a copy of her family tree put together by a geneticist (**Figure**).

Figure: Family history representing four generations. Circle = female; square = male; diamond = fetus in vignette; blue = fragile X syndrome; more intense blue = earlier onset and greater severity.



Of the following, the type of genetic error MOST likely associated with this syndrome is:

○	**A.**	deletion of a nucleic acid (frame shift)
○		

	B.	deletion of a part of a chromosome
✓	**C.**	expansion of a trinucleotide repeat
	D.	substitution of a nucleic acid causing an amino acid switch
	E.	substitution of a nucleic acid resulting in a stop codon

Correct

After Down syndrome, fragile X syndrome (FXS) is the most common genetic cause of cognitive disability. Fragile X syndrome occurs in 1 in 4,000 males and 1 in 8,000 females in the United States. One in 130 to 250 females and 1 in 250 to 800 males carry the mutation. A syndrome of familial cognitive disability was originally described in 1943 by Martin and Bell. In 1969 Lubs noted the syndrome to be associated with extra genetic material that visibly extends from the X chromosome in affected males and unaffected female relatives. The gene product missing in FXS is called FMRP (fragile X mental retardation protein). The associated gene, *FMR-1*, is located on the long arm of the X chromosome. The function of FMRP is not fully characterized. It is important in trafficking messenger RNA in neurons and dendrites. It participates in the formation of synaptic connections and downregulates a glutamate receptor, mGluR5, which increases NMDA receptor activity in the brain.

Children with FXS have little problem with development until the second postnatal year. Delays gradually become apparent; cognitive disability is common. Typical signs and symptoms include:

- feeding difficulties
- speech and language delay
- lack of fine motor skills
- perseveration and echolalia
- poor short-term memory and problem solving
- depression and anxiety
- autisticlike behavior (poor eye contact, hand flapping)
- attention deficit hyperactivity, especially in boys
- macro-orchidism in adult males

The type of the mutation in FXS is expansion of a sequence of trinucleotide repeats (in this case, CGG) that normally occur in the nontranscribed portion of X chromosome DNA located near the promoter of FMR-1. This portion of DNA normally contains 15 to 34 CGG repeats. Expansion to 55 to 200 CGG repeats is called *premutation*. Individuals with premutation may have slightly lower than expected IQ, but usually have no symptoms or signs of FXS. They are, however, likely to produce offspring with more repeats (in the 200 to 4,000 range).

Hypermethylation of the whole region tends to occur when more than 200 CGG repeats are present, modifying the nearby promoter and shutting off the production of FMRP messenger. The number of repeats beyond 200 correlates with age at the onset of FXS and severity of symptoms and signs. The number of CGG repeats tends to increase with each generation in a family with FXS. Therefore, each generation tends to experience increasingly severe forms of FXS than the previous one, with earlier onset. This phenomenon is known as "genetic anticipation."

The tendency to expand the length of this particular trinucleotide repeat is not completely understood, but evidence points to it occurring during repair processes in the oogonium of the fetus. The oogonium undergoes the first step of meiosis and then arrests in that stage for many years. During that time, injuries to the DNA, such as oxidation of a guanine ring to 8-oxoguanine, occur and are repaired via excision and gap-filling synthesis. The usual result is a faithful replication of the original strand. However, this kind of repair occurs about 50,000 times a day, providing many opportunities for even low probability mistakes to happen. With each repair there is a small chance of producing a loop or hairpin of newly synthesized DNA longer than the original. Because there are a relatively high number of normal repeats, it becomes more likely that the new synthesis will mistakenly produce more repeats than the original number.

In contrast to the process seen in oogonia, spermatogonia tend to excise excessively sized trinucleotide repeats as they develop into mature spermatocytes. This helps to explain why FXS is seen more frequently among the offspring of female carriers than male carriers. Because half of all females with *FXS* inherit from their fathers, they tend to have less disease or less severe forms of the disease than males. Regardless of whether a man carries a premutation or a full mutation on his X chromosome, his spermatozoa carry only premutations because of the excision of CGG repeats beyond 200 copies in his spermatogonia. Therefore, his daughters will inherit only premutations but may pass on the syndrome to his grandsons. His sons will not inherit the abnormal gene because they receive his Y, not his X, chromosome.

The genetic code is composed of four symbols sequentially embedded in the structure of DNA (A,T,G,C for nucleic acids adenine, thymine, guanine, and cytosine). These four symbols are combined to form three-letter codons resulting in 4^3 (64) possible codons. Each unique codon directs the sequence of nucleic acids *transcribed* into messenger RNA (mRNA). Each complementary codon in mRNA is *translated* by the ribosome to add a particular amino acid to a nascent structural or enzymatic protein fragment or to start or stop the synthesis of the protein. (See link: http://scienceblogs.com/oscillator/genetic%20code.jpg)

The most common kind of genetic mutation is the substitution of a variant nucleic acid for a normal one within a gene, resulting in the substitution of one amino acid for another in a protein, and is called a *missense* mutation. A nucleic acid substitution can also result in a premature stop codon, leading to a truncated protein. A frame shift mutation involves the complete loss (deletion) of a nucleic acid from a codon leading to errors in all of the codons downstream. This is called a *nonsense* mutation.

An example of a disease caused by a single nucleic acid substitution is sickle cell anemia. However, any particular mutation may diminish or eliminate the biologic function of a protein, or it may have no effect at all. An abnormal stop codon inserted into a gene produces syndromes such as retinitis pigmentosa, Duchenne muscular dystrophy, and hemophilia. Single nucleic acid deletions resulting in a frame shift are responsible for Tay-Sachs disease, familial hypercholesterolemia, and Crohn disease. Finally, the deletion of a whole codon results in the most common form of cystic fibrosis (loss of codon #508 or ΔF508). However, just about any of the substitution or deletion mechanisms listed herein altering the same gene can result in cystic fibrosis. Cri du chat syndrome, DiGeorge syndrome, and Duchenne muscular dystrophy are associated with even larger deletions. Some of these examples point out that a particular syndrome may be caused by more than one mechanism of mutation.

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American Board of Pediatrics Content Specification(s)

Genetics/Dysmorphism: Know the clinical features and diagnosis of fragile X syndrome

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Question View: All (10)

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **9**

Question: 1

The state laboratory calls you about a newborn metabolic screen that suggests that a child has phenylketonuria (PKU). As you prepare to discuss this with the family, you find that the incidence of PKU is approximately 1 in 10,000 live births. You research a few more conditions for comparison.

Of the following, the MOST common single-gene disorder is:

○	**A.**	adult polycystic kidney disease
○	**B.**	Duchenne muscular dystrophy
✓	**C.**	hereditary hemochromatosis
○	**D.**	Rett syndrome
○	**E.**	spinal muscular atrophy

Correct

At least 4,000 disorders exhibit mendelian inheritance. Serious single-gene disorders affect 1 in 200 live births, and over a lifetime will affect 1 in 50 people. By contrast, aneuploidy is seen in 1 in 160 live births. Approximately half of the single-gene disorders are autosomal dominant, a smaller proportion are autosomal recessive, about 5% are X-linked, and a rare few are Y-linked or mitochondrial. The **Table** lists several single-gene disorders and their estimated incidences. Of the disorders in the vignette, hemochromatosis is the most common.

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Hereditary hemochromatosis (1 in 500 live births) is a recessive disorder nearly always involving the *HFE* gene at 6p21.3. The exact mechanism is still not known, but it is thought that the abnormal gene product interferes with transferrin, and the resulting abnormal transferrin activity is thought to signal increased iron absorption. Production of the liver enzyme hepcidin may also be impaired. The clinical disorder is characterized by

increased iron deposition in parenchymal cells, resulting in organ dysfunction of the heart, liver, pancreas, and pituitary. Symptoms such as heart failure or diabetes may occur as early as the third decade of life, but are generally not seen until the fifth or sixth decades. Treatment is by frequent phlebotomy or iron chelation.

Symptoms may be mild, or may not be seen at all, in many hemochromatosis homozygotes. It is estimated that, for every symptomatic patient with hemochromatosis, there are two or three asymptomatic homozygotes. Heterozygotes also show increased iron absorption over normal gene carriers, although no iron overload is seen. The origin of the gene defect is postulated to be one Celtic ancestor.

Adult polycystic kidney disease (1 in 1,000 to 2,500 live births) is an autosomal dominant disorder involving the *PKD1* (85% of patients) and *PKD2* (15% of patients) genes on chromosomes 16 and 4, respectively. The gene products, polycystin 1 and polycystin 2, take part in cell-to-cell signal transduction. Abnormalities in either of these genes results in bilateral renal cysts, usually becoming symptomatic in the third or fourth decade. Cysts can be seen at birth, leading to difficulties distinguishing adult polycystic kidney disease from the more severe autosomal recessive polycystic kidney disease seen in neonates.

In adult polycystic kidney disease, up to 5% of nephrons will form nonfunctioning cysts, but will allow normal function in the other nephrons initially. The disorder progresses with aging, causing interstitial fibrosis, nephrocalcinosis, tubular atrophy, renal stones, hypertension, and renal failure in 50% of patients by age 60 years. Adult polycystic kidney disease accounts for 10% of end-stage renal disease in the United States. Extrarenal manifestations may include intracranial aneurysms, colonic diverticuli, and cysts of the liver, spleen, pancreas, and ovaries.

Duchenne muscular dystrophy (1 in 5,000 to 18,000 live-born males) is an X-linked recessive disorder involving the *DMD* gene at Xp21. The gene product dystrophin is involved in the stability of the proteins forming the sarcolemma in muscle fibers. Abnormalities of dystrophin predispose to tears of the muscle cell membrane, and eventually result in muscle fiber necrosis. Symptoms of progressive weakness usually present at age 3 to 5 years, but occasionally can be present at birth. The heart muscle may also be involved. Diagnosis is based on creatine kinase concentrations, muscle biopsy, and DNA analysis. Death, usually from pneumonia, occurs in the second or third decade, but may be delayed several years with glucocorticoid treatment.

Rett syndrome (1 in 20,000 live births) is an X-linked dominant disorder involving the *MECP2* gene at Xq28. The gene product is a DNA-binding protein that regulates expression of other genes involved in brain development. Male fetuses usually do not live to term, and when they do they succumb to severe encephalopathy by 2 years of age. In female infants, symptoms begin at 6 to 18 months of age, and can include slow head growth, seizures, repetitive hand movements, loss of developmental milestones, intellectual disability, scoliosis, and death in the third or fourth decade. Severity of symptoms may vary depending on varying amounts of X-inactivation of the abnormal gene. Treatment is based on symptoms.

Spinal muscular atrophy (1 in 10,000 live births) is an autosomal recessive disorder involving the survivor motor neuron (*SMN*) gene on chromosome 5q13. The gene product is essential for gene-splicing in the nucleus, especially in motor neurons. Symptoms include muscle weakness and atrophy before or shortly after birth, areflexia, tongue fasciculations, problems sucking and swallowing, inability to handle respiratory secretions, and death usually within the first year. Milder forms of the disorder with longer life spans are associated with other abnormalities of the *SMN* gene. With a carrier rate of 1 in 40 to 60 people, some advocates have suggested universal preconception testing for *SMN* abnormalities.

Suggested Readings

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American Board of Pediatrics Content Specification(s)

Genetics/Dysmorphism: Know the incidence of various single-gene disorders

Complete Assessment

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Table: Estimated Incidence of Several Single-Gene Disorders*

Disorder	Incidence per live birth
Autosomal Dominant	
Familial hypercholesterolemia	1:500
Polycystic kidney disease, adult	1:1,000 - 1:2,500
Marfan syndrome	1:5,000
Osteogenesis imperfecta	1:20,000
Autosomal Recessive	
Hereditary hemochromatosis	1:500
Cystic fibrosis	1:2,000 - 1:3,500
Spinal muscular atrophy	1:10,000
Phenyketonuria	1:10,000
Galactosemia	1:47,000
X-linked Dominant	
Hereditary hypophosphatemic rickets	1:20,000
Rett syndrome	1:20,000
Incontinentia pigmenti	1:40,000
X-linked Recessive	

Red-green color blindness	1:12 - 1:20 males
Hemophilia	1:5,000 males
Duchenne muscular dystrophy	1:5,000 - 1:18,000 males
Y-linked	
Hypertrichosis pinnae auris	1:3 - 1:20 males
Mitochondrial	
Leber hereditary optic neuropathy	1:50,000

Data from OMIM.

Question: 1

The *stat... ...laboratory calls you about a newborn metabolic screen that suggests that a child has phenylketonuria (PKU). As you prepare to discuss this with the family, you find that the incidence of PKU is approximately 1 in 10,000 live births. You research a few more conditions for comparison.

Of the following, the MOST common single-gene disorder is:

○	**A.**	adult polycystic kidney disease
○	**B.**	Duchenne muscular dystrophy
✓	**C.**	hereditary hemochromatosis
○	**D.**	Rett syndrome
○	**E.**	spinal muscular atrophy

Correct

At least 4,000 disorders exhibit mendelian inheritance. Serious single-gene disorders affect 1 in 200 live births, and over a lifetime will affect 1 in 50 people. By contrast, aneuploidy is seen in 1 in 160 live births. Approximately half of the single-gene disorders are autosomal dominant, a smaller proportion are autosomal recessive, about 5% are X-linked, and a rare few are Y-linked or mitochondrial. The **Table** lists several single-gene disorders and their estimated incidences. Of the disorders in the vignette, hemochromatosis is the most common.

Hereditary hemochromatosis (1 in 500 live births) is a recessive disorder nearly always involving the *HFE* gene at 6p21.3. The exact mechanism is still not known, but it is thought that the abnormal gene product interferes with transferrin, and the resulting abnormal transferrin activity is thought to signal increased iron absorption. Production of the liver enzyme hepcidin may also be impaired. The clinical disorder is characterized by increased iron deposition in parenchymal cells, resulting in organ dysfunction of the heart, liver, pancreas, and pituitary. Symptoms such as heart failure or diabetes may occur as early as the third decade of life, but are generally not seen until the fifth or sixth decades. Treatment is by frequent phlebotomy or iron chelation.

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December

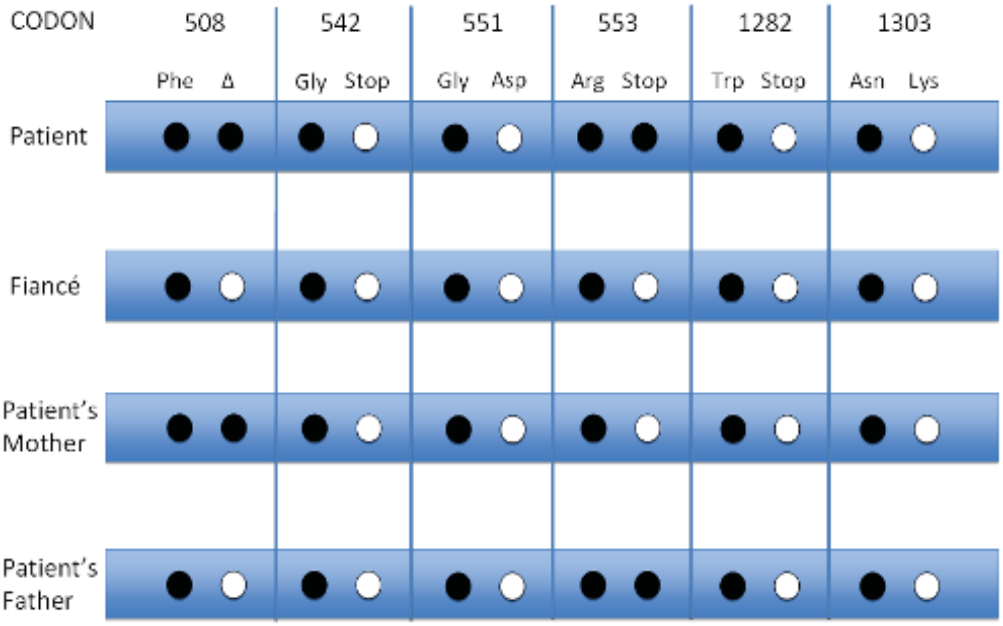
Question View: All (15)

ASSESSMENT PROGRESS: Total Questions: **15** Questions Answered: **10** Correct Answers: **9**

Question: 4

A 19-year-old woman with cystic fibrosis (CF) was diagnosed with a sweat test when she was 5 years old. At that time she had a chronic productive cough, abnormal stools, and poor weight gain in spite of a voracious appetite. She had no family history of CF. Since then, she has been treated by the multidisciplinary team of a CF program and has been doing fairly well. She is now engaged to a 22-year-old man with no family history of CF. Ancestors of both families were northern European. They are aware that CF might affect her fertility, but they are considering having children. First, they would like an estimate of their risk for transmitting CF. The couple and her parents were tested for the six more common mutations within the gene for CF (**Figure**).

Figure: Results of testing for six common mutations of the *CFTR* gene. A DNA specimen was extracted from peripheral blood samples and regions of the *CFTR* gene were amplified using polymerase chain reaction. Oligonucleotide probes relating to the six suspect codons are fixed to the membrane in pairs of circles. In each pair of circles, the left one represents the normal codon and the right circle is the mutant codon. Positive reaction is indicated by black color. Below the codon numbers are the normal amino acid (left) and the result of the mutation (right). Phe = phenylalanine, Asp = aspartate, Trp = tryptophane, Lys = lysine, Gly = glycine, Arg = arginine, Asn = asparagine, Δ = deletion of all three nucleotides in codon, STOP = stop codon.



Of the following, the chance for each of their future children to have CF is CLOSEST to:

✓	**A.**	<1%
	B.	17%
	C.	25%
	D.	50%
	E.	100%

Correct

PC I-C P

Cystic fibrosis (CF) is the most common fatal genetic disease in the white population, affecting 1 in 3,200 of their newborns. In the United States, the carrier rate is 1 in 29 among whites, 1 in 46 among Hispanics, 1 in 65 among blacks, and 1 in 90 among Asians. CF is an autosomal recessive disorder characterized by hyperviscous dehydrated mucus secretions that are difficult to clear and adversely affect the respiratory tract, pancreas, gastrointestinal tract, sweat glands, and genital ducts. The end result can be total obstruction of a passageway (eg, pancreatic duct, vas deferens) and/or frequent infections (especially with *Pseudomonas* and *Staphylococcus aureus*). Sweat glands do not secrete mucus, but the composition of sweat is altered in CF, leading to excessive salt loss and an increased risk of dehydration.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

The usual cause of death from CF is pulmonary failure; the median age of survival is currently in the mid to late 30s with marked variation. Currently, lung transplantation is the only treatment for the inexorable pulmonary failure associated with CF. Newborn infants with CF rarely exhibit respiratory symptoms, but can manifest meconium ileus or meconium peritonitis. In addition, thick secretions in the biliary tract can produce a form

of cholestatic jaundice in newborn infants. Pancreatic insufficiency is common later in childhood but not always present. Sterility caused by CF is more common in men than women, but female fertility also can be impaired because of thick cervical mucus.

The genetic code is composed of four symbols sequentially embedded in the structure of DNA (A,T,G,C for nucleic acids adenine, thymine, guanine, and cytosine). These four symbols are combined to form three-letter codons resulting in 4^3 (64) possible codons. Each unique codon directs the sequence of nucleic acids *transcribed* into messenger RNA (mRNA). Each complementary codon in mRNA is *translated* by the ribosome to add a particular amino acid to a nascent structural or enzymatic protein fragment or to start or stop the synthesis of the protein. (See http://scienceblogs.com/oscillator/genetic%20code.jpg)

The most common kind of genetic mutation is the substitution of a variant nucleic acid for a normal one within a gene, resulting in the substitution of one amino acid for another in the associated protein. This is called a missense mutation. A nucleic acid substitution can also result in a premature stop codon, leading to a truncated protein. A frame shift mutation involves the complete loss (deletion) of a nucleic acid from a codon, leading to errors in all of the codons downstream. This is also called a nonsense mutation. More extensive deletions also lead to loss of normal downstream amino acid sequences. A particular mutation may diminish or eliminate the biologic function of a protein, or it may have no effect at all. CF has been associated with each of the substitution and deletion mechanisms described herein.

The gene in CF is called *CFTR* (cystic fibrosis transmembrane conductance regulator). *CFTR* is located on chromosome 7 and consists of 250,000 base pairs. More than 1,600 known mutations of *CFTR* have been identified. The CFTR protein is a cyclic adenosine monophosphate–regulated chloride channel embedded in the apical portions of mucosal epithelia. Its function is to excrete the chloride ion which, in turn, results in passive transport of sodium and water into the lumen of a passageway. A deletion of the three nucleotides normally translated to the phenylalanine located at the 508^{th} position in the CFTR protein is the most common CF mutation (70%). Currently, a panel of the 25 most common mutations is recommended for carrier screening. This number might be reduced if targeted for a particular ethnicity. However, no current screen can positively rule out carriage of all mutations.

On inspection of the genetic tests in the figure, the woman in the vignette appears to have two different mutations: ΔF508 (Δ for deletion, F for phenylalanine) on one chromosome 7 and R553X (R for Arg, changed to X for STOP) on the other. The figure shows that the first was inherited from her mother and the other from her father. Her fiancé has none of the six mutations tested for, but still has a small chance of carrying another one not represented. Because a mutant allele from each parent is necessary to inherit CF, their offspring would have a less than 1% chance of receiving a CF mutation from their father, but all of them would be carriers.

Suggested Readings

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American Board of Pediatrics Content Specification(s)

Genetics/Dysmorphism: Demonstrate understanding of inheritance patterns and recurrence risks for autosomal recessive disorders

Maternal-Fetal Medicine: Know the rationale, methods, and interpretation of results of screening for carrier status of genetic diseases such as cystic fibrosis, Tay Sachs, and hemoglobinopathies

Genetics/Dysmorphism: Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

Gastroenterology: Know the diagnosis and management of cystic fibrosis in newborn infants