During attending rounds in the neonatal intensive care unit, you present a newborn who has megalencephaly, short limbs, frontal bossing, midface hypoplasia, shortened and splayed fingers, limited elbow extension, and normal respiratory efforts. Both parents are of normal stature.

Of the following, the MOST likely diagnosis for this child is:

1. achondroplasia
2. FGFR-related craniosynostosis
3. hypochondroplasia
4. SADDAN dysplasia
5. thanatophoric dysplasia

You selected 3, the correct answer is 1.

Achondroplasia is the most common bone dysplasia, with a prevalence of 1 in 15,000 to 40,000 live births. At birth, rhizomelic limb shortening, large head, frontal bossing, midface hypoplasia, trident hand (fingers short, tapered, and splayed), and limited elbow extension are present, as described for the infant in the vignette. Respiratory compromise usually is absent. Radiographic features include progressive narrowing of the spinal canal, with short vertebral pedicles, lumbar lordosis, kyphosis, small iliac wings, short tubular bones, and short proximal and mid-phalanges. Among the associated complications of achondroplasia are obstructive apnea (hypotonia, midface hypoplasia, and large head), central apnea (brainstem compression due to small foramen magnum and hydrocephalus), hydrocephalus (brainstem compression), and hyperreflexia of the lower extremities (spinal cord stenosis within the lumbar vertebra). Long-term problems include obesity, lumbar lordosis, bowlegs, thoracolumbar gibbus, symptomatic spinal cord compression, and short stature. Intelligence usually is normal. The diagnosis is established by characteristic clinical and radiographic findings and molecular genetic testing for mutation in the FGFR3 gene located on chromosome 4p16.3. In 98% of patients, the mutation is a Gly380Arg substitution, resulting from a G-to-A point mutation at nucleotide 1138 of the FGFR3 gene. In 1% of patients, a G-to-C point mutation at nucleotide 1138 of the FGFR3 gene causes the disorder. These mutations affect the transmembrane domain of the FGFR3 gene. Although more than 80% of affected infants have de novo mutations, with both parents being unaffected, autosomal dominant inheritance is characteristic. Therefore, the offspring of an affected individual have a 50% risk of having the disorder. Older paternal age may contribute to de novo mutations of the FGFR3 gene. If both parents have achondroplasia, the risk of normal stature is 25%, heterozygous achondroplasia is 50%, and homozygous achondroplasia (lethal) is 25%.

Rare syndromes associated with FGFR3 gene mutations include two FGFR-related craniosynostoses and SADDAN dysplasia. Seven FGFR-related craniosynostosis syndromes have been characterized by craniosynostosis, variable hand and feet abnormalities, and distinctive facial features; clinical presentations vary in severity. Two of these syndromes are associated with FGFR3 mutations on chromosome 4p16.3: Muenke syndrome and Crouzon syndrome with acanthosis nigricans. The other FGFR-related craniosynostoses include those whose genetic defects are located in FGFR1 (Pfeiffer syndrome) and FGFR2 (Crouzon syndrome, Jackson-Weiss...
Muenke syndrome is rare; the incidence is unknown. Phenotype-genotype variability exists, with some individuals being identified only after the birth of a phenotypically affected child. The characteristic physical findings include unilateral or bilateral coronal craniosynostosis and/or megalencephaly, midface hypoplasia, ocular hypertelorism, carpal-tarsal fusion (diagnostic if present), brachydactyly, carpal bone malsegregation, and coned epiphyses. Intellectual function is normal. A point mutation (P252R) in the \textit{FGFR3} gene is found with this syndrome. Although megalencephaly and midfacial hypoplasia are seen with Muenke syndrome, craniosynostosis is not evident. Furthermore, the shortened limbs and fingers and limited elbow extension of the infant in the vignette are not found in Muenke syndrome. Crouzon syndrome with acanthosis nigricans is characterized by proptosis, strabismus, mandibular prognathism, normal-appearing extremities with radiographic shortening of the metacarpal and phalangeal bones, and acanthosis nigricans. Intelligence is normal. An A391E mutation at the \textit{FGFR3} gene is responsible for this disorder.

Hypochondroplasia usually is not evident at birth, and it may be difficult to diagnose during the neonatal period because the rhizomelic limb shortening and frontal bossing are mild. They become increasingly apparent with age. The prevalence is approximately 1 in 200,000 births. Midface hypoplasia and abnormalities of the hands and spine are mild if they are present. Mental retardation is present in fewer than 20% of cases. Bowed legs and inversion of the feet due to the long fibula can cause chronic pain and genu varum. Radiographic features include short and widened diaphyses and flared metaphyses of the long bones and long fibula. Interpedicular distance narrows in the lumbosacral spine. Hypochondroplasia is diagnosed based on clinical findings and confirmed using genetic testing. Inheritance is autosomal dominant, and, similar to achondroplasia, the phenotype is consistent within families and older paternal age is associated with de novo mutation of the \textit{FGFR3} gene. Several gene mutations have been identified in patients who have hypochondroplasia, but most cases are associated with two \textit{FGFR3} N540K mutations that result in a lysine-to-asparagine substitution at codon 540.

\textbf{SADDAN dysplasia} has a more severe presentation than described for the infant in the vignette and includes tibial bowing and acanthosis nigricans. Additionally, \textbf{SADDAN dysplasia} is rare compared with achondroplasia. This rare severe variant of achondroplasia is characterized by extremely short stature, severe tibial bowing, profound developmental delay, and acanthosis nigricans. Obstructive apnea may complicate the course. Unlike patients who have thanatophoric dysplasia, survival beyond infancy has been reported. An \textit{FGFR3} K650M mutation has been identified in affected patients.

Thanatophoric dysplasia is another rare bone disorder due primarily to mutations in the \textit{FGFR3} gene. This disorder generally is lethal, although rare survivors have been reported who have profound developmental abnormalities and severe short stature. Death usually results from a small thoracic cage and respiratory compromise. Clinical findings include megalencephaly, brain malformations, hydrocephalus, hypotonia, short limbs, flat vertebra, and depressed nasal bridge. The eyes are protuberant, fingers are small and sausagelike, scapulae are small and square, and the pelvis is square and short. It is inherited in an autosomal dominant pattern. The \textit{FGFR3} mutations that cause thanatophoric dysplasia affect the extracellular domain of \textit{FGFR3} (type I) and the intracellular domain of \textit{FGFR3} (type II).

References:


Content Specifications:
Recognize clinical features associated with autosomal dominant disorders

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

Know the long-term outcome and survival of infants with various congenital abnormalities
A term newborn is delivered vaginally following a breech presentation. Physical examination of the hips reveals decreased abduction but no asymmetry of the gluteal and thigh folds. The Barlow test is positive for bilateral subluxation of the hips.

Developmental dysplasia of the hip is MOST likely to occur in

1. African-American infants
2. both hips rather than one hip
3. first-born infants
4. infants of diabetic mothers
5. male infants

You selected 4, the correct answer is 3.

Developmental dysplasia of the hip (DDH) comprises a spectrum of abnormalities involving the hip joint. At the mild end of the spectrum, the hip joint can be subluxed, and at the severe end, it is dislocated fully. In the subluxable hip, the femoral head is located within the acetabulum at rest, but it can be dislocated with a provocative maneuver, such as the Barlow test. In the dislocated hip, the femoral head is out of the acetabulum at rest, but it can be placed back into a normal position with another provocative maneuver, such as the Ortoloni test. Asymmetry of gluteal and thigh skinfolds is a sensitive but nonspecific indicator of subluxation of the hip if the disease is unilateral. Decreased abduction of the hip also is a sign of DDH and warrants further evaluation.

DDH occurs more commonly in first-born infants and is inherited as a multifactorial trait. It is unilateral in 80% of cases, with the left side involved more commonly than the right. The reason for the increased susceptibility of the left hip is unknown.

DDH is four to six times more common among female than male infants, and it is more prevalent among Caucasian than African-American infants. The incidence is estimated at 1 per 1,000 live births in the Caucasian population and 1 per 5,000 live births in the African-American population. The explanation for these gender and ethnic differences is unclear.

The risk of major congenital malformations is increased among infants born to mothers who have type 1 diabetes mellitus. However, the only musculoskeletal malformation associated with maternal diabetes mellitus is the caudal regression syndrome.

References:

Content Specification(s):
Know the causes of maternal and neonatal complications and the management of abnormal presentations, such as breech, shoulder dystocia, etc.
Please remember that you must answer all 10 of the questions in order to claim CME credit for this month.

A 3.5 kg infant who was born at home has angulation deformities of the lower extremities. Radiographic studies reveal multiple fractures.

Of the following, the MOST likely cause of this infant's fractures is

<table>
<thead>
<tr>
<th></th>
<th>achondroplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>birth trauma</td>
</tr>
<tr>
<td>3</td>
<td>hypophosphatasia</td>
</tr>
<tr>
<td>4</td>
<td>intrauterine compression</td>
</tr>
<tr>
<td>5</td>
<td>osteogenesis imperfecta</td>
</tr>
</tbody>
</table>

You selected 5, the correct answer is 5.

The finding of multiple fractures in a newborn almost always is associated with osteogenesis imperfecta (OI), a class of disorders that result from defects in collagen synthesis. OI type III, which can occur in both autosomal dominant and autosomal recessive forms, presents with multiple fractures at birth in an infant who usually is born at or near term. Some affected infants will have prenatal longitudinal growth deficiency. Blue sclerae also may be evident in the neonatal period, and skull radiographs may reveal the presence of wormian bones (undermineralized calvarium), although this finding may not be evident for several weeks or months. All affected patients experience poor growth and progressive kyphoscoliosis that leads to respiratory compromise in most cases. Early mortality can be due to severe skeletal deformity, pulmonary hypertension, and cardiac failure. The underlying defect is the mutation of one of two genes, COL1A1 or COL1A2, which encode the pro-a-1(I) and pro-a-2(I) chains of type I collagen. The recessive form of OI type III is less common, except among South African blacks. In most families, recurrence has been rare, suggesting that most cases result from new dominant mutations. Prenatal identification of affected fetuses by ultrasonography is possible.

Achondroplasia, the most common chondroplasia, presents in the newborn period with reduced longitudinal growth, short limbs, and macrocephaly. Fractures are not present. Birth trauma is unlikely to result in fractures of both lower extremities. Hypophosphatasia is an autosomal recessive disorder that results from the deficiency of alkaline phosphatase. It is characterized by lack of ossification and presents with bowed extremities and thoracic skeletal abnormalities that usually lead to respiratory insufficiency and death in the newborn period. Intrauterine compression can cause deformations, including clubfoot, but not skeletal fractures.

References:

Content specification(s):
Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc.
You are consulted by a perinatologist regarding a fetus found to have dolichocephaly on an ultrasonogram. The family is inquiring about the possibility of other abnormalities in the infant and the perinatologist asks you to meet with them.

Of the following, the MOST common clinical pattern associated with dolichocephaly is:

1. Apert syndrome
2. Crouzon syndrome
3. Nonsyndromic craniosynostosis
4. Pfeiffer syndrome
5. Saethre-Chotzen syndrome

You selected 3, the correct answer is 3.

The cranium develops beginning about 5 weeks into gestation when the mesenchymal tissue from the area of the notochord forms cartilaginous plates which grow, ossify, and fuse to form most of the cranial base. The mesenchyme enveloping the developing brain forms five primary ossification centers (two frontal, two parietal, and one occipital) which grow radially. Sutures form where two of these centers meet. Fontanelles form at the junction of bone from three or more centers. The patency of the sutures is most affected by the biology of the dura rather than by the osteogenic activity of the cranial bones. Proximity to the dura results in suture growth in response to growth of the underlying soft tissues, such as the brain. A number of studies have related dural abnormality to suture closure. Incomplete dural development in microcephaly contributes to absence of sutures in some cases of microcephaly. Metopic suture closure is associated with abnormal dural anatomy in holoprosencephaly. By the time of birth, the neurocranium has achieved 63% of its ultimate growth. At ages 1 and 10 years, 88% and 95% of ultimate brain growth has occurred, respectively, and growth is complete by 16 years of age. Although all sutures are clinically closed by 6 to 12 months of age, complete ossification does not occur until after 30 years.

Craniosynostosis occurs in about 1 case per 2,000 to 3,000 births. Primary craniosynostosis lacks association with any identifiable cause and is the most common form. These cases of craniosynostosis are nonsyndromic and may have single- or multiple-suture involvement, usually affecting the shape of the cranium and lacking facial, limb, or peripheral abnormalities (Table 1).
Of the single-suture varieties, sagittal synostosis constitutes 35% of cases and is characterized by increased anterior-posterior growth of the head (parallel to the affected suture) resulting in scaphocephaly, also called dolichocephaly. The presence of dolichocephaly makes nonsyndromic craniosynostosis most likely for the infant in the vignette. Unilateral coronal synostosis is noted among 15% of cases and results in plagiocephaly, or sloping of the calvarium due to disproportionate growth between the sides of the calvarium. Metopic synostosis constitutes 5% of cases and results in trigonocephaly, with a keel-like ridge notable in some patients.

Nonsyndromic craniosynostosis may also involve multiple sutures, resulting in characteristic distortions of the calvarium. Bilateral coronal synostosis is characterized by brachycephaly, an anterior-posterior shortening of the skull and increased bitemporal diameter. Oxyccephaly results from a combination of closures at the sagittal, coronal, and lambdoid sutures. When brachycephaly is present, careful examination of the facial features, extremities, and other organs is important, because brachycephaly is associated with many of the syndromic forms.

Table 1. Nonsyndromic Craniosynostosis

<table>
<thead>
<tr>
<th>Nonsyndromic</th>
<th>Cranial Suture Involved</th>
<th>Facial Growth Not Affected</th>
<th>Limbs Usually Normal</th>
<th>Evaluate for Intracranial Hypertension</th>
<th>Mental Usually normal</th>
<th>Sporadic, with 10% to 14% Recurrence Risk</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaphocephaly or dolichocephaly</td>
<td>Sagittal</td>
<td>None</td>
<td>None</td>
<td>18% intracranial hypertension</td>
<td></td>
<td>Most common. 1 in 1000 births. M:F is 4:1. Up to 10% may be Autosomal dominant.</td>
<td></td>
</tr>
<tr>
<td>Brachycephaly</td>
<td>Bilateral coronal</td>
<td>None</td>
<td>None</td>
<td>30% intracranial hypertension</td>
<td></td>
<td>Female predominance</td>
<td>Must evaluate for Muenke syndrome</td>
</tr>
<tr>
<td>Anterior plagiocephaly</td>
<td>Unilateral coronal</td>
<td>None</td>
<td>None</td>
<td>12% intracranial hypertension</td>
<td></td>
<td>Female predominance</td>
<td></td>
</tr>
<tr>
<td>Trigonocephaly</td>
<td>Metopic</td>
<td>Vertical keel on forehead</td>
<td>Evaluate for intracranial abnormality (holoprosencephaly, absent corpus callosum)</td>
<td></td>
<td></td>
<td>Male predominance</td>
<td></td>
</tr>
<tr>
<td>Posterior plagiocephaly</td>
<td>Unilateral lambdoid fusion with rhomboidal head shape</td>
<td>Flattened occiput, inferior and posterior displacement of ipsilateral ear</td>
<td>None</td>
<td>Present at birth</td>
<td></td>
<td>True lambdoid, synostosis only 3% of craniosynostoses</td>
<td></td>
</tr>
<tr>
<td>Deformational plagiocephaly</td>
<td>Positional effect with parallelogram head shape</td>
<td>Flattened occiput, anterior displacement of ipsilateral ear</td>
<td>Usually normal at birth, shape of head changes due to positional effect</td>
<td></td>
<td></td>
<td>True lambdoid, synostosis only 3% of craniosynostoses</td>
<td></td>
</tr>
</tbody>
</table>
of craniosynostosis. Muenke’s syndrome is possible with isolated brachycephaly or unilateral anterior plagiocephaly. Therefore, testing for the fibroblast growth factor receptor 3 (FGFR3) gene is recommended for all cases of brachycephaly because of the inheritance potential. Although most cases of nonsyndromic craniosynostosis are sporadic, familial occurrence is noted in 4% to 10% of patients, suggesting a potential genetic contribution.

Secondary causes of craniosynostosis include external factors and internal factors. Compression of the fetal head has been implicated in some cases, albeit not commonly. Internal factors include a number of teratogens and maternal metabolic disorders (Table 2).

Table 2. Some Internal Factors Associated with Craniosynostosis

<table>
<thead>
<tr>
<th>Teratogens</th>
<th>Maternal Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminopterin</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Diphenylhydantoin</td>
<td>Rickets</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Hurler syndrome</td>
</tr>
<tr>
<td>Oxymetazoline hydrochloride</td>
<td>Morquio syndrome</td>
</tr>
<tr>
<td>Isotretinoin (possibly)</td>
<td>Beta-glucuronidase deficiency</td>
</tr>
<tr>
<td></td>
<td>Mucolipidosis III</td>
</tr>
</tbody>
</table>

Craniosynostosis also may result from lack of mechanical stretch forces, as seen with shunted hydrocephaly or microcephaly.

Craniosynostosis has been associated with more than 70 malformation syndromes. Some features of the more common syndromes are summarized in Table 3. In contrast to sporadic craniosynostosis, studies of the syndromic forms have yielded significant genetic and molecular biological information. Abnormalities of the FGFR genes have been described in a number of the syndromic forms of craniosynostosis, but findings of FGFR studies among patients with nonsyndromic disease are similar to those seen in unaffected individuals. The syndromic forms have a high likelihood of abnormalities of facial development or involvement of the cranial base; some have associated abnormalities of the extremities or of the upper respiratory, urogenital, cardiovascular, gastrointestinal (anal), or central nervous systems.

Although most syndromes associated with craniosynostosis have autosomal dominant inheritance, some have autosomal recessive, x-linked dominant, or other patterns. Some of the specific genetic abnormalities are included in Table 3.

Table 3. Syndromic Craniosynostosis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Synostosis</th>
<th>Facial Features</th>
<th>Extremities</th>
<th>Other Significant Features</th>
<th>Mental Performance</th>
<th>Inheritance</th>
<th>Genetic Mutation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antly-Bixler</td>
<td>Brachycephaly, may be trapezoidcephaly</td>
<td>Frontal bossing, depressed nasal bridge, midfacial hypoplasia, dysplastic ears</td>
<td>Radiohumeral synostosis, multiple joint contractures (fingers, wrists, knees, ankles), tapering fingers, rocker-bottom feet</td>
<td>Severe respiratory compromise (with death or tracheotomy)</td>
<td>Probably normal</td>
<td>FGFR2 gene mutations at</td>
<td></td>
</tr>
<tr>
<td>Apert</td>
<td>Acrocephaly, brachycephaly or turricephaly-coronal</td>
<td>Flat facies, hypertelorism, Syndactyly</td>
<td>Upper airway</td>
<td>Mental retardation, usually associated with Autosomal dominant, most cases sporadic, advanced</td>
<td>FGFR2 gene mutations at</td>
<td>FGFR2 gene mutations at</td>
<td></td>
</tr>
<tr>
<td>Syndrome</td>
<td>Craniofacial Features</td>
<td>Other Features</td>
<td>Genetics</td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baller-Gerold</td>
<td>All patients have craniosynostosis of any or all sutures</td>
<td>Low set ears and/or micrognathia</td>
<td>Autosomal recessive</td>
<td>1 in 55,000 births</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpenter</td>
<td>Brachycephaly with coronal, variable sagittal and lamboid</td>
<td>Shallow supraorbital ridges, flat nasal bridge, hypoplastic maxilla or mandible</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniofrontonasal dysplasia</td>
<td>Females: Coronal with brachycephaly; Males: craniosynostosis rare.</td>
<td>Hypertelorism, facial asymmetry, broad nasal root, bifid nasal tip</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crouzon</td>
<td>Brachycephaly, trigonocephaly or oxycephaly-coronal (most), lamboid, metopic and/or sagittal</td>
<td>Frontal bossing, ocular proptosis, hypertelorism, hypoplastic maxilla</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muenke</td>
<td>Brachycephaly due to coronal, either uni- or bilateral</td>
<td>Mild maxillary hypoplasia, hypertelorism</td>
<td>Autosomal dominant, variable expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfeiffer Type I</td>
<td>Brachycephaly with coronal, sometimes sagittal</td>
<td>Full, high forehead, hypertelorism, proptosis, small nose-low nasal bridge, narrow maxilla</td>
<td>Autosomal dominant, incidence is 1 in 200,000 births</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfeiffer Types II and III</td>
<td>Cloverleaf skull with coronal, sagittal, lamboid and basilar synostosis</td>
<td>Kleeblattschadel (cloverleaf) shape with severe proptosis</td>
<td>Autosomal dominant, incidence is 1 in 200,000 births</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brachycephaly with coronal,</td>
<td>High flat forehead, low</td>
<td>Autosomal dominant, variable expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* (acrocephalosyndactyly) (common), irregular of others.
* maxillary hypoplasia
* compromise
* Radial aplasia, absent or hypoplastic thumbs, missing wrist and hand bones, fused carpels
* Anal anomalies 40%, urogenital anomalies 35%, mortality 25% in first year
* Mental deficiency in 50%
* IQ range from 52 to 104. Mental delay not seen in all cases
* Variable Unaffected X-linked dominant Xp22
* Variable, may relate to effect of intracranial pressure, up to 60% have intracranial hypertension
* Variable due to marked variability of expression
* May have brachydyactyly, clinoactyly, thimblelike middle phalanges, carpal/tarsal fusion, broad hallices
* May have ptosis, hearing loss
* Hands and feet more affected with FGFR2 mutations
* Hands and toes, elbow ankylosis, or synostosis
* Severe central nervous system involvement
* Upper airway abnormality, high early mortality
* Cutaneous syndactyly
* Normal to near normal
* Most normal, Autosomal dominant, variable expression
* Single point mutation of FGFR3 gene on 4p
* Mutations of FGFR1 (Pro252Arg) at 8p11.22-p12 and FGFR2 at 10q25-10q26
* 90% associated with FGFR2 mutations on 10q25-10q26
* As in Pfeiffer I
* Mutations of TWIST gene at 7p21-p22. Deletions at 7p21-p22
* Mutations of FGFR1 (Pro252Arg) at 8p11.22-p12 and FGFR2 at 10q25-10q26
* 90% associated with FGFR2 mutations on 10q25-10q26
* As in Pfeiffer I
* Mutations of TWIST gene at 7p21-p22. Deletions at 7p21-p22

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saethre-Chotzen</td>
<td>lambdoid, and/or sagittal synostosis (craniosynostosis is variable in this syndrome), frontal hairline, facial asymmetry, hypertelorism, ptosis of eyelids, 2 and 3 fingers or 3rd and 4th toes, Brachydactyly, clinodactyly, Short clavicles, some with mild full to moderate mental deficiency, some with moderate full to moderate mental deficiency, with wide variance in expression, 7p21.1 add significant learning difficulties to features of the syndrome</td>
</tr>
</tbody>
</table>

Adapted from references cited below.

Although increased intracranial pressure may occur in both forms of craniosynostosis, it occurs more often among patients with syndromic craniosynostosis and its presence is associated with greater neurodevelopmental risk. Treatment options are complicated and are discussed at some length in the references.

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:


American Board of Pediatrics Content Specification(s):

Recognize the clinical features of the syndromes associated with craniosynostosis
A term baby is delivered to a mother whose history is remarkable for the diagnosis of systemic lupus erythematosus (SLE) four years ago and for documented presence of anti-Ro and anti-La antibodies. The baby has Apgar scores of 7 and 7 at 1 and 5 minutes, respectively. He is noted to have a resting heart rate of 55 bpm to 67 bpm. He is otherwise comfortable. There is no respiratory distress and no sign of congestive heart failure. The blood pressure is 74 / 49 mmHg. An echocardiogram reveals normal anatomy and cardiac function.

Of the following, the MOST accurate statement regarding neonatal lupus erythematosus (NLE) is that:

1. Among anti-Ro-positive women, the risk of having a baby with NLE is low.
2. Children who had NLE uniformly develop autoimmune disease later in life.
3. Major clinical manifestations of NLE are transient.
4. Most babies with NLE have involvement of multiple organs.
5. Nearly all mothers of babies with NLE have symptoms of autoimmune disease at delivery.

You selected 4, the correct answer is 1.

The infant in this vignette has neonatal lupus erythematosus (NLE), an uncommon autoimmune disease occurring in a small subset of infants whose mothers have anti-Ro and anti-La autoantibodies. These autoantibodies cross the placenta and are pathogenic. The major clinical findings are cutaneous, cardiac, hepatobiliary, and hematologic. However, in most babies, only one organ is affected (Table 1).
Cutaneous findings were the first NLE findings recognized, and it is these findings that give NLE its name. The usual onset of cutaneous disease is a few days or weeks after birth, although in some cases lesions are present at birth. Cutaneous lupus lesions resolve spontaneously within weeks or months, occasionally leaving residual dyspigmentation but more often leaving no marks. Females are somewhat more likely to be affected than males. The characteristic cutaneous lesion is an annular or polycyclic erythematous plaque. Individual annular lesions are often about 1 cm in diameter, but there may be extensive confluent erythema, especially around the eyes, giving a "raccoon-eye" or "owl-eye" appearance. The head almost always is affected, but lesions also are common on the trunk and extremities. In many children, lesions are initiated or exacerbated by sun exposure. Of all NLE manifestations, only the cutaneous lesions are characteristic of the lesions seen in adult lupus. A second, less common cutaneous lesion is telangiectasia that may not resolve. The diagnosis of cutaneous NLE often is made on a clinical basis in a child whose mother has anti-Ro, anti-La, or in selected cases, anti-U1RNP autoantibodies. Only a third of children with cutaneous lupus have other organ system involvement. There are no clinical clues or laboratory test that can predict accurately the babies who will have multiple organ involvement. Only a third of children with cutaneous lupus have other organ system involvement. There are no clinical clues or laboratory test that can predict accurately the babies who will have multiple organ involvement.

NLE is the most common cause of isolated complete congenital heart block, which usually begins in the second or third trimester of pregnancy. The initial finding may be first-, second-, or third-degree heart block, but almost all cases ultimately progress to third-degree heart block. Once complete heart block is established, it is permanent, as the atrioventricular nodal area is replaced by scar tissue. Although some babies are able to compensate for the slow heart rate, most require a pacemaker. In some babies, dilated cardiomyopathy also occurs and is frequently life-threatening. Cardiomyopathy usually is evident at birth or shortly thereafter, but a few cases have developed a few months after birth. Heart block and cardiomyopathy are the most characteristic manifestations of cardiac NLE. However, other less clinically significant abnormalities have been observed. In a study of 21 anti-Ro-positive infants with no other evidence of cardiac disease, nine had transient QT interval prolongation. Another study of 78 anti-Ro/La-positive infants noted sinus bradycardia in three children. There is no gender predominance in cardiac NLE. In a large series reported by the NLE Research Registry United States, the mortality rate of cardiac NLE was 20%. As with cutaneous NLE, most babies with cardiac NLE have no other organ systems affected. In about 10% of cases reported, cardiac and cutaneous NLE may be present in the same individual.
Unlike cutaneous and cardiac NLE, hepatobiliary NLE seems to occur infrequently as the sole manifestation of NLE. Three major phenotypes have been reported:

1. fulminant liver failure presenting at or shortly after birth,
2. cholestasis with direct hyperbilirubinemia but minimal transaminase elevations occurring as a transient, but sometimes rather dramatic, phenomenon at a few weeks after birth, and
3. otherwise unexplained transient mild to moderate transaminase elevations occurring a few weeks or months after birth.

Autopsy findings in babies with fulminant liver failure have shown iron deposition as in neonatal hemochromatosis.

Thrombocytopenia has been noted in about 10% of children with other manifestations of NLE, but it occurs infrequently as the sole manifestation of NLE. Thrombocytopenia usually is clinically silent. There are a few reports of neutropenia, anemia, and recurrent pancytopenia.

Diagnosis of NLE usually is established by a compatible clinical picture and NLE-associated autoantibodies in maternal or infant sera. Almost all contain antibodies to the Ro, or SSA, 60-kDa protein. Autoantibodies to 60-kDa Ro frequently coexist with autoantibodies to La (also called SSB), and especially with autoantibodies to 52 kDa Ro. The presence of any of these three autoantibodies fulfills the autoantibody requirement for diagnosis. In a small number of babies with cutaneous NLE, autoantibodies to U1RNP are present when autoantibodies to Ro and La proteins are absent. Assays for anti-Ro, La, and U1RNP are commercially available. Other autoantibodies for which there may not be readily available assays have been described in NLE sera.

Children who had NLE may be expected to have at least a modestly increased risk of developing autoimmunity later in life, if for no other reason than their family history of autoimmunity (mothers with autoantibodies). The magnitude of the risk is not yet known. In a report from the NLE Research Registry/US, 49 children who had NLE and their 45 unaffected siblings, all older than age 8 years, were tested for autoantibodies and queried on development of autoimmune symptoms or disease. Seven of the 49 children who had had NLE developed autoimmune or possible autoimmune disease, most of them by age 12. Two of their 45 siblings had positive antinuclear antibodies, although none had symptoms. Although more information is needed, it appears there may be significant risk for the development of autoimmune disease, even in childhood, among individuals who had NLE.

Mothers who have had a child with NLE may be considered to have autoimmunity, as they have circulating autoantibodies, but 50% are asymptomatic when the NLE diagnosis is made. Long-term followup studies by several groups have shown that even the initially asymptomatic women eventually develop signs and symptoms of autoimmune disease, particularly Sjögren's syndrome, systemic lupus erythematosus, and undifferentiated connective tissue disease.

There is a clear association between NLE and the SS-A/Ro or SS-B/La autoantibodies in the mother. The antibodies are of the immunoglobulin (Ig) G class and can, therefore, cross the placental barrier and enter the fetal circulation. The timing of the antibody transfer is unknown, although onset has been reported as early as the 16th weeks of gestation. Antibodies are present in the neonatal circulation for up to three months after birth. The risk for having a baby with NLE among unselected anti-Ro-positive women is low, perhaps about 2%. Some other factor, such as human leukocyte antigen (HLA) type, in utero environment, or timing of antibody transfer to the fetus may be necessary for NLE development. It is not known whether the risk is higher for symptomatic anti-Ro-positive women. For women who have had a baby with NLE, the risk of having another affected child ranges widely but is about 25%. Although the disease process in NLE itself is transient, cardiac NLE in particular may be life-threatening or permanently
disabling.

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References:


Content Specification(s):

Identify the effects of maternal immunologic diseases, including transplacental passage of immunoglobulins, and their management and treatment on the fetus

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

Understand the physiologic consequences of a dysrhythmia in a newborn infant

Plan appropriate management of dysrhythmia in a newborn infant, including noninvasive and invasive management of electrophysiologic disturbances, and understand the potential adverse effects of approaches and drugs used

Understand the pathophysiology, natural history, and clinical features of conduction pathway abnormalities and other dysrhythmias
A 13-day-old male infant has diffuse swelling of the left leg and thigh and increased resistance to movement of that extremity. He was Rh(D)-positive and was born at 35 weeks' gestation by cesarean section due to early fetal hydrops and frank breech presentation. This is the mother's fourth pregnancy, and she is Rh(D)-negative and sensitized. The infant had anemia and hyperbilirubinemia at birth followed by a rapidly rising serum bilirubin concentration. He was treated with two double-volume exchange transfusions using the left umbilical artery and vein, which corrected the anemia. Thereafter the bilirubin concentration was controlled with phototherapy. An intravenous infiltration in the left leg occurred on day 12. Vital signs are within normal limits, including an axillary temperature of 37.3°C. Physical examination reveals an alert, pink infant, in no apparent distress, who consumed a full feeding per nipple eagerly. White blood cell count is 17,000/mm³; differential count shows 65% neutrophils and no excess of immature forms. Ultrasonography of the hip shows widening of the joint space and soft tissue swelling.

Of the following, the BEST course of management for this infant is to:

1. Apply a splint to keep the hips in abduction.
2. Aspirate the hip joint.
3. Give diuretic therapy and elevate the limb.
4. Observe for systemic signs of sepsis.
5. Repeat imaging study in 7 to 10 days.

You selected 3, the correct answer is 2.

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Two distinct clinical syndromes have been described in newborn infants with suppurative bone and/or joint infections. The most common is the "benign form," in which systemic signs of sepsis are not evident (including the leukocyte count and differential), and the findings are limited to swelling with or without tenderness and/or limited movement in the affected limb. A "severe form" presents with systemic signs of sepsis, after which local bone or joint involvement is discovered. The infant in this vignette displays the classic signs of the benign form.

The infant in this vignette has suppurative arthritis of the hip and could have osteomyelitis of adjacent bone. Although he lacks signs of systemic illness, the combination of lack of
motion, swelling, and joint-space widening on ultrasonography strongly suggest septic arthritis and warrant direct aspiration of the joint. Septic arthritis is thought to be initiated by a transient bacteremia. The prevalent organisms found in bacteremia tend to cause septic arthritis, although gram-positive organisms, especially *Staphylococcus aureus*, predominate. However, *Candida* species and gram-negative organisms, including *Neisseria gonorrhoea*, also can be the cause. The factors predisposing to septic arthritis seen in this vignette include prematurity, breech presentation, prior use of umbilical catheters, and male sex.

Successful treatment of major suppurative bone or joint disease in the newborn depends on

- prompt recognition and identification of the offending organism,
- prompt drainage of any significant collection of pus (open drainage is usually required for hip and shoulder disease to preserve the osteal head), and
- specific and adequate intravenous antibiotic treatment based upon measures of antibiotic sensitivity.

For these reasons, direct aspiration of joint fluid is needed in addition to cultures done in a general evaluation for sepsis. The adequacy of therapy can be determined thereafter with serial measurements of C-reactive protein or of erythrocyte sedimentation rate.

Splinting of the affected extremity can help preserve circulation and reduce pain. Although this symptomatic management may be included in the infant’s therapy, splinting alone is not sufficient therapy for the infant in this vignette. Breech presentation also is associated with congenital hip dysplasia. This problem is more common in first-born infants and in girls. It is rarely symptomatic in the newborn period and is not associated with local swelling. It can be detected with specific physical maneuvers. Splinting is used in this condition, but hip dysplasia is unlikely to be the problem in this vignette.

Diuretic therapy is not indicated for localized swelling. One should attempt to find the cause of the swelling and treat it more specifically.

Given that the infant in this vignette is at risk for septic arthritis and is manifesting signs consistent with the syndrome, expectant management would lead to an undue delay in treatment and worsened prognosis. Delay of specific treatment might increase the risk of loss of an osteal head, extension of disease into bone and surrounding tissues, necrosis of bone, and long-term orthopedic problems.

The infant in this vignette does not have signs of systemic sepsis. Without the localizing signs and the confirming imaging study, an isolated workup for sepsis would not be indicated. With the local signs, the workup is used as an adjunct and definitely is indicated to identify the specific organism causing the joint infection as well as finding other possible sites of infection. If joint aspiration and culture do not yield the organism, blood or cerebrospinal fluid might.

A radiograph of the femur in 7 to 10 days might confirm that osteomyelitis was also present by demonstrating foci of bone necrosis or rarefaction and/or calcification of elevated periosteum. Neonates can have one or more of these signs in 7 to 10 days, whereas radiographic signs of osteomyelitis in older children may not appear for up to 3 weeks. Delaying direct joint evaluation pending serial imaging would not be appropriate for this infant.
Do you want to add anything to your Learning Plan?
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References:


American Board of Pediatrics Content Specification(s):

Understand the causes of osteomyelitis and septic arthritis

Understand the clinical and laboratory features and differential diagnosis of osteomyelitis and septic arthritis

Understand the treatment of osteomyelitis and septic arthritis

Understand the complications of osteomyelitis and septic arthritis
You are examining a newborn infant with an unusual head shape (Figure 1).

Figure 1: View of the top of head of the infant who is in a supine position.

The infant was born after an uncomplicated delivery by repeat cesarean section and appears clinically healthy.

Of the following, the cranial suture(s) MOST affected by synostosis in the infant in this vignette is (are) the:

1. coronal
2. lambdoidal
3. metopic
4. multiple
5. sagittal

You selected 4, the correct answer is 1.

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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 (ie, premature fusion of the sutures of the skull) or deformational plagiocephaly.
Craniosynostosis may be either a primary disorder or one secondary to other precipitating illnesses or pathobiologic factors. Secondary craniosynostosis is associated with factors that alter the membranous growth of the cranial bones, such as rickets, hyperthyroidism, glycogen storage disease, polycythemia vera, thalassemia, teratogens, and intrauterine constraint. In addition, craniosynostosis may be isolated or associated with congenital anomalies. Nonsyndromic, or simple, craniosynostosis occurs when there is isolated fusion of one or more cranial sutures that causes cranial and facial abnormalities. 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%, 3:1 male predominance) and coronal (25%, slight female predilection) sutures. Multiple suture synostoses occur in 15% of cases. Metopic and lambdoidal synostosis are unusual. Although most nonsyndromic synostosis cases are sporadic, 10% of coronal and 2% of sagittal synostosis are familial. Syndromic craniosynostosis is defined by the presence of closed sutures, facial dysmorphism, and skeletal and extraskeletal malformations. The prevalence of syndromic craniosynostosis is estimated to be a fraction of craniosynostosis cases (10% to 20%). Of note, the extent of sutural fusion varies amongst individuals. Thus, the degree of abnormality of head shape and facial dysmorphism will also vary.

The development, differentiation, and pathobiology of the membranous neurocranium that leads to craniosynostosis are not well understood. The cranial bones are derived by membranous ossification from bony spicules in five primary ossification centers located in the paired frontal and parietal centers and a single occipital center. 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 twoossification 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 implicate 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 in this vignette has anterior plagiocephaly (oblique head) because of synostosis of the right coronal suture (Figure 2).

Figure 2: Plagiocephaly due to right coronal synostosis. View of the top of head of an infant who is in a supine position. Right coronal synostosis (double red line), compensatory growth (dotted red arrows) causing bossing of the contralateral forehead, and normal frontal cranial vault (dotted blue line) are indicated. (Adapted from Gorland RJ. [password required]. Accessed August 24, 2006.)
As a result of unilateral right craniosynostosis, growth of the right frontal bone is restricted so that it appears flattened, and compensatory growth of the contralateral frontal bone causes bossing of the contralateral forehead. Anomalies of the orbit and sutures of the cranial base (sphenozygomatic, sphenofrontal, sphenethmoidal sutures) are frequently associated with coronal craniosynostosis. The orbit on the side of the coronal synostosis is shallow, and the zygoma is shortened. The superolateral margin of the orbit is also elevated and positioned in a more posterior position than normal. The sutures of the cranial base comprise the "coronal ring" and abnormalities of these sutures alter the growth of the anterior cranial fossa. Because of the number of sutural and bony abnormalities associated with coronal synostosis, surgical correction is more involved and complex than anticipated from the clinical appearance alone. Coronal synostosis is more often found in female infants.

Lambdoidal craniosynostosis is an infrequent cause of posterior plagiocephaly. Right lambdoidal synostosis restricts and flattens the right side of the occipital bone (Figure 3).

Figure 3: Posterior plagiocephaly due to synostosis of the right lambdoidal suture. View of the top of head of an infant who is in a supine position. Right occipital synostosis (double red line), compensatory growth (dotted red arrows) causing protuberance of the contralateral occiput, and normal occipital cranial vault (dotted blue line) are indicated. (Adapted from Gorland RJ. http://gateway.ut.ovid.com/gw2/ovidweb.cgi [password required]. Accessed August 24, 2006.)

Compensatory growth of the contralateral side of the occipital bone may cause some protuberance of the contralateral occiput. Posterior plagiocephaly is more often caused by deformatinal events that occur in utero or during the first months after birth. Deformational plagiocephaly that presents at birth results from prenatal factors that cause pressure to be applied to the bones of the skull. Uterine anomalies (such as bicornuate uterus), uterine tumors, and uterine crowding due to multiple fetuses, a large fetus, or severe oligohydramnios are examples of such
factors. Skull deformations that develop after birth are usually the result of positioning. Posterior plagiocephaly has become more prevalent since 1992 when supine positioning during sleep in early infancy was recommended to reduce the risk of sudden infant death syndrome. Skull deformations also may occur after birth because of a behavioral preference for a particular position, torticollis, congenital disorders of the vertebrae (such as hemivertebrae or Klippel-Feil syndrome), or evolving craniosynostosis (especially with Crouzon syndrome and secondary to systemic disorders such as rickets and hyperthyroidism). Posterior plagiocephaly caused by lambdoidal craniosynostosis can be differentiated from deformational plagiocephaly by the presence of occipital flattening at birth and position of the ear (posterior and inferior position in lambdoidal craniosynostosis versus anterior position in deformational plagiocephaly). Lambdoidal craniosynostosis is also associated with the foramen magnum positioned toward the side of the affected suture whereas in deformational plagiocephaly the foramen magnum is placed normally.

Metopic craniosynostosis results in trigonocephaly (Figure 4).

Figure 4: Trigonocephaly due to synostosis of the metopic suture. View of the top of head of an infant who is in a supine position. Metopic synostosis (double red line), compensatory growth (dotted red arrows) causing protuberance of the forehead in the midline, and normal frontal cranial vault (dotted blue line) are indicated. (Adapted from Gorland RJ. http://gateway.ut.ovid.com/gw2/ovidweb.cgi [password required]. Accessed August 24, 2006.)

Metopic synostosis limits lateral growth of the frontal bones, and compensatory growth anteriorly causes protuberance of the forehead in the midline. Because the volume of the anterior cranial vault is lower than normal, the eyes are often closely set and lateral canthi are elevated. Temporal hollowing is commonly present. Some infants with trigonocephaly have associated malformations of the brain, including holoprosencephaly and agenesis of the corpus callosum. Males are more often affected than females.

A variety of head shapes can result when craniosynostosis affects multiple sutures. Although fusion of multiple sutures occurs frequently in syndromic craniosynostosis isolated involvement of more than one suture is not rare. Brachycephaly (short head) results when bilateral coronal and/or lambdoidal sutures are fused (Figure 5).

Figure 5: Brachycephaly due to synostosis of multiple sutures (bilateral coronal and lambdoidal sutures). View of the top of head of an infant who is in a supine position. Bilateral coronal and lambdoidal synostosis (double red lines), compensatory growth (dotted red arrows) causing protuberance of the head in the lateral and upward (inset) directions, and normal cranial vault (dotted blue line)
In the infant head shape depicted in Figure 5, both coronal and lambdoidal sutures are involved. The compensatory growth is lateral and upward. Turricephaly (towering head), acrocephaly (peaked head), oxycephaly (pointed head), hypsicephaly (high head), and kleeblattschadel (cloverleaf head) all result from fusion of multiple cranial sutures.

Synostosis of the sagittal suture results in scaphocephaly (boat head), dolichocephaly (long head), and clinocephaly (saddle head) (Figure 6).

Figure 6: Scaphocephaly due to synostosis of the sagittal suture. View of the top of head of an infant who is in a supine position. Saffittal suture synostosis (double red lines), compensatory growth (dotted red arrows) causing protuberance of the head in the anterior and posterior directions (see inset for lateral view), and normal cranial vault (dotted blue line) are indicated. (Adapted from Gorland RJ. [Link](http://gateway.ut.ovid.com/gw2/ovidweb.cgi) [password required]. Accessed August 24, 2006.)

Compensatory growth occurs in both anterior and posterior directions. The common physical features include frontal bossing, temporal narrowing, and occipital prominence. Associated anomalies, increased intracranial pressure, or
developmental delay are unusual.

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References:


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
You are called to the delivery of a term child whose mother has myasthenia gravis. She had been receiving immunosuppressant therapy during the first trimester, but improved in the second and third trimesters, as is typical with myasthenia gravis, and has not required any recent medications.

Of the following, the MOST likely effect of maternal myasthenia gravis on the newborn is:

1. arthrogryposis
2. cardiac failure
3. dysmorphic facies
4. normal muscle tone and activity
5. ventilator dependency

You selected 3, the correct answer is 5.

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Myasthenia gravis is a chronic autoimmune disease involving immunoglobulin G (IgG) antibodies against the nicotinic acetylcholine receptor of the neuromuscular junction. Its prevalence is between 50 and 125 cases per million population, and it is associated with 1 in 15,000 pregnancies. Neonates born to mothers with myasthenia gravis have a 10% to 20% probability of being affected; most newborns have normal muscle tone and activity.

A transient form of neonatal myasthenia syndrome can result from transplacental passage of the IgG autoantibodies from the mother. Newborns may have no symptoms in the first days after birth due to transplacental passage of maternal medications and high fetal and maternal concentrations of alpha-fetoprotein (which inhibits autoantibody binding to acetylcholine receptors). Symptoms may include hypotonia, decrease in spontaneous movements, poor feeding, and respiratory insufficiency. The diagnosis is suggested by high concentrations of antibodies to the acetylcholine receptor in the infant's blood, and by a decremental response to repetitive nerve stimulation on electromyography.

Treatment is most often symptomatic, with gavage feeding and respiratory management as needed, and occasionally with medication. Edrophonium is contraindicated because of the chance of cardiac arrhythmias, but other cholinesterase inhibitors (eg, prostigmine) may be helpful, especially in
establishing the diagnosis. The muscarinic effects of cholinesterase inhibitors, such as diarrhea, tracheal secretions, and abdominal distention, may need to be treated with atropine or atropinelike agents.

The prognosis of transient neonatal myasthenia gravis is good, with most affected children showing full recovery within 2 months. The children are not at any increased risk of exhibiting symptoms of myasthenia gravis later in life.

Arthrogryposis is seen in fewer than 2% of infants born to mothers with myasthenia gravis. Multiple joint contractures are nonprogressive and result from a lack of fetal movement causing an inhibition of normal joint development. There is a high risk of recurrence in subsequent pregnancies, independent of maternal symptoms or antibody levels.

Maternal myasthenia gravis has been reported to cause severe birth defects in a few newborns. The rare syndrome includes dysmorphic facies, arthrogryposis, abnormal genitalia, central nervous system atrophy, and lung hypoplasia.

A rare form of newborn myasthenia is permanent. This form is autosomal recessive and is caused by abnormalities of acetylcholinesterase or its receptor. Antinuclear antibodies are not found in this syndrome. There is no relation to maternal myasthenia gravis.

References:


American Board of Pediatrics Content Specification(s):

Know the effects on the fetus of maternal myasthenia gravis and its management

Understand the pathogenesis, evolution, management, and outcomes of neonatal arthrogryposis
A 12-week-old male infant, whose birthweight was 636 g and estimated gestational age at birth was 24 weeks, has a swelling in the right thigh. Physical examination reveals tenderness to touch, paucity of movement of right lower limb, and slight erythema of the skin. Prior clinical course is characterized by the development of bronchopulmonary dysplasia, chronic treatment with furosemide, and multiple episodes of feeding intolerance with need for prolonged parenteral nutrition. Family history is negative for inherited bone disease.

Laboratory serum data reveal:

- total calcium 9.6 mg/dL (2.4 mmol/L)
- ionized calcium 4.8 mg/dL (1.2 mmol/L)
- phosphorus 3.4 mg/dL (1.1 mmol/L)
- alkaline phosphatase 962 U/L (16 μkat/L)
- 25-hydroxyvitamin D 32 ng/mL (80 mmol/L)
- parathyroid hormone 35 pg/mL (35 ng/L)

A radiograph of the right lower limb reveals fracture of the femur (Figure 1).

**Figure 1: Fracture of right femur**

To understand the pathophysiology of bone disease in this infant, you analyze the biochemical markers of bone turnover (bone formation and bone resorption).

Of the following, the MOST sensitive and specific biochemical marker of bone formation is:

1. collagen pyridinium crosslinks
2. hydroxyproline
3. osteocalcin
4. procollagen I carboxy-terminal propeptide
5. tartrate-resistant acid phosphatase
The infant in this vignette has fracture of the right femur. Increased fragility of bones is the likely cause of this fracture, which might have occurred spontaneously or with handling of the infant during care. In the absence of family history of bone disease, the likely cause of increased fragility of bones in this infant is osteopenia and/or osteomalacia. These bone abnormalities are associated with the following:

- Extremely preterm infants with bronchopulmonary dysplasia
- Treatment with drugs such as furosemide and corticosteroids
- Deficient supply of minerals and vitamins
- Gastrointestinal malabsorption of nutrients
- Chronic liver disease with cholestasis
- Prolonged immobilization
- Parenteral nutrition–related toxicity from trace metals such as aluminum

The laboratory data in the infant in this vignette are consistent with hypophosphatemia. The elevated serum alkaline phosphatase concentration is indicative of, but not specific for, increased bone turnover.

Bone is a dynamic tissue; its formation and resorption are continuous processes that account for its constant turnover and remodeling. Bone formation is largely driven by osteoblasts, whereas bone resorption is mostly performed by osteoclasts. The osteoblasts, derived from mesenchymal precursor cells, function to synthesize the organic matrix of the bone (osteoid). Approximately 90% to 95% of the osteoid is composed of type I collagen. The incorporation of minerals (calcium, phosphorus, and others) into the osteoid accounts for mineralization of the bone. Normally, the inorganic mineral phase of the bone makes up about two thirds of the weight of the bone. The osteoclasts, derived from hematopoietic precursors of mononuclear phagocyte lineage, function to resorb the organic matrix of the bone.

The term osteopenia refers to a decreased amount of bone tissue. Structurally, osteopenia is characterized by decreased thickness of the bone cortex and/or decreased thickness or number of the bone trabeculae. Osteopenia is caused by either insufficient deposition or increased resorption of the organic bone matrix. The term osteomalacia refers to a decreased incorporation of minerals into the organic bone matrix. Functionally, osteomalacia is characterized by decreased bone mineral density and resultant increased fragility of the bone.

Bone matrix proteins or enzymes synthesized by osteoblasts or osteoclasts as well as osteoclast-generated degradation products of bone matrix serve as useful biochemical markers of bone formation and bone resorption. The concentrations of these markers in blood or urine depend on the amount of marker secreted during bone formation or released during bone resorption, on the peripheral metabolism of the marker, and on other biologic factors such as circadian variation. The usefulness of each marker depends on its specificity for bone and on the precision of its assay. Currently these markers are used in investigational settings and are not generally available to clinicians.

The most sensitive and specific biochemical marker of bone formation is osteocalcin. Osteocalcin, a gamma-carboxy-glutamic acid (GLA)–containing protein, also referred to as bone GLA protein, is synthesized and secreted by osteoblasts. The secretion of osteocalcin from its precursor, pro-osteocalcin, requires gamma-carboxylation under the influence of vitamin K. Circulating osteocalcin is metabolized mainly in kidneys and excreted in the urine. The serum concentration of osteocalcin correlates with both static and dynamic parameters of bone formation.
Procollagen I carboxy-terminal propeptide (PICP) is a soluble, trimeric, globular protein. Following its release into the circulation as type I collagen, it is assembled into fibers in the organic bone matrix. Although most type I collagen is found in the bone, it is not specific for bone, because significant amounts are found in soft tissue. Also, the current immunoassay for the measurement of PICP may not be optimal. Thus, the serum concentration of PICP does not have the specificity or the sensitivity to be a useful marker of bone formation.

Collagen pyridinium crosslinks are markers of bone resorption. These crosslinks are derived from complex amino acids, pyridinoline and deoxypyridinoline, which are generated from hydroxylysine and lysine during posttranslational modification of collagen. These crosslinks are released into circulation during resorption of the organic bone matrix and are excreted unchanged in the urine. Thus, this marker of bone resorption is assessed by its urinary excretion rather than by its circulating concentration.

Hydroxyproline is a product of posttranslational hydroxylation of proline in the procollagen moiety. Because hydroxyproline is not reused in the synthesis of collagen, measurement of its excretion in the urine provides a measure of bone resorption. However, hydroxyproline is not specific for bone; it is a constituent of different types of collagen in other tissues. Also, hydroxyproline is influenced by dietary protein. For these reasons, measurement of urinary hydroxyproline is a poor marker of bone resorption.

Acid phosphatase is a lysosomal enzyme localized in bone, prostate, platelets, erythrocytes, and spleen. The bone acid phosphatase is resistant to inhibition by tartrate. This tartrate-resistant acid phosphatase (TRAP) is present in osteoclasts and thus is a potential marker of bone resorption. However, the drawbacks of serum TRAP include its lack of specificity for bone, instability in frozen samples, chelation with calcium, and degradation by other enzymes. For these reasons, the usefulness of this marker in the assessment of bone turnover is questionable.

References:


Klein GL. Metabolic bone disease of total parenteral nutrition. *Nutrition.* 1998;14:149-152


American Board of Pediatrics Content Specification(s):

Recognize the relationship between the calcium and phosphorus content of parenteral nutrition solutions and osteopenia

Understand the etiology, clinical manifestation, radiographic features, and approach to treatment of osteopenia of prematurity

Understand the clinical and laboratory manifestations of deficiencies of fat-soluble vitamins
A 3.4-kg male infant was delivered by a 24-year-old primigravida at 38 weeks’ gestation. Antenatal course was remarkable for a diagnosis of absent radii bilaterally in the fetus at 20 weeks’ gestation. Amniocentesis revealed a normal fetal karyotype. After delivery, physical examination revealed malformed upper extremities (Figure 1); the rest of the physical examination findings were normal.

The infant was vigorous and nursing well. A complete blood count a few hours after birth revealed a total white cell count of 18,000/μL (18×10^9/L), hematocrit of 45%, and platelet count of 47×10^3/μL (47×10^9/L). A skeletal survey was obtained (Figures 2 and 3). Ultrasonographic findings of the brain and heart were within normal limits.
Of the following, the MOST likely diagnosis for the infant in this vignette is:

- **1.** DiGeorge syndrome
- **2.** Fanconi anemia
- **3.** Holt-Oram syndrome
- **4.** Thrombocytopenia with absent radii syndrome
- **5.** Wiskott-Aldrich syndrome

You selected **4**, the correct answer is **4**.

The infant in this vignette has a constellation of findings (bilateral absent radii, with presence of thumbs bilaterally and thrombocytopenia presenting in the neonatal period) that is sufficient to make a diagnosis of thrombocytopenia and absent radii (TAR) syndrome. Figure 1 shows shortening of both the upper and lower arms. The hands are not seen completely in Figure 1. The skeletal survey in Figures 2 and 3 shows bilateral absence of radii, normal-appearing thumbs bilaterally, hypoplastic ulnae, hypoplastic left humerus, and flexion deformity of the right fourth finger. No other bony abnormality is seen.

The syndrome of thrombocytopenia and absent radii was first described in 1956, and since then, over 100 cases have been reported. Skeletal abnormalities associated with this syndrome are shown in the Table.
Platelet counts in neonates with TAR generally are lower than 50×10^3/μL (50×10^9/L). Bone marrow aspiration reveals a decrease in megakaryocytes; however, this test is not required to make the diagnosis. Half of the patients develop hemorrhagic manifestations in the first week of life and most develop thrombocytopenia by 4 months of age. Patients have mucocutaneous bleeding, especially in the first year of life, when the thrombocytopenia is most pronounced. As infants, these patients may require transfusions of single-donor, irradiated platelets. Approximately 40% of patients die in early infancy as a result of hemorrhage. Thrombocytopenia during infancy can be precipitated by viral illness, particularly gastrointestinal infection. After the first year of life, platelet-transfusion dependence usually diminishes.

“Leukemoid” granulocytosis is seen in 62% of patients, especially during bleeding episodes, and eosinophilia is seen in 53% of patients. Anemia is attributed to hemorrhage and secondary iron deficiency. Although many disorders of hematopoietic failure have an increased risk of malignant transformation, such a risk has not been documented for TAR syndrome. Cow milk protein allergy or intolerance is common in TAR syndrome (47% of cases) and can be a significant problem. Introduction of cow milk may precipitate thrombocytopenia, eosinophilia, and/or leukemoid reactions. Cardiac defects are seen in one third of these patients, the most common being tetralogy of Fallot, atrial septal defect, and ventricular septal defect.

The differential diagnosis of TAR syndrome includes Fanconi anemia, thalidomide embryopathy, Holt-Oram syndrome, Roberts syndrome, and DiGeorge syndrome.

Patients with Fanconi anemia are rarely thrombocytopenic in the neonatal period; rather they develop progressive bone marrow failure as children and adults. Radial abnormalities are seen in only 30% of patients with Fanconi anemia, whereas abnormalities of the radius are *sine qua non* for TAR syndrome. In a patient with TAR syndrome, thumbs are uniformly present in the absence of radii, whereas in Fanconi anemia, absence of the radius always is accompanied by absent thumbs. Despite these differences, it is prudent to test patients with a clinical picture of TAR syndrome for increased chromosomal fragility to formally rule out Fanconi anemia.

Thalidomide embryopathy is associated with osseous abnormalities similar to TAR syndrome; however, thrombocytopenia is not a common finding and maternal intake of this drug in pregnancy is now rare.

Holt-Oram syndrome (hereditary heart disease plus variable skeletal malformations) and Roberts syndrome (tetraphocomelia, cleft lip and palate, intrauterine growth retardation, failure to thrive) are rarely associated with thrombocytopenia.

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral absent radii</td>
<td>100</td>
</tr>
<tr>
<td>Abnormalities of ulna</td>
<td>50</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>100</td>
</tr>
<tr>
<td>Bilateral absence</td>
<td>20</td>
</tr>
<tr>
<td>Bilateral absence</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal humerus</td>
<td>50</td>
</tr>
<tr>
<td>Bilateral absence</td>
<td>5-10</td>
</tr>
<tr>
<td>Abnormal shoulder joint</td>
<td></td>
</tr>
<tr>
<td><em>The thumbs are always present but may be hypoplastic</em></td>
<td></td>
</tr>
<tr>
<td>Lower limb abnormalities</td>
<td>50</td>
</tr>
<tr>
<td>Hip dislocation</td>
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<tr>
<td>Subluxation of knees</td>
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<td>Coxa valga</td>
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<td>Dislocation of patella</td>
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<tr>
<td>Abnormal fibulibular joint</td>
<td></td>
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<tr>
<td>Ankylosis of halluc</td>
<td></td>
</tr>
<tr>
<td>Small feet</td>
<td></td>
</tr>
<tr>
<td>Abnormal toe placement</td>
<td></td>
</tr>
<tr>
<td>Absence of tibia</td>
<td></td>
</tr>
</tbody>
</table>
Thrombocytopenia and radial abnormalities are rarely seen in DiGeorge syndrome and other syndromes belonging to the deletion of chromosome 22q11 spectrum. Chromosomal analysis looking specifically for this deletion should be carried out to exclude this syndrome.

Wiskott-Aldrich syndrome is an X-linked syndrome that is characterized by immunodeficiency, eczema, and thrombocytopenia secondary to decreased production. Often only the thrombocytopenia is recognizable at birth. Skeletal abnormalities are not a feature of this syndrome.

**References:**


**American Board of Pediatrics Content Specification(s):**

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

Understand the clinical manifestations of neonatal thrombocytopenia and thrombocytosis

Understand the treatments of neonatal thrombocytopenia and thrombocytosis

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

Understand the association between anemia and congenital anomalies
A 3.4-kg male infant was delivered by a 24-year-old primigravida mother at 38 weeks’ gestation. The antenatal course was remarkable for a diagnosis of absent radii bilaterally in the fetus at 20 weeks’ gestation. Amniocentesis revealed a normal fetal karyotype. After delivery, physical examination revealed malformed upper extremities (Figure 1); the rest of the physical examination findings were normal.

The infant was vigorous and nursing well. A complete blood count several hours after birth revealed a total white blood cell count of 18,000/µL (18×10^9/L), hematocrit of 45% and platelet count of 47,000×10^3/µL (47×10^9/L). A skeletal survey is obtained (Figures 2 and 3). Ultrasonographic findings of the brain and heart were within normal limits.
Of the following, this condition is characterized by:

1. cow milk protein allergy in infancy
2. leukemia in adult life
3. lifelong need for platelet transfusions
4. thrombopoietin deficiency
5. X-linked recessive inheritance

You selected 4, 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 infant in the vignette has thrombocytopenia and absent radii (TAR) syndrome. Figure 1 shows shortening of both the upper and lower arms. The hands are not seen completely in Figure 1. The skeletal survey in Figures 2 and 3 shows bilateral absence of radii, normal-appearing thumbs bilaterally, hypoplastic ulnae, hypoplastic left humerus and flexion deformity of the right fourth finger. No other bony abnormality is seen.

The syndrome of thrombocytopenia and absent radii was first described in 1956 and, subsequently, more than 100 cases have been reported. Skeletal abnormalities associated with this syndrome are shown in the Table.

Table
Cow milk protein allergy or intolerance is common in TAR syndrome (47% of cases) and can be a significant problem. Introduction of cow’s milk may precipitate thrombocytopenia, eosinophilia, and/or leukemoid reactions. The cause for this association is unknown.

Platelet counts in neonates with TAR syndrome generally are lower than 50,000×10³/μL (50×10⁹/L). Bone marrow aspiration reveals a decrease in megakaryocytes; however, this test is not required to make the diagnosis. Defective signal transduction through the thrombopoietin receptor (c-mpl) pathway for megakaryocyte production has been suggested as the cause of thrombocytopenia. Thrombopoietin concentrations have been reported to be normal or high in several case series.

Infants with TAR syndrome may have mucocutaneous bleeding, especially during the first year of life, when the thrombocytopenia is most pronounced. Half of the patients develop hemorrhagic manifestations in the first week after birth and most develop thrombocytopenia by 4 months of age. As infants, these patients require transfusions of single-donor, irradiated platelets. About 40% of patients die in early infancy as a result of hemorrhage. Thrombocytopenia during infancy can be precipitated by viral illness, particularly gastrointestinal infection. After the first year of life, platelet-transfusion dependence usually diminishes. Corticosteroids, intravenous immunoglobulin, and splenectomy have been tried, but the beneficial effects for TAR-associated thrombocytopenia have been inconsistent. Successful treatment with interleukin 6 and erythropoietin has been described in one case each.

“Leukemoid” granulocytosis is seen in 62% of patients, especially during bleeding episodes, and eosinophilia is seen in 53% of patients. Anemia is attributed to hemorrhage and secondary iron deficiency. Although many disorders of hematopoietic failure have an increased risk of malignant transformation, such a risk has not been documented for TAR syndrome; however, two cases of leukemia in TAR syndrome have been reported.

Cardiac defects are seen in one third of these patients, the three most common being tetralogy of Fallot, atrial septal defect, and ventricular septal defect.

Table. Skeletal Abnormalities Associated with the Syndrome of Thrombocytopenia and Absent Radii

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
The inheritance pattern of TAR syndrome in limited case series is reported to be autosomal recessive. However, the incidence among siblings of 1:7 is lower than the expected rate. Both males and females are affected, but there is a predominance among females, thus making a X-linked recessive pattern of inheritance unlikely.

References:


American Board of Pediatrics Content Specification(s):

Understand the etiologies and pathophysiologies of neonatal thrombocytopenia and thrombocytosis

Understand the clinical manifestations of neonatal thrombocytopenia and thrombocytosis

Understand the treatments of neonatal thrombocytopenia and thrombocytosis

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

Understand the association between anemia and congenital anomalies
A full-term infant was born by cesarean section after several attempts at vaginal delivery with forceps assistance. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Initial physical examination revealed a depressed region over the right parietal bone; the infant was otherwise clinically stable, with a hematocrit count of 51.3% (0.51).

Of the following, the NEXT step in the evaluation of a suspected skull fracture in this infant is:

- computed tomography of the head
- magnetic resonance imaging study of the head
- plain radiography of the skull
- transillumination of the head
- ultrasonography of the head

You selected 2, the correct answer is 3.

Depressed skull fractures can occur from compression of the skull—either after forceps application or against the ischial spines or the pubic symphysis. Usually such fractures result from inward collapse of the calvarial bones. Injury of the intracranial structures (dural attachments and major vessels) may result in hemorrhage. On clinical examination, an underlying fracture should be suspected when there is an obvious and palpable bony defect. Plain radiography is the diagnostic test of choice in such cases.

Computed tomography (CT) remains the primary imaging choice in acute situations, and would be the correct choice if this infant demonstrated clinical or laboratory signs of hypovolemia, acute anemia, or coagulopathy. CT is most reliable for detecting extracerebral (subdural and subarachnoid) and posterior fossa (cerebellar or subdural) hemorrhage. Whereas normal vascular grooves, lacunar skull, and ripple lines (soft-tissue folds in the scalp) may be mistaken for fractures on plain radiography, CT scans may be helpful in these circumstances. Given the known risks (exposure to ionizing radiation) associated with CT scans, this is not the imaging modality of choice for initial evaluation of a stable infant with a suspected skull fracture.

The National Cancer Institute is encouraging providers to perform CT scans only when absolutely necessary. According to their recommendations, radiologists should review the indications and be available for consultation before every pediatric scan. Some reports suggest up to 30% of CT scans performed in the pediatric population are unnecessary. Radiation doses from a single pediatric head CT scan can range from about 30 mSv to 60 mSv; three scans would be expected to triple the cancer risk of a single scan.
Transillumination of the skull is a valuable aid in determining the degree of hydrocephalus and in the diagnosis of hydranencephaly, as well as unilateral hygromata and Dandy-Walker syndrome. It is a low risk procedure, but it has little benefit in diagnosing skull fractures.

Although CT is more reliable, high-resolution ultrasonography using transfontanelle and transcranial approaches, including the mastoid view, can detect extracerebral and posterior fossa hemorrhage, including subdural hematomas. While ultrasonography may provide important screening information, particularly with regard to hemorrhage and trauma, it is currently not the screening modality of choice to detect or to evaluate skull fracture.

Magnetic resonance imaging (MRI) is not the imaging modality of choice in acute situations in which skull fracture is suspected; the procedure is time consuming and neonates often require sedation to reduce motion artifact. Nonetheless, MRI frequently provides superior diagnostic specificity compared with CT or ultrasonography for delineating hemorrhagic processes, including staging of hemorrhage and clot formation based on hemoglobin breakdown. In the presence of an atypical or unexplained intracranial hemorrhage, MRI may distinguish hemorrhagic infarction from hematoma.

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:

Barnes PD. Magnetic resonance imaging of the fetal and neonatal central nervous system. NeoReviews. 2001;2:12-21


American Board of Pediatrics Content Specification(s):

Understand the indications for and limitations of various neuroimaging studies (including ultrasonography, magnetic resonance imaging study, positron emission tomography, and near infrared spectroscopy), and be able to recognize normal and abnormal structures
An infant is born at 36 weeks' gestation, and appears healthy. At 24 hours of age, you perform a neurologic examination.

Of the following, the figure MOST likely to represent the resting posture in this infant is:

You selected 2, the correct answer is 3.

Muscle tone and posture are important components of the motor examination of the newborn, because abnormalities may suggest central nervous system (CNS) and/or neuromuscular dysfunction. Operationally, passive tone is defined as the resistance to movement, experienced by the examiner, while the infant's relaxed limbs are gently manipulated about the joints. Active tone, in contrast, is associated with voluntary or spontaneous movements of the infant, and is generally higher than passive tone. Hypotonia refers to decreased resistance to passive movement, and is more common than hypertonia, or increased resistance.

Posture of the limbs at rest is determined, in part, by the tone of various muscles, and is useful...
in the assessment of tone. Hypotonia may be indicated by unusual posture, such as the “frog leg” configuration, in which the supine infant’s lower extremities are externally rotated and abducted.

However, assessment of tone and the dependent resting posture must be made in the context of gestational age, as a caudocephalic progression of the development of tone occurs in the last 3 months of gestation. With increasing maturity, the fetus passes from a hypotonic posture dominated by extension, to one with increased appendicular and axial flexor tone, first in the lower extremities and then in the upper extremities.

At 28 weeks' gestation, there is minimal resistance to passive range of motion. At rest in the supine position, the arms and legs are extended or very slightly flexed (Figure 1).

![Figure 1](image1)

By 32 weeks' gestation, distinct flexor tone becomes apparent in the lower limbs, and the legs are now slightly flexed (Figure 2).

![Figure 2](image2)

By 36 weeks' gestation, as in the vignette, flexor tone in the lower extremities is strongly developed, and some flexor tone is detectable in the upper limbs (Figure 3).

![Figure 3](image3)

At 40 weeks' gestation, strong flexor tone exists in all limbs, in addition to adduction (Figure 4).

![Figure 4](image4)

At any gestational age, opisthotonic posturing (Figure 5), with marked leg extension and strong arm flexion, deviates from the normal evolution of tone, and suggests underlying CNS abnormality.

![Figure 5](image5)
The progressive maturation of tone and posture, in addition to neurologic features such as reflexes, has been mapped, and is useful both in assessing gestational age and in the neurologic evaluation at varying gestational ages. An example of the use of this neurologic mapping in the day-to-day assessment of infants is the tool by Dubowitz and Dubowitz (first published in 1981, and revised by Dubowitz and colleagues in 1999.)

Tone can also be assessed by gentle manipulation of the infant's limbs. Passive supination, pronation, flexion, and extension of the limbs, and gentle shaking of the hands and feet are common means of assessing tone. The measurement of limb angles has been used to assess tone as well. As an example, the popliteal angle is measured by maximum extension of the leg at the knee with the hip fully flexed. The popliteal angle decreases from 180 degrees at 28 weeks' gestation to less than 90 degrees at term.

In addition, responses to multiple maneuvers reflecting tone have been mapped to gestational age. Examples include:

- **Scarf sign:** Performed by wrapping the infant's arm across its chest toward the neck on the contralateral side; in the preterm infant, the elbow reaches the opposite shoulder, but is not brought beyond midline in the term infant.
- **Ventral (horizontal) suspension:** The infant's trunk is supported in the outstretched prone position, with observation of the back, limb flexion, and head position in relation to the trunk; the term infant will hold the head erect, and flex the limbs against gravity, while holding the back straight; the infant of 32 weeks' gestation or less will droop against gravity.
- **Traction maneuver (head lag):** The infant is pulled toward sitting posture by traction on both wrists; the head lags with considerably little resistance until after 30 weeks' gestation, but by term, the head follows the trunk before falling forward.
- **Vertical suspension:** The infant is held upright by the axillae; the premature infant will slip through the hands of the examiner, while the term infant will hang firmly.

Of interest, the term newborn infant demonstrates a consistent preference for position of the head toward the right side. This preference has not been associated with differences in lighting, care practices, or other factors, but is thought to reflect a normal asymmetry of cerebral function in the newborn.

**References:**


American Board of Pediatrics Content Specification(s):

Distinguish between active and passive tone

Identify the various maneuvers used to evaluate extremity, shoulder, hip, trunk, and neck tone

Know the normal pattern of evolution of extremity and axial (neck and trunk) tone from fetus through infancy

Characterize the normal resting posture of term and preterm infants at varying gestational ages
A 23-year-old primigravida presents in labor at 37 weeks’ gestation. She has had prenatal care, and her fetus has been diagnosed with a lethal skeletal dysplasia. Amniotic fluid volume is normal. There is no history of consanguinity. Both parents are of normal stature. After delivery, the infant develops severe respiratory failure. Physical examination reveals a female infant with symmetrical short limbs, marked bowing of long bones, and redundant skin folds. The head is disproportionately large with wide open fontanelles. Frontal bossing, depressed nasal bridge, and midfacial hypoplasia are also present. The trunk appears normal in length. The thorax is narrow, and the abdomen is markedly protuberant (Figure 1). A skeletal survey is obtained (Figures 2 through 5).

Figure 1

Figure 2
Of the following, the MOST likely diagnosis in this infant is:

- **1** achondrogenesis
- **2** campomelic dysplasia
- **3** chondrodysplasia punctata
- **4** hypophosphatasia
- **5** thanatophoric dysplasia

You selected **3**, the correct answer is **5**.
The infant in this vignette has classic clinical and radiographic features of thanatophoric dysplasia (TD), the most common lethal skeletal dysplasia (Figures 2 through 5).

**Figure 2:** Classic radiologic features of thanatophoric dysplasia type I. Radiographs demonstrate thin flattened vertebrae (platyspondyly), short ribs, flaring ilia, extremely short long tubular bones, and markedly short and curved femora (telephone receiver–like appearance) and relatively normal looking skull.

**Figure 3:** Radiologic features of thanatophoric dysplasia type I

**Figure 4:** Thanatophoric dysplasia type I
Skeletal dysplasias are a heterogeneous group of disorders characterized by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton and disproportionate long bones, spine, and head. The overall incidence of skeletal dysplasias is approximately 1 in 4,000 to 5,000 births. The four most common skeletal dysplasias are thanatophoric dysplasia, achondroplasia, osteogenesis imperfecta, and achondrogenesis. Thanatophoric dysplasia and achondrogenesis account for 62% of all lethal skeletal dysplasias. Achondroplasia is the most common nonlethal skeletal dysplasia. Among infants with skeletal dysplasias detected at birth, approximately 13% are stillborn and 44% die during the perinatal period. The overall frequency of skeletal dysplasias in infants who die in the perinatal period is 9.1 per 1,000 births.

Skeletal dysplasias can be classified based on morphologic, clinical, and radiographic criteria. This system takes into consideration the region of bone involved (epiphysis, metaphysis, or diaphysis), spinal involvement, and the relative proportion of limbs to trunk. Disproportionate short stature can result from a short limb or a short trunk. Short limbs can be further classified according to the location as rhizomelic (proximal), mesomelic (middle), or acromelic (distal) segment shortening. Descriptive terms are also used in relation to the appearance of the
bones such as diastrophic (twisted), campomelic (curved or bent limb), metatropic (changing), or thanatophoric (death bringing).

The evaluation of patients with skeletal dysplasias includes a careful clinical examination, detailed radiographic examination, history (length at birth, growth curves, etc) and pedigree analysis, followed by anthropometric measurements with special emphasis on body proportions. Skeletal dysplasias that may manifest at birth can be classified as lethal or nonlethal (Table). An algorithm for the differential diagnosis of lethal skeletal dysplasias is presented in Figure 6.

<table>
<thead>
<tr>
<th>Lethal</th>
<th>Nonlethal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thanatophoric dysplasia</td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Achondrogenesis</td>
<td>Asphyxiating thoracic dystrophy of DeJeune</td>
</tr>
<tr>
<td>Chondrodysplasi punctata</td>
<td>Chondrodysplasia punctata</td>
</tr>
<tr>
<td>Homozygous achondroplasia</td>
<td>Chondroectodermal dysplasia</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>Diastrophic dwarfism</td>
</tr>
<tr>
<td>Osteogenesis imperfecta type II</td>
<td>Hypochondroplasia</td>
</tr>
<tr>
<td>Campomelic dysplasia</td>
<td>Hypophosphatasia tarda</td>
</tr>
<tr>
<td></td>
<td>Mesomelic dwarfism</td>
</tr>
<tr>
<td></td>
<td>Metatropic dwarfism</td>
</tr>
<tr>
<td></td>
<td>Spondyloepiphyseal dysplasia congenita</td>
</tr>
</tbody>
</table>

Thanatophoric dysplasia is divided into type I, characterized by micromelia with bowed femurs ("telephone receiver" femurs); and type II, characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity (kleeblattschaedel) (Figure 7). Other features common to type I and type II include short ribs, narrow thorax, macrocephaly, frontal bossing, depressed nasal bridge, midfacial hypoplasia, proptotic eyes, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die shortly after birth.

![Figure 6: Algorithm for lethal types of neonatal dwarfism (adapted from Clark [1990]). Blue boxes indicate clinical/laboratory characteristic; red boxes, skeletal dysplasia; and green boxes, abnormal gene product.](http://emb.aap.org/courseprodv2/Index.asp)

![Figure 7: Cloverleaf skull deformity (kleeblattschaedel) in thanatophoric dysplasia type II](http://emb.aap.org/courseprodv2/Index.asp)
Prenatal diagnosis is possible with ultrasonographic examination and molecular genetic testing. Shortening of the long bones may be visible as early as 12 to 14 weeks' gestation. Several other skeletal disorders may give rise to prenatal ultrasonographic findings similar to those of TD. Therefore, the diagnosis of TD is based on postnatal physical examination, radiographic studies, and genetic testing. *FGFR3* is the only gene associated with TD. Up to 99% of mutations causing TD type I and more than 99% of mutations causing TD type II can be identified through molecular genetic testing of *FGFR3*, which is available on a clinical basis.

Achondrogenesis is a lethal skeletal dysplasia characterized by severe micromelia, macrocephaly, narrow thorax, protuberant abdomen, short trunk, and pseudohydrops. The hydropic fetal appearance is caused by the abundance of soft tissue relative to the short skeleton.

Infants with achondrogenesis are frequently born preterm. Death occurs prenatally or shortly after birth. Two types are recognized.

- **Achondrogenesis type I (autosomal recessive):** Characterized by poor mineralization of both the skull and vertebral bodies as well as rib fractures.
- **Achondrogenesis type II (sporadic, new autosomal dominant mutations):** Characterized by hypomineralization of the vertebral bodies but normal mineralization of the skull, and absence of rib fractures.

Campomelic dysplasia (CD) is a skeletal dysplasia characterized by cleft palate with Pierre Robin sequence, shortening and bowing of long bones, pretibial skin dimples, and club feet (Figure 8). Other findings include laryngotracheomalacia with respiratory compromise and ambiguous genitalia or normal female external genitalia in most individuals with a 46,XY karyotype. The diagnosis of CD is usually based on clinical and radiographic findings. Molecular genetic testing of *SOX9*, the only gene known to be associated with CD, is available in clinical laboratories and detects mutations or chromosome rearrangements in approximately 95% of affected individuals.

**Figure 8:** Radiographs showing bowing of the long bones in campomelic dysplasia
Chondrodysplasia punctata, also known as rhizomelic chondrodysplasia punctata type 1 (RCDP1), an autosomal recessive inheritance, is a peroxisome biogenesis disorder (PBD) characterized by proximal shortening of the humerus and to a lesser degree of the femur (rhizomelia), enlarged joints, contractures, punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities, coronal clefts of the vertebral bodies, and cataracts that are usually present at birth or appear in the first few months after birth (Figure 9). The diagnosis of RCDP1 is based on clinical findings and confirmed with clinically available biochemical or molecular genetic tests. Biochemical tests of peroxisome function include red blood cell concentration of plasmalogens, plasma concentration of phytanic acid, and plasma concentration of very-long-chain fatty acids. PEX7, which encodes the receptor for a subset of peroxisomal matrix enzymes, is the only gene known to be associated with RCDP1.

Figure 9: Punctate calcifications in the epiphyses at the knee joint in chondrodysplasia punctata
Hypophosphatasia is characterized by defective bone mineralization and a deficiency of tissue nonspecific alkaline phosphatase activity because of mutations in the liver/bone/kidney alkaline phosphatase gene. Clinical expression ranges from stillbirth without mineralized bone to pathological fractures developing late in adulthood. Six clinical forms are currently recognized, depending on the age at diagnosis and the severity of the symptoms: perinatal lethal; infantile; childhood; adult; odontohypophosphatasia; and, more recently described, perinatal benign. In the perinatal lethal form of hypophosphatasia, patients show markedly impaired mineralization in utero. They have skin-covered osteochondral spurs protruding from the forearms or legs that are often diagnostic for hypophosphatasia. In the perinatal benign form of hypophosphatasia, despite prenatal symptoms, skeletal defects spontaneously improve. The patients manifest limb shortening and bowing, and often have dimples overlying the long bone anomalies.

References:


American Board of Pediatrics Content Specification(s):

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodental dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc.
October: Question 6

A 4-day-old female infant, who weighed 3,410 g at birth at an estimated gestational age of 40 weeks, has an anterior chest wall abnormality (Figure 1).

Figure 1: Anterior chest wall abnormality. Note the sternal defect, the abdominal raphe connecting the defect and the umbilicus, and the surgical marker placed prior to surgery (arrow).

A pulsating heart covered with thin skin is visible through the thoracic midline defect. A midline abdominal raphe extends from the thoracic defect to the umbilicus (Figure 1). Chest radiographs (Figures 2 and 3) reveal superior mediastinal widening with an increased distance between the sternal ends of the clavicles, indicative of complete absence of the sternum.

Figure 2: Chest radiograph (anteroposterior view) of sternal agenesis
No other congenital anomalies or dysmorphic features are apparent. The infant is breathing spontaneously in room air without distress and is receiving full enteral feeds of breast milk by mouth. You review with the parents the type of the sternal defect and its implications for their infant.

Of the following, the MOST common sternal defect reported in cleft sternum is:

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>complete cleft</td>
</tr>
<tr>
<td>2</td>
<td>inferior cleft</td>
</tr>
<tr>
<td>3</td>
<td>minimal cleft with skin ulceration</td>
</tr>
<tr>
<td>4</td>
<td>superior partial U-shaped cleft</td>
</tr>
<tr>
<td>5</td>
<td>superior total V-shaped cleft</td>
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</tbody>
</table>
Cleft sternum, also called bifid sternum, is a congenital anomaly of the sternum typically characterized by the presence of a normally placed heart, normal skin coverage, an intact pericardium, and a sternal defect of variable degree and location. Normally, the sternum consists of three parts: the manubrium, the body, and the xiphoid process (http://www.nlm.nih.gov/medlineplus/ency/imagepages/1740.htm). The manubrium at each of its borders has the clavicular notch and the first costal notch for articulation with the clavicle and the first rib. The junction between the manubrium and the body has the second costal notch for articulation with the second rib. The body of the sternum at each of its borders has the costal notches three through seven for articulation with the remainder of the ribs. To understand the congenital anomalies of the sternum, it is important to review the development of the sternum during fetal life.

The sternum and pectoral muscles originate from the lateral plate mesoderm. The earliest embryologic evidence of the sternum can be found at 6 weeks of gestation, when the sternum is detected as two parallel lateral mesenchymal bands in the anterior thoracic wall. By 10 weeks of gestation, the sternal bands fuse craniocaudally in the midline to form the manubrium and the body of the sternum. At 20 to 24 weeks of gestation, the sternum begins to lay cartilage (chondrification), including the formation of the mostly cartilaginous xiphoid process, and then deposit bone (ossification). This ossification begins as a single center in the manubrium and proceeds in a cephalocaudal direction. In the body of the sternum, the ossification centers typically are observed in pairs. This process of ossification usually is complete within the first year after birth. Most isolated sternal defects result from a failure of the lateral mesenchymal bands to fuse during the eighth week of gestation.

Sternal defects are classified depending on their location and extent as superior, inferior, and complete. The most common sternal defect, seen in approximately 40% of cases of cleft sternum, is the superior partial U-shaped cleft that involves the manubrium and the upper half of the body of the sternum up to the level of the fourth costal notch. The second most common sternal defect (30% of cases) is the superior total V-shaped cleft that involves the manubrium and the whole body of the sternum extending to the xiphoid process. The third most common sternal defect (20% of cases) is the complete cleft, identified as absence or agenesis of the sternum, as in the infant in this vignette. The fourth most common sternal defect (8% of cases) is the inferior cleft that involves the xiphoid process and the lower half of the body of the sternum below the level of the fourth costal notch. The least common sternal defect (2% of cases) is the midline, barely perceptible cleft with a breech in the overlying skin.

Most superior sternal clefts are isolated abnormalities with no intrinsic cardiac or other defects. Often associated are abdominal raphes (bandlike scars) that extend from the inferior aspect of the sternal defect to the umbilicus, as seen in the infant in this vignette. Conversely, most inferior sternal clefts are often accompanied by other severe anomalies, notably ectopia cordis and the pentalogy of Cantrell. The latter consists of a midline supraumbilical abdominal wall defect, a defect of the lower sternum, a deficiency of the diaphragmatic pericardium, a deficiency of the anterior diaphragm, and intracardiac anomalies.

Although most cases of sternal clefts are sporadic in occurrence, an autosomal recessive familial association has been reported. Female infants outnumber male infants in most reported case series. Sternal clefts can be a part of the PHACES syndrome, a disorder included in the sternal malformation-vascular dysplasia spectrum. The PHACES syndrome is a term applied to the association of posterior fossa brain malformations, hemangiomas (especially facial), arterial anomalies in the cranial vasculature, coarctation of the aorta/cardiac defects, eye abnormalities, and sternal clefting.

The optimal time for surgical repair of the sternal defect is during the neonatal period, when the chest wall is most compliant for achieving complete closure. Corrective surgery often improves respiratory function, provides protection to the heart and great vessels, and improves physical appearance of the infant. The infant in this vignette underwent successful surgery...
primary closure of the sternal defect and has remained in a healthy condition.

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References:


American Board of Pediatrics Content Specification(s):

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 of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transection

Recognize the radiographic features of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transection
A 23-year-old primigravida presents in labor at 37 weeks' gestation. She has had prenatal care and her fetus has been diagnosed with a lethal skeletal dysplasia. Amniotic fluid volume is normal. There is no history of consanguinity. Both parents are of normal stature. After delivery, the infant develops severe respiratory failure. Physical examination reveals a female infant with symmetrical short limbs, marked bowing of long bones, and redundant skin folds. The head is disproportionately large with wide open fontanelles. Frontal bossing, depressed nasal bridge, and midfacial hypoplasia are also present. The trunk appears normal in length. The thorax is narrow and the abdomen is markedly protuberant. A skeletal survey is obtained (Figures 1 through 4).

Figures 1 through 4: Radiograph demonstrating thin flattened vertebrae (platyspondyly), short ribs, flaring ilia, extremely short long tubular bones, and markedly short and curved femora (telephone receiver–like appearance) and relatively normal looking skull
Of the following, the gene product MOST likely to be abnormal in this infant is:

1. alkaline phosphatase
2. fibroblast growth factor receptor
3. peroxisomal receptor
4. SOX9 DNA binding protein
5. type I collagen

You selected 5, the correct answer is 2.
The infant in this vignette has classic clinical and radiographic features of thanatophoric dysplasia (TD), the most common lethal skeletal dysplasia presenting in neonates. The genetic mutation associated with this disorder involves the fibroblast growth factor receptor 3 gene (FGFR3).

Skeletal dysplasias are a heterogeneous group of disorders characterized by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton and disproportion of the long bones, spine, and head. The overall incidence of skeletal dysplasias is approximately 1 per 4,000 to 5,000 births. The true incidence may be twice as high because many skeletal dysplasias present later during childhood. Lethal skeletal dysplasias are estimated to occur in 0.95 per 10,000 deliveries. The four most common skeletal dysplasias are TD, achondroplasia, osteogenesis imperfecta, and achondrogenesis. TD and achondrogenesis account for 62% of all lethal skeletal dysplasias. Achondroplasia is the most common nonlethal skeletal dysplasia. Among infants with skeletal dysplasias detected at birth, approximately 13% are stillborn, and 44% die during the perinatal period.

The evaluation of patients with skeletal dysplasias warrants a multidisciplinary approach involving clinical geneticists, radiologists, molecular biologists, and a host of surgical specialists. A careful clinical examination and detailed radiographic evaluation of the skeleton are the first steps toward an accurate diagnosis. A detailed history (length at birth, growth curves, etc) and pedigree analysis, followed by anthropometric measurements with special emphasis on body proportions are important. A skeletal survey is important and includes plain radiographs of the skull, spine, pelvis, one leg, and one arm. Skeletal dysplasias that manifest at birth can be classified as lethal or nonlethal.

Thanatophoric dysplasia is the most common short-limb dwarfism syndrome that is lethal in the perinatal period. TD is divided into type I, characterized by micromelia with bowed femurs (“telephone receiver” femurs); and type II, characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity (kleeblattschaedel). Other features common to type I and type II include short ribs, narrow thorax, macrocephaly, frontal bossing, depressed nasal bridge, midfacial hypoplasia, proptotic eyes, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die soon after birth. Death is often secondary to pulmonary hypoplasia caused by the small thoracic cavity, or to foramen magnum stenosis and resultant failure of respiratory control. Rare long-term survivors have been reported.

Up to 99% of mutations causing TD type I and more than 99% of mutations causing TD type II can be identified through molecular genetic testing of FGFR3, the only gene known to cause TD. Mutations for TD type I have been described in FGFR3 exons 7, 10, 15, and 19; and for TD type II...
The FGFR3 mutation p.Lys650Glu has been identified in all individuals with TD type II. Targeted mutation analysis of FGFR3 is available clinically. TD is inherited in an autosomal dominant manner; the majority of probands have a de novo mutation in FGFR3. Risk of recurrence for parents who have had one affected child is not significantly increased over that of the general population.

Thus the gene product most likely to be abnormal in the infant in this vignette with classic features of TD is fibroblast growth factor. Abnormalities in alkaline phosphatase, peroxisomal receptor, SOX9 DNA binding protein, and type I collagen are responsible for other less common lethal skeletal dysplasias. Mutations in the alkaline phosphatase gene cause perinatal lethal and infantile forms of hypophosphatasia. Abnormalities in genes that encode the peroxisomal biogenesis factors (PEX) are responsible for rhizomelic chondrodysplasia punctata and Zellweger syndrome. Mutations in the gene coding for the SRY-box 9 protein (SOX9) cause camptometelic dysplasia. Mutations in the procollagen I genes (COL1A1, COL1A2) cause various types of osteogenesis imperfecta.

The clinical, radiographic, laboratory, and genetic characteristics of other less common lethal skeletal dysplasias are summarized in the Table. An algorithm for the differential diagnosis of lethal skeletal dysplasias is presented in Figure 5.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Major Clinical Manifestations</th>
<th>Laboratory/X-ray</th>
<th>Inheritance</th>
<th>Gene Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thanatophoric dysplasia type I</td>
<td>Short ribs, narrow thorax, macrocephaly, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs</td>
<td>Marked platyspondyly, short ilia, bowed femur with broad metaphyses</td>
<td>AD</td>
<td>FGFR3, fibroblast growth factor receptor 3</td>
</tr>
<tr>
<td>Thanatophoric dysplasia type II</td>
<td>Short ribs, narrow thorax, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs, macrocephaly, clover leaf skull anomaly</td>
<td>Platyspondyly, straight femur</td>
<td>AD</td>
<td>FGFR3, fibroblast growth factor receptor 3</td>
</tr>
<tr>
<td>Achondrogenesis type I</td>
<td>Flat nose, short limbs, hydrops, narrow thorax, short trunk, large head</td>
<td>Short tubular bones, poor mineralization of vertebral bodies and skull, rib fractures present</td>
<td>AR</td>
<td>DTDSTSLC26A2 (diastrophic dysplasia sulfate transporter)</td>
</tr>
<tr>
<td>Achondrogenesis type II</td>
<td>Flat nose, short limbs, hydrops, narrow thorax, short trunk, large head</td>
<td>Short tubular bones, hypomineralization of vertebrae, normal mineralization of skull, no rib fractures</td>
<td>AD</td>
<td>COL2A1 (Collagen 2 α1 chain)</td>
</tr>
<tr>
<td>Camptometelic dwarfism</td>
<td>Shortening and bowing of the long bones of the legs, dimples over tibia, clubfeet, narrow chest, hypoplastic scapulae, large calvarium with disproportionality</td>
<td>Short bowed femur and tibia; narrowed ilia, hypoplastic scapulae</td>
<td>AD</td>
<td>SOX9 (HMG-type DNA binding protein/transcription factor)</td>
</tr>
<tr>
<td>Disorder</td>
<td>Clinical Features</td>
<td>Cause</td>
<td></td>
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<td>---------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Chondrodysplasia punctata (AR)</td>
<td>Rhizomelic shortening of limbs, disproportionate short stature, enlarged joints, contractures</td>
<td>Epiphyseal stipplings on the proximal humerus, both ends of the femora, and lower spine</td>
<td>AR</td>
<td>PEX7 (peroxisomal receptor/importer) and other peroxisomal enzymes</td>
</tr>
<tr>
<td>Homozygous achondroplasia</td>
<td>Relatively normal-sized trunk, narrow thorax, large head, rhizomelic shortening of limbs, lumbar lordosis, and trident hands</td>
<td>Abnormal pelvis with small square iliac wings, horizontal acetabular roofs, and narrowing of the greater sciatic notch, an oval translucent area at the proximal ends of the femora, caudal narrowing of the interpedicular distances in the lumbar region, short pedicles, and lumbar lordosis</td>
<td>AD</td>
<td>FGFR3, fibroblast growth factor receptor 3</td>
</tr>
<tr>
<td>Severe hypophosphatasia</td>
<td>Severe shortening of the long bones, small thorax, hypomineralization of the skull and long bones</td>
<td>Very short underossified long bones with spikes; absence of liver and bone isoenzymes of alkaline phosphatase</td>
<td>AR, AD</td>
<td>TNSALP (Tissue non-specific alkaline phosphatase)</td>
</tr>
<tr>
<td>Osteogenesis imperfecta type II</td>
<td>Early prenatal onset of severe bone shortening</td>
<td>Multiple fractures affecting all long bones and ribs, poor mineralization of the skull</td>
<td>AD</td>
<td>COL1A1, COL1A2 (collagen 1 α1, α2 chains)</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive.

**Figure 5: Algorithm for lethal types of neonatal dwarfism (adapted from Clark [1990])**
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(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

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

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 4 Correct Answers: 2

Question 4

A 2-day-old male infant of a 34-year-old primiparous woman, who weighed 2,870 g at birth at an estimated gestational age of 36 weeks, is being evaluated for a neuromuscular disorder. Decreased fetal movements, polyhydramnios, and spontaneous preterm labor had led to a cesarean section delivery for breech presentation. The infant’s Apgar scores were 6 and 7 at 1 and 5 minutes after birth, respectively. The family history is negative for neuromuscular disorders, congenital malformations, or chromosomal syndromes.

Physical examination of the infant reveals no congenital malformations, dysmorphic features, or muscle contractures. Central nervous system examination reveals a semialert state of consciousness with poor response to stimulation, pronounced hypotonia of all extremities, and decreased spontaneous movements and tendon reflexes. Facial weakness is prominent, but no ptosis or tongue fasciculations are observed. The infant is unable to handle oral secretions from an inability to suck and swallow.

Cranial magnetic resonance imaging reveals decreased myelination, enlarged extra-axial spaces, and mild hypodensity of cerebral white matter. Electroencephalography findings are normal with no evidence of seizures. Nerve conduction studies are normal. Serum concentration of creatine kinase is markedly elevated; serum concentrations of other metabolites, including glucose, electrolytes, and amino acids are normal. There are no indications of sepsis or meningitis based on clinical history, blood cell counts, inflammatory markers, or cerebrospinal fluid findings. Molecular genetic studies are pending.

A muscle biopsy (Figure 1) shows marked atrophy of muscle fibers with some variation in fiber size and a pronounced increase in fibrous connective tissue.

Figure 1: Muscle biopsy showing atrophy of muscle fibers, variation in fiber size, and increased fibrous connective tissue. (Image courtesy of James Atkinson, MD)
Of the following, the neuromuscular disorder of this infant is MOST likely to be:

- A. central core muscle disease
- B. merosin-deficient congenital muscular dystrophy
- C. myotubular centronuclear myopathy
- D. nemaline rod body myopathy
- E. spinal muscular atrophy

Correct

The clinical features in the infant in this vignette are characteristic of a lower motor neuron disorder. The lower motor neuron extends from the anterior horn cell in the spinal cord through peripheral nerve and neuromuscular junction to the skeletal muscle. Each lower motor neuron disorder has a characteristic pattern of symptoms and signs, and the diagnosis is aided by laboratory tests that include brain imaging, serum enzyme analysis, nerve conduction assessment, electromyography, nerve and/or muscle biopsy, and molecular genetic studies. Location of the site of involvement in a neuromuscular disorder is helpful in understanding the pathogenesis of the specific disorder, its inheritance and progression, and potential outcome.

The symptoms and signs as well as the muscle biopsy findings in the infant in this vignette are consistent with the diagnosis of merosin- deficient congenital muscular dystrophy. Merosin, preferably termed laminin-2, is an extracellular matrix protein found in the basement membrane of skeletal muscle fibers and in the basal lamina of axonal Schwann cells. Laminin-2, one of the 10 laminin isoforms, is a heterotrimeric protein molecule composed of alpha, beta, and gamma chains (α2β1γ1). A mutation in laminin alpha-2 gene (LAMA2) on chromosome 6q22-23, acquired sporadically or inherited in an autosomal recessive manner, accounts for a deficiency of merosin that varies from partial deficiency to total absence. Total absence of merosin manifests phenotypically as marked muscle atrophy, progressive development of diffuse joint contractures, inability to achieve ambulation, and often death in infancy from cardiorespiratory complications including pulmonary aspiration. A milder phenotype of the disease is associated with partial merosin deficiency.
A markedly elevated creatine kinase concentration in serum is typical in merosin-deficient congenital muscular dystrophy. Cranial magnetic resonance imaging (MRI) often shows diffuse demyelination of cerebral hemispheres. Electroencephalography (EEG) typically shows no abnormalities. Muscle biopsy, as seen in the infant in this vignette (Figure 1), is characterized by marked degeneration of muscle fibers with variation in fiber size, and endomysial and perimysial proliferation of fibrous and fatty tissue.

Central core muscle disease is an inheritable myopathy associated with mutations in the gene encoding the ryanodine receptor (RYR1) located on chromosome 19q13.1. Often inherited in an autosomal dominant manner, these mutations result in a defective calcium release in the skeletal muscle during excitation and consequent muscle weakness. Presentation is rare in the neonatal period. Hypotonia typically manifests in late infancy or early childhood with motor developmental delay. The distribution of muscle weakness is typically proximal with prominent involvement of the hip girdle; the upper extremities are relatively spared. The tendon reflexes are usually preserved. Hypermobility of the joints and laxity of ligaments are common, whereas muscle contractures are rare. Facial muscle weakness, dysphagia, and respiratory difficulties are extremely uncommon. Patients with central core muscle disease are susceptible to hyperthermia, which can be fatal if unsuspected or untreated.

In central core muscle disease, serum creatine kinase concentration is typically normal or only mildly elevated. Cranial MRI and EEG typically show no abnormalities. The pathognomonic feature of central core muscle disease is evident on muscle biopsy (Figure 2).

Figure 2: Muscle biopsy showing central cores highlighted by staining for mitochondrial oxidative enzymes

Most muscle fibers, especially the more vulnerable type 1 fibers, show well-demarcated, centrally located cores. Identification of the cores is facilitated by staining for a mitochondrial oxidative enzyme (nicotinamide adenine dinucleotide-tetrazolium reductase). Whereas such staining is distributed evenly throughout a normal muscle fiber, the staining is markedly diminished from absence of oxidative enzymes in the central core regions of the affected muscle fibers.

Myotubular centronuclear myopathy is an inheritable myopathy that is classified into three forms: X-linked, autosomal dominant, and autosomal recessive. The X-linked form is the most severe with infantile onset and rapid progression of the disease, whereas both autosomal dominant and recessive forms are relatively milder with onset generally after the age of 12 years and much slower progression of the disease. The X-linked infantile form is caused by mutations in the myotubular myopathy gene (MTM1) located on chromosome Xq28 that encodes myotubulin. Myotubulin, a phosphatidyl inositol tyrosine phosphatase, is required for normal muscle cell differentiation. In the absence of myotubulin, skeletal
muscle development is arrested in its fetal stages. The disorder manifests phenotypically with severe generalized hypotonia. Involvement of respiratory muscles often leads to ventilatory failure. Ptosis, extraocular muscle weakness (ophthalmoplegia), and facial weakness are typically pronounced. Impairment of bulbar function often contributes to difficulties with sucking and swallowing. A deletion of a gene contiguous to MTM1 gene is frequently associated with cryptorchidism and male hypogenitalism.

In myotubular centronuclear myopathy, serum creatine kinase concentration is typically normal or only mildly elevated. Cranial MRI and EEG typically show no abnormalities. The pathognomonic feature of myotubular centronuclear myopathy is evident on muscle biopsy (Figure 3).

**Figure 3: Muscle biopsy showing fetal muscle cells with central nuclei**

Muscle pathology in infantile cases is characterized by the presence of small muscle fibers with centrally placed nuclei. These muscle fibers resemble fetal muscle cells, called myotubules, in which the nuclei have failed to migrate to the periphery of the cells in contrast to normally differentiated skeletal muscle cells. Necrosis, fibrosis, fatty deposition, and inflammation are usually not seen.

Nemaline rod body myopathy is an inheritable myopathy that is classified into three forms: neonatal onset, childhood onset, and adult onset. The neonatal onset form, often inherited in an autosomal recessive manner, is the most severe with presentation at birth, rapid progression of the disease, and death in infancy from cardiomyopathy, respiratory failure, or recurrent pneumonia. Mutations in five different genes encoding sarcomeric proteins have been reported to cause nemaline rod body myopathy. These mutations include:

- alpha-actin gene (*ACTA1*) on chromosome 1q42
- nebulin gene (*NEB*) on chromosome 2q21.1-q22
- slow alpha-tropomyosin 3 gene (*TPM3*) on chromosome 1q22-23
- beta-tropomyosin 2 gene (*TPM2*) on chromosome 9p13.1-p13.2
- slow troponin T gene (*TNNT1*) on chromosome 19q13.4

Approximately 60% to 75% of cases of neonatal onset nemaline rod body myopathy are caused by mutations in the *ACTA1* gene. This disorder manifests phenotypically with severe generalized hypotonia with a greater involvement of distal limb muscles. Involvement of respiratory muscles often leads to ventilatory failure. Although facial weakness is pronounced, ptosis and ophthalmoplegia are rare. Progressive cardiomyopathy is the leading cause of death.

In nemaline rod body myopathy, serum creatine kinase concentration is typically normal or only mildly elevated. Cranial MRI and EEG typically show no abnormalities. The
The pathognomonic feature of nemaline rod body myopathy is the presence of threadlike rods, called nemaline bodies, in muscle cells (Figure 4A and B).

**Figure 4:** A, Muscle biopsy showing rods in muscle cells stained with hematoxylin and eosin stain

B, Muscle biopsy showing rods in muscle cells stained with Gomori trichrome stain

These rods represent condensation of alpha-actinin and actin seen mostly in type 1 muscle fibers. Identification of the rods is facilitated by staining with Gomori trichrome stain.

Spinal muscular atrophy is an autosomal recessive neuromuscular disorder characterized by a progressive degeneration of anterior horn cells in the spinal cord. This disorder is classified into four forms: type I (onset before 6 months of age), type II (onset between 6 and 18 months), type III (onset after 18 months in childhood), and type IV (adult onset). The type I form, called Werdnig-Hoffman disease, is the most severe with rapid progression of the disease and death during the first 2 years of age without mechanical respiratory support. The genetic defect involves the survival motor neuron gene (SMN) located on chromosome
Sq11.2-q13.3. This disorder manifests phenotypically with generalized hypotonia with a greater involvement of proximal muscles, lower extremities, and axial musculature of the trunk and neck. Tendon reflexes are absent. Facial motility is relatively preserved, and extraocular movements are normal. Fasciculations of the limbs and of the tongue are often seen.

In type I spinal muscular atrophy, serum creatine kinase concentration is typically normal. Cranial MRI and EEG typically show no abnormalities. The pathognomonic feature of type I spinal muscular atrophy is the presence of group atrophy on muscle biopsy (Figure 5A and B).

Figure 5: A, Muscle biopsy showing group atrophy of muscle fibers and compensatory hypertrophy of other muscle fibers resulting in marked variation in fiber size stained with hematoxylin and eosin stain.

B, Muscle biopsy showing group atrophy of muscle fibers and compensatory hypertrophy of other muscle fibers resulting in marked variation in fiber size stained with adenosine triphosphatase stain.

Whereas a normal muscle shows a checkerboard pattern with muscle fibers of equal size, this pattern is lost with progressive anterior horn cell degeneration. The group of muscle
fibers supplied by degenerated anterior horn cells show atrophy, whereas other muscle fibers 
supplied by adjacent intact anterior horn cells show compensatory hypertrophy. In more 
severe and later stages of the disorder, the anterior horn cell degeneration is more 
widespread, and the muscle biopsy shows panfascicular atrophy with involvement of all 
muscle fibers in a fascicle. A concomitant increase in connective tissue is observed with a 
marked atrophy of the muscle.

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Boyle KB, Anderson JM. Visual diagnosis: hypotonia and poor feeding in a newborn. 
[subscription required]. Accessed November 18, 2009

American Board of Pediatrics Content Specification(s):

15_Neurology: Know the basis for (including genetic), clinical and laboratory features 
(including associated abnormalities), differential diagnosis, management, and outcomes of 
neonatal hypotonia/neuro- muscular weakness

15_Neurology: Know the pathogenesis, evaluation, clinical and laboratory features, 
management, and outcomes of neonatal arthrogryposis

16_Development_Behavior: Know how a newborn infant’s posture, spontaneous activity, and 
elicited movements are influenced by postmenstrual age and neurologic status

16_Development_Behavior: Know the significance of abnormal tone (eg, hypotonia and 
hypertonia) in infancy

16_Development_Behavior: Know the significance of persistent neuromotor abnormalities in 
infancy (including asymmetries)
September

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Overview
ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 10 Correct Answers: 2

Question 10

A 12-week-old female infant who weighed 2,640 g at birth at an estimated gestational age of 38 weeks, is being evaluated for a skeletal disorder. Fetal limb shortening and long bone fractures had been detected on ultrasonography at 30 weeks' gestation. The family history is negative for skeletal disorders, congenital malformations, or chromosomal syndromes.

Physical examination of the infant reveals short stature, with a crown-heel length of 48.0 cm (markedly below 10th percentile for postmenstrual age), body weight of 4,200 g (10th percentile), and occipito-frontal circumference of 39.0 cm (25th percentile). All extremities are severely shortened with involvement of both proximal and middle segments and appearance of increased skin creases at the joints. The hands and feet appear normal. Cranial examination reveals brachycephaly, sloped forehead, triangular facies, and prominent eyes with blue sclerae. The infant is alert, in no distress, and breathing spontaneously in room air. She is receiving full oral feeds of fortified human milk.

Skeletal radiography shows fractures of long bones and shortening of all extremities (Figures 1 through 4), fractures of ribs in various stages of callus formation (Figure 5), poorly ossified flat vertebral bodies with kyphosis of spine (Figure 6), and undermineralized skull (Figures 7 and 8). Molecular genetic studies reveal a glycine substitution mutation (Gly367Glu) in collagen 1 alpha-2 (COL1A2) gene, which confirms the diagnosis of osteogenesis imperfecta.

Figure 1: Skeletal radiography right arm
Figure 2: Skeletal radiography left arm
Figure 3: Skeletal radiography right leg

Figure 4: Skeletal radiography left leg
Figure 5: Skeletal radiography chest

Figure 6: Skeletal radiography spine
Figure 7: Skeletal radiography skull anterior-posterior view
Figure 8: Skeletal radiography skull lateral view
Of the following, the clinical and laboratory features in this infant are MOST consistent with osteogenesis imperfecta:

- A. type I
- B. type II
- C. type III
- D. type IV
- E. type V

Incorrect:
Correct Answer: C

Osteogenesis imperfecta (OI) is a genetic disorder characterized by increased bone fragility, low bone mass, and other connective tissue manifestations. In most patients (90% of cases), the disorder is caused by a mutation in one of two genes that encode collagen type 1, the major protein constituent of bone and connective tissue. The collagen type 1 molecule consists of three polypeptide chains (two alpha-1 and one alpha-2) that form a triple-helical structure. For the three chains to intertwine correctly, they must possess a glycine residue at every third position of the amino acid sequence. The most typical sequence abnormality associated with OI is a point mutation that affects a glycine residue in either collagen 1 alpha-1 (COL1A1) gene (an 18-kb gene
located on the long arm of chromosome 17) or collagen 1 alpha-2 (COL1A2) gene (a 38-kb gene located on the long arm of chromosome 7). The resulting phenotype varies from mild to lethal depending on which of the two alpha chains is affected, the position in the triple helix at which the glycine substitution arises, and the amino acid that substitutes for glycine. The infant in this vignette has a glutamine substitution for glycine in position 367 of the COL1A2 gene that typically manifests with a moderate to severe phenotype.

Osteogenesis imperfecta is classified into seven types based on the inheritance pattern, genetic mutation, and phenotypic expression (Table).

<table>
<thead>
<tr>
<th>Table: Classification of Osteogenesis Imperfecta*</th>
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<tr>
<td>Type</td>
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<td>VII</td>
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* Adapted from Rauch and Glorieux (2004).

OI type III, the appropriate classification for the infant in this vignette, is the most severe form of the disorder that affects children surviving the neonatal period. Typical clinical features, detectable at birth, include progressive deformities of limbs from repeated fractures, short stature from limb and spine deformities, and potential respiratory difficulties from rib fractures. Typical extraskeletal manifestations include blue or grey sclera, abnormal dentin (dentinogenesis imperfecta), hyperlaxity of ligaments and skin, hearing impairment from abnormal ossicles, and presence of wormian bones on skull radiography. Although the typical inheritance pattern is autosomal dominant, spontaneous de novo mutations involving glycine substitution in COL1A1 or COL1A2 genes can occur.

Osteogenesis imperfecta type I is the least severe form of the disorder. The typical inheritance pattern is autosomal dominant, and the genetic mutation involves a premature stop codon in COL1A1 gene. Although the affected children are predisposed to bone fractures, mostly in preschool years, limb deformities are rare, and the stature remains normal. Typical extraskeletal manifestations include blue sclera, hyperextensible joints, and hearing loss beginning in the second to third decade. The teeth are usually normal without discoloration.

Osteogenesis imperfecta type II is the perinatal lethal form of the disorder. The typical inheritance pattern is autosomal dominant, and the genetic mutation involves a glycine substitution in COL1A1 or COL1A2 gene. The characteristic bone changes that can be detected on fetal ultrasonography as early as at 14 weeks’ gestation include markedly undermineralized skull, platyspondyly, broad beaded ribs, and deformed micromelic long bones. Most affected infants are either stillborn or die of respiratory failure within 24 hours after birth.
Osteogenesis imperfecta type IV is a moderately severe form of the disorder. The typical inheritance pattern is autosomal dominant, and the genetic mutation involves a glycine substitution in COL1A1 or COL1A2 gene. The phenotype is characterized by mild to moderate limb deformities from bone fractures, mild to moderate shortening of stature, white or grey sclera, abnormal dentin, and variable hearing loss.

Osteogenesis imperfecta type V, akin to type VI and type VII, is a newly classified form of the disorder. The typical inheritance pattern is autosomal dominant, and the genetic mutation remains undefined. The phenotype is similar to that seen in OI type IV except for normal dentition and white sclera. Additional distinguishing features of OI type V include interosseous calcification of forearm, dislocation of radial head, and excessive callus formation at fracture sites.

References:


Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

05_Genetics_Dysmorphism: Recognize clinical features associated with autosomal dominant disorders

05_Genetics_Dysmorphism: Know how age at presentation (in utero, neonate, infancy or later) affects the differential diagnosis of the clinical presentation of genetic disorders

05_Genetics_Dysmorphism: Recognize the clinical features and know how to diagnose and manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodysplasia epiphysial dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

05_Genetics_Dysmorphism: Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis
A 27-day-old infant, who had been born at 25 weeks’ gestation, develops painful erythema and swelling of her left lower extremity. Plain radiographs of the leg are negative for fracture or focal abnormality. Her white blood cell count is 17,000/μL (17.1×10⁹/L), and C-reactive protein concentration is 36.9 mg/dL (3514.3 nmol/L). Blood cultures yield *Staphylococcus aureus*. After 10 days of treatment with oxacillin, a follow-up radiograph of the left lower leg is obtained (Figure 1).

**Figure 1: Radiograph of right and left lower leg**

Of the following, the MOST accurate statement regarding infection in this neonate is that:

- A. multiple bone involvement is rare
- B. radiographic findings are unusual 10 days after onset
- C. the cartilaginous growth plate provides a barrier against spread of infection
- D. the metaphysis is the most common site of origin
- E. the tibia is rarely affected
The neonate in the vignette has clinical and radiographic findings consistent with osteomyelitis of her left tibia. As is most common, she exhibited redness and swelling of the affected extremity with diminished spontaneous movement without systemic manifestations. Plain radiography demonstrates an extensive periosteal reaction along the proximal aspect of her tibia (Figure 2).

Osteomyelitis refers to inflammation of bone caused by infection. In neonates, osteomyelitis typically is an acute process, resulting from hematogenous dissemination in the course of septicemia. Direct inoculation from heel capillary blood sampling, for example, or indirect contamination from surrounding soft tissue infection also provide routes for microorganisms to reach skeletal tissues. The most common causative organism is *Staphylococcus aureus*, which is responsible for up to 85% of cases. This predominance may be related to the capacity of *S. aureus* to express bacterial adhesins that promote attachment to extracellular bone matrix. Other organisms to consider in the neonate include *Streptococcus agalactiae*, *Streptococcus pneumoniae*, enteric gram-negative bacteria, and *Candida albicans*.

Because of the rich vascular supply, the metaphyseal region of the long bone is most often the primary site of neonatal osteomyelitis. Infecting organisms travel to metaphyseal capillary loops adjacent to the cartilaginous growth plate. In this region, blood flows slowly, providing pathogens an ideal environment for replication and subsequent local inflammation. The large vascular space and thin spongy structure of the infant’s metaphyseal cortex permit early decompression of infection into the subperiosteal space. As a result, the bone marrow compartment seldom is involved in neonatal osteomyelitis. In addition, the bony metaphyses of children younger than 18 months are vascularized by persistent fetal vessels that penetrate the cartilaginous epiphyseal plates and end in the epiphyses and joint spaces. Consequently, osteomyelitis in neonatal long bones often leads to epiphysitis, resulting in severe and usually irreparable damage to the cartilaginous growth plate. Furthermore, septic arthritis is a common sequel, particularly in the hip joint, in which the metaphysis is intracapsular. By 18 months of age, the vascular connections between metaphysis and epiphysis are obliterated, and the cartilaginous growth plate provides a barrier for the spread of infection.

In the neonate, osteomyelitis most frequently affects the femur (39% of cases), followed by the humerus (18%), tibia (14%), radius (5%), and maxilla (4%). Multiple bone involvement is common in the neonate, occurring in 33% or more of cases. Vertebral involvement is rare in the neonate.

Laboratory and radiographic studies aid in the diagnosis of osteomyelitis. At presentation, the peripheral white blood cell count may be normal or elevated (average count of 17,000/μL [17.0×10^9/L]). More sensitive than erythrocyte sedimentation rate, C-reactive protein concentration is elevated in 98% of cases, peaks within 48 hours of infection, and returns to normal 7 to 10 days after initiation of appropriate treatment. Blood and bone cultures result in pathogen identification in up to 80% of cases.

During the first few days of infection, plain radiographs may demonstrate swelling of soft tissues around the site of infection. The first distinct evidence of bone involvement includes periosteal and lytic changes, and requires involvement of at least one third of the bony matrix. Unlike older children in whom radiographic changes are delayed up to 3 weeks, the neonate with osteomyelitis almost always demonstrates signs of bone destruction after only 7 to 10 days. Because of the efficient vasculature, the reparative phase begins within 2 weeks and involves the formation of subperiosteal bone. Bone destruction may continue,
with rapid absorption of necrotic foci and deposition of new bone. Remodeling of the shaft takes several months (Figure 3). A skeletal survey helps to identify multiple sites of infection.

Similarly, ultrasonography may detect periosteal thickening and subperiosteal collections as early as 48 hours after onset of infection, but a normal study does not exclude osteomyelitis. Skeletal scintigraphy, using technetium-labeled methylene diphosphonate isotope, is 80% to 100% sensitive within 72 hours of onset of infection. Scintigraphy is useful for detecting multiple foci of infection and in cases in which suspicion is high, yet radiographic or ultrasonographic results are equivocal. Computed tomography provides good definition of cortical bone, is sensitive for early detection of bony changes, and is helpful in diagnosing osteomyelitis of the skull associated with an infected cephalohematoma. Magnetic resonance imaging (MRI) affords excellent anatomic detail of muscle, soft tissue, and contrasting bone. MRI aids in early detection of inflammatory or destructive intramedullary disease, and is useful in the evaluation of vertebral involvement and growth plate involvement.

Antibiotic treatment of osteomyelitis is directed at the infecting organism, and a duration of 3 to 6 weeks is indicated to avoid relapse. The incidence of sequelae from neonatal osteomyelitis ranges from 6% to 50% of cases. Delay in diagnosis (>3-4 days), inadequate duration of treatment, and young age at presentation are risk factors for complications. Disturbance in bone growth, limb length discrepancies, joint deformities (particularly with hip and knee joints), arthritis, abnormal gait, and pathologic fractures may be seen. Long-term follow-up beyond infancy is indicated.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Infectious Diseases: Know the causative infectious agents and pathogenesis of osteomyelitis and septic arthritis

Infectious Diseases: Know the clinical and laboratory features and differential diagnosis of osteomyelitis and septic arthritis

Infectious Diseases: Know the management and complications of osteomyelitis and septic arthritis

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Figure 2: Extensive periosteal reaction along the proximal aspect of the left tibia, with mottling noted throughout tibia.
Figure 2: Extensive periosteal reaction along the proximal aspect of the left tibia, with mottling noted throughout tibia
Figure 3: A, Acute periosteal reaction at 10 days. B, Osseous remodeling with thick periosteal new bone formation 1 month after onset of infection.
**Question: 10**

A woman with no prenatal care arrives in your hospital with a footling breech presentation. You are called to the urgent cesarean section. As you scrub, you are told that the presenting foot has six toes: an extra toe is next to the fifth or little toe.

Of the following, the MOST common syndrome presenting with postaxial polydactyly is:

- **A.** Down
- **B.** Ellis-van Creveld
- **C.** Greig
- **D.** Meckel-Gruber
- **E.** Patau

**Correct**

Polydactyly of the feet (Figure 1), hands (Figure 2), or both, is found in 1 in 3,000 white live births in the United States, and 1 in 300 births in the African-American population. It can be described as preaxial (radial or large toe side), postaxial (ulnar or little toe side), or mesoaxial (involving the middle three fingers). Most cases (85%-95%) are isolated, with no abnormalities beyond the limbs. Patau syndrome is the most common syndrome to be associated with postaxial polydactyly.

Asyndromic, isolated polydactyly is autosomal dominant with incomplete penetrance. The
expression of the severity of polydactyly in a family is highly variable. The risk of polydactyly being associated with another anomaly, including another limb anomaly such as syndactyly, is 15% in one large study. The risk decreases to 7% if the polydactyly is postaxial and in the foot. The risk of another anomaly increases to 20% if the polydactyly is preaxial, 23% if both hand and foot postaxial polydactyly are found in the same child, and 50% if the polydactyly is mesoaxial.

If other limb anomalies are excluded, only 6% of patients with polydactyly are found to have another congenital anomaly, almost exclusively as part of a syndrome. Most (75%) of these syndromic cases are explained by Patau, Down, or Meckel-Gruber syndromes. The other 25% of syndromic cases is composed of more than 100 other syndromes.

Patau syndrome, or trisomy 13, occurs in 1 in 5,000 live births. Characteristics include holoprosencephaly, deformed lip or palate, postaxial polydactyly, hyperconvex nails, cutis aplasia of the scalp, and cardiac malformations.

Down syndrome, or trisomy 21, is found in 1 in 660 live births. It is not associated with postaxial polydactyly. The few cases of polydactyly found in patients with Down syndrome have been preaxial.

Meckel-Gruber syndrome, or dysencephaly splanchnocystica, affects 1 in 135,000 live births. Abnormalities include occipital encephalocele, cystic renal dysplasia, hepatic cysts, and polydactyly. Inheritance is autosomal recessive and may involve several loci, including chromosome regions 17q21-24, 11q13, and 8q24.

Greig syndrome, or cephalopolysyndactyly, involves 1 in 100,000 live births. It is characterized by polydactyly, syndactyly, and frontal bossing. Inheritance is autosomal dominant and involves the GLI3 gene at chromosome region 7p13. This gene is part of the Sonic hedgehog pathway of limb development.

Pallister-Hall syndrome also involves the gene GLI3, and seems to be a severe form of gene disruption. Features include polydactyly, imperforate anus, and hypothalamic hamartoblastoma. Inheritance is autosomal dominant with just over 100 cases reported.

Ellis-van Creveld syndrome, or chondroectodermal dysplasia, occurs in 1 in 60,000 live births, or 1 in 200 live births in the Old Amish community. It is characterized by polydactyly, nail hypoplasia, short distal extremities, a short upper lip with accessory frenula to the alveolar ridge, and an atrial septal defect. Inheritance is autosomal recessive and involves chromosome region 4p16.

Additional readings:
NeoReviewsPlus, February 2006, Question 5.

NeoReviewsPlus, June 2006, Question 2.

Suggested Readings


Everman DB. Hands and feet. Human Malformations and Related Anomalies. 2nd ed.
American Board of Pediatrics Content Specification(s)

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
Print

Figure 1: Postaxial polydactyly of the left foot (from PREP Self-Assessment 2005 Item 4; courtesy M. Rimsza, MD).

September

Question View: [All (10)]

Mode: [Learner] [Exam]

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 10 Correct Answers: 9
Figure 2: Postaxial polydactyly of the right hand (from PREP Self-Assessment 2010 Item 119; courtesy D. Krowchuk, MD).
Question: 10

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Suggested Readings


American Board of Pediatrics Content Specification(s)

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
October

**Question: 1**

A male infant was born at 39 weeks’ gestation with a birthweight of 2,910 g (25%-50%), length of 30.8 cm (<10%), and head circumference measuring 38 cm (>90%). Fetal ultrasonography at 20 weeks’ gestation revealed short humeri, radii, ulnas, and tibias with normal-sized hands and feet. The infant’s femurs were short, bowed, and curved. In addition, the ribs appeared short with a small chest. A radiograph of the chest and abdomen is shown in Figure 1. Skull radiographs were normal. Testing of a fibroblast growth factor receptor 3 gene on exon #7 confirmed the diagnosis.

**Figure 1**
Of the following, the MOST likely skeletal abnormality found in infants with this disorder is:

- A. acromelia
- B. amelia
- C. micromelia
- D. phocomelia
- E. rhizomelia

Correct

Short-limb dysplasias are developmental disorders of chondro-osseous tissues that result from mutations in genes expressed in these tissues (primary dysplasia) or extraosseous factors impairing bone development (secondary dysplasia). At present, skeletal dysplasias are classified into 37 groups based on molecular causes, radiographic findings, and clinical features. Shortening of the extremities can involve the entire limb (micromelia), the proximal segment (rhizomelia), the proximal and intermediate segment (phocomelia), the intermediate segment (mesomelia), or the distal segment (acromelia) (Figure 2, Table 1).

The constellation of findings in the infant in this vignette is most consistent with
Thanatophoric dwarfism (TD). This congenital disorder is the most common type of lethal neonatal skeletal dysplasia, occurring in approximately 1 in 20,000 to 50,000 live births. In Greek, the term thanatophoric means death-bearing. This dysplasia is caused by a mutation of the fibroblast growth factor receptor 3 gene (FGFR3) on the short arm of chromosome 4.

Two forms of TD have been identified with the characteristics shown in Table 2. Type I is the more common form, recognized by bowed “telephone receiver” femurs (Figure 3) while type II is characterized by a cloverleaf skull and short, straight long bones. The term cloverleaf refers to the three leaves formed by the prominent frontal bone in the middle and the two temporal bones on the sides. This form of craniosynostosis results from premature closure of the coronal and lambdoid sutures. Almost all affected infants with TD, regardless of type, have megalencephaly, which most often involves the temporal lobes. Affected individuals also have a prominent forehead, a normal trunk length, and flat, underdeveloped vertebral bodies, known as platyspondyly.

The radiographic images of the infant in this vignette demonstrate rhizomelia (Figure 3), which is the most common skeletal abnormality found in affected individuals with either type of TD. Rhizomelia is also commonly found in infants with achondroplasia, asphyxiating thoracic dystrophy (Jeune syndrome), the rhizomelic type of chondrodysplasia punctata, congenital short femur, and diastrophic dysplasia.

Rhizomelia is characterized by short humeri and femurs; this diagnosis requires comparison of the dimensions of each segment of the upper and lower extremities.

Although the infant in this vignette has radiographic findings of mesomelia, this finding is typically infrequent in infants affected by TD (Figure 3). Mesomelia is characterized by shortening of the forearm (radius-ulna) and leg (tibia-fibula) and found in individuals with mesomelic dwarfism. In rare instances, the distal segments are also involved, leading to acromesomelic dwarfism. The diagnosis of mesomelia requires comparison of the dimensions of each segment of the upper and lower extremities.

Acromelia refers to shortening of the hands and feet. The short distal abnormalities are usually associated with shortened stubby digits with the most prominent shortening found in the metacarpals and metatarsals. Some syndromes characterized by acromelia may be associated with craniofacial, ectodermal, and other organ abnormalities. Many affected individuals have abnormalities of patterning genes that are important in early limb bud formation. Ellis-Van Creveld syndrome, also known as chondroectodermal dysplasia, is characterized by acromelic limb shortening, polydactyly, and ectodermal dysplasia involving the nails, teeth, and gums; congenital heart disease is also common.

Amelia is the absence of skeletal parts distal to a defect in an extremity. Complete amelia involves all four limbs. This malformation is usually caused by a disruption of normal development as a result of a teratogenic exposure, mechanical event (eg, amniotic band syndrome), or vascular accident.

Micromelia is the abnormal shortening of all three segments of one or more limbs. In most cases, all four limbs are affected. In general, affected bone segments are extremely hypoplastic and the shafts of the long bones appear very small and curved. Several disorders are affected by micromelia, including achondrogenesis, diastrophic dysplasia, fibrochondrogenesis, osteogenesis imperfecta, type II, and short rib-polydactyly syndromes, types I and III.

Phocomelia is the absence or shortening of the proximal and intermediate upper limbs. The term phoco (=seal) is based on the similar appearance of the infant’s arm and a seal’s flipper. Although the fingers of the hands may be fused, the hands are usually of normal size. In severe cases, the legs may also be affected, leading to an appearance of an infant with hands and feet that are attached directly to the body (known as tetraphocomelia). Phocomelia was observed as a side effect in fetuses exposed to...
maternal thalidomide during the first trimester.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Genetics/Dysmorphism: Recognize the clinical features and know how to diagnose and manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc
Figure 2: Shortening of the extremities can involve the entire limb (micromelia), the proximal segment (rhizomelia), the proximal and intermediate segment (phocomelia), the intermediate segment (mesomelia), or the distal segment (acromelia).

**Question: 1**

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### Table 1: Variations in Shortening of the Extremities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Involved Area</th>
<th>Some Associated Dysplasias</th>
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<tbody>
<tr>
<td>Acromelia</td>
<td>Shortening of distal segment of extremities</td>
<td>Ellis-Van Creveld syndrome</td>
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<tr>
<td>Mesomelia</td>
<td>Shortening of intermediate segment of extremities</td>
<td>Mesomelic dysplasia</td>
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<tr>
<td>Micromelia</td>
<td>Shortening of entire limb</td>
<td>Achondrogenesis</td>
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<td></td>
<td></td>
<td>Diastrophic dysplasia</td>
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<tr>
<td></td>
<td></td>
<td>Fibrochondrogenesis</td>
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<td></td>
<td></td>
<td>Osteogenesis imperfecta, type II</td>
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<td></td>
<td></td>
<td>Short rib-polydactyly syndromes, types I and III</td>
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<td>Phocomelia</td>
<td>Shortening of proximal and intermediate segment of extremities (arms more affected than legs)</td>
<td>Effects of thalidomide</td>
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<td>Roberts tetraphocomelia syndrome</td>
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<tr>
<td>Rhizomelia</td>
<td>Shortening of proximal segment of extremities</td>
<td>Achondroplasia</td>
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<td>Asphyxiating thoracic dystrophy (Jeune syndrome)</td>
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<td></td>
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<td>Thanatophoric dwarfism</td>
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### Table 2: Comparison of the Two Types of Thanatophoric Dwarfism (TD)

<table>
<thead>
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<th>Feature</th>
<th>Type I TD</th>
<th>Type II TD</th>
</tr>
</thead>
<tbody>
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<td>Skeleton</td>
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<td>Marked underdevelopment of the entire skeleton</td>
</tr>
<tr>
<td></td>
<td>Extreme rhizomelia</td>
<td>Rhizomelia</td>
</tr>
<tr>
<td></td>
<td>Short, bowed long bones with metaphyseal flaring (&quot;telephone receivers&quot;)</td>
<td>Short, straight long bones with flared and cupped metaphyses</td>
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<tr>
<td></td>
<td>Normal trunk length</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal hands except fingers short</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal feet</td>
<td></td>
</tr>
<tr>
<td>Vertebrae</td>
<td>Flat and underdeveloped</td>
<td>Flat (not as severe as Type I TD)</td>
</tr>
<tr>
<td></td>
<td>Platypondyly (vertebral bodies with a small vertical diameter)</td>
<td>Platypondyly (vertebral bodies with a small vertical diameter)</td>
</tr>
<tr>
<td></td>
<td>Large intervertebral spaces</td>
<td>Large intervertebral spaces</td>
</tr>
<tr>
<td>Cloverleaf skull</td>
<td>May or may not be present</td>
<td>Present in almost all affected individuals</td>
</tr>
<tr>
<td>Other</td>
<td>Narrow thorax</td>
<td>Narrow thorax</td>
</tr>
<tr>
<td></td>
<td>Relatively large head</td>
<td>Relatively large head</td>
</tr>
<tr>
<td></td>
<td>Prominent forehead</td>
<td>Prominent forehead</td>
</tr>
</tbody>
</table>

**Assessment Progress:** Total Questions: **10**  Questions Answered: **10**  Correct Answers: **9**
Print

Figure 3: The radiographic findings found in this figure are consistent with thanatophoric dwarfism, type I. Rhizomelia is evident with shortened humeri and femurs. Mesomelia is also apparent because of the infant’s shortened radii and ulnae. The femurs and humeri are bowed, which is often referred to as “telephone receiver” configuration of bone. No fractures are identified. The chest appears small with shortened ribs. The pelvis is abnormal with horizontal bilateral acetabular roof. The cervical vertebrae show platyspondyly. The ossification of the bones is normal. Cardiac silhouette looks prominent because of the small size of the chest.
Question: 10

You are seeing a 4-month-old infant in the neurodevelopmental follow-up clinic. He was born at 32 weeks’ gestation and his neonatal course was complicated by mild respiratory distress syndrome and necrotizing enterocolitis. His mother is concerned about his head shape. On physical examination, marked flattening of the right occiput is noted. Looking down at his head from above, you note right frontal bossing and anterior deviation of the right ear, such that his head is shaped like a parallelogram (Figure 1). The remainder of the physical examination demonstrates mild generalized hypotonia.

Figure 1: Vertex view. Adapted and reprinted with permission from Kabbani H, Raghuveer TS. Craniosynostosis. Am Fam Physician. 2004;69:2863-2870.

Of the following, the skull deformity in this infant is MOST likely the result of:

- [ ] A. coronal synostosis
- [ ] B. deformational plagiocephaly
- [ ] C. lambdoid synostosis
- [ ] D. metopic synostosis
Craniosynostosis is the premature fusion of one or more of the calvarial sutures. In full-term infants, well-formed skull bones are separated by strips of connective tissue, sutures, and fontanelles (Figure 2). The calvarial sutures permit head malleability during passage through the birth canal, and serve as growth sites where new bone is deposited as the neurocranium expands.

Craniosynostosis occurs in 1 in 2,500 births, and 20% of cases are syndromic. The cause of craniosynostosis is unclear. Among isolated synostoses, 2% to 6% of sagittal and 8% to 14% of coronal synostoses are familial and transmitted in an autosomal dominant fashion. Fetal osteogenic growth is regulated in part by fibroblast growth factor receptor (FGFR), and mutations in the genes coding for FGFR1 and FGFR2 are implicated in syndromic craniosynostoses, specifically Pfeiffer syndrome (FGFR1) and Apert and Crouzon syndromes (FGFR2).

Premature fusion of calvarial sutures is a prenatal event, but initial physical examination findings may be subtle and delay diagnosis for several months. A persistent palpable ridge at the suture line in association with an abnormally shaped head suggests craniosynostosis. Plain radiography demonstrates bony bridging across the suture, sclerosis, and loss of suture clarity. Computed tomography assesses fusion of the suture, evaluates for structural abnormalities, and can exclude other causes of asymmetric cranial vault growth.

In addition to skull deformity, untreated craniosynostosis may result in inhibition of brain growth, increase in intracranial and intra-orbital pressure, asymmetry of the face, and malocclusion. Developmental delays and reduced IQs are associated with untreated craniosynostosis. Treatment options include strip craniectomy and cranioplasty, with intervention optimally occurring by 9 months of age.

Recognizable patterns of skull deformity or calvarial shape characterize each type of sutural synostosis (Figure 3). Growth restriction occurs in a plane perpendicular to the plane of the fused suture. Compensatory changes occur frequently and in a plane parallel to the fused suture. Clinical diagnosis can be made by viewing the infant’s head from the top (vertex view) and assessing head shape. Likewise, the shape of the head can distinguish craniosynostosis, particularly lambdoid synostosis, from plagiocephaly without synostosis.

Deformational plagiocephaly, occipital plagiocephaly or plagiocephaly without synostosis, is a benign cause of skull deformity associated with occipital flattening. Typically, the head is round at birth with progressive deformation noted over weeks to months. The cause is related to positioning of the head in the same manner over a prolonged period. Risk factors for deformational plagiocephaly include abnormal fetal positioning, torticollis, hypotonia, and back-to-sleep positioning. Deformational plagiocephaly is characterized by asymmetric occipital flattening and ipsilateral forehead bossing as deforming forces are exerted in a ventral direction (Figure 4). The following features distinguish deformational plagiocephaly from lambdoid synostosis:

- Absence of posterior bossing (contralateral in lambdoid synostosis)
• Prominent ipsilateral frontal bossing (absent or contralateral in lambdoid synostosis)
• Anterior displacement of the ipsilateral ear (posteriorly displaced toward the fused suture in lambdoid synostosis)
• Parallelogram-shaped head (trapezoid-shaped in lambdoid synostosis)

With positional plagiocephaly, examination of the face may show flattening of the malar eminence and the mandible contralateral to the occipital flattening, with the nasal radix remaining midline. The infant in the vignette has abnormalities of his head shape consistent with deformational plagiocephaly. Treatment is nonsurgical. Conservative measures such as intentional change in positioning can improve head shape, and the use of a customized molding helmet before age 1 year can be successful in severe cases.

Coronal synostosis comprises 20% to 30% of cases of craniosynostosis. Unilateral coronal synostosis results in flattening of the forehead and frontoparietal region ipsilateral to the fused suture, with compensatory bulging of the contralateral frontoparietal region. Additional characteristic features include anterior displacement of the ipsilateral ear and deviation of the tip of the nose to the contralateral side. Bilateral coronal synostosis results in anteroposterior shortening of the skull, flattening of the occiput and temporal convexity (brachycephaly, Figure 3), and elevation of the height of the skull (turribrachycephaly).

Metopic synostosis comprises fewer than 10% of cases of craniosynostosis and results in restriction of transverse growth of the frontal bones and trigonocephaly or a triangular-shaped head (Figure 3). Narrowing of the temporal regions reduces the intermedial canthal distance, but true hypotelorism does not exist. Mild metopic synostosis may cause elevation of the suture, but no trigonocephaly.

Lambdoid synostosis is uncommon. Unilateral fusion is characterized by ipsilateral parieto-occipital flattening, contralateral parietal occipital compensatory bulging, and posterior displacement of the ipsilateral ear as the petrous portion of the temporal bone is pulled toward the closed suture. Forehead asymmetries may be associated, resulting in a trapezoid-shaped head (Figure 3). The presence of ipsilateral forehead flattening and posterior displacement of the ear help to distinguish unilateral lambdoid synostosis from deformational plagiocephaly (Figure 4). Bilateral lambdoid synostosis results in occipital flattening and increased biparietal diameter (brachycephaly).

Sagittal synostosis is the most frequently observed form of craniosynostosis, occurring in 40% to 60% of cases. Affected boys outnumber girls 4:1. Fusion of the sagittal suture is characterized by restriction in transverse growth of the skull, biparietal and temporal narrowing, and compensatory growth in the frontal and/or occipital region. The resultant head shape is scaphocephaly (dolichocephaly) (Figure 3).

More than 150 syndromes include craniosynostosis as a feature, with Apert and Crouzon syndromes accounting for the majority of cases. Typically, multiple sutures are involved. Apert syndrome is characterized by bilateral coronal synostosis with turribrachycephaly, midface hypoplasia, and complex syndactyly of the hands and feet. Crouzon syndrome is characterized by bilateral coronal synostosis, hypertelorism, midface hypoplasia with associated exorbitism, but no abnormalities of the hands or feet. These syndromes are inherited in an autosomal dominant fashion, though 50% of cases result from spontaneous mutation.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Genetics/Dysmorphism: Recognize the clinical features and know how to diagnose and manage craniofacial anomalies

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Figure 3: Characteristic calvarial shape secondary to sutural synostoses. Adapted and reprinted with permission from Kabbani H, Raghuvir TS. Craniosynostosis. Am Fam Physician. 2004;69:2863-2870.

- Metopic synostosis
- Unilateral lambdoid synostosis
- Sagittal synostosis
- Coronal synostosis
Figure 4: Parallelogram-shaped cranium secondary to deformational plagiocephaly (left). Trapezoid-shaped cranium secondary to lambdoid synostosis (right). Adapted and reprinted with permission from Kabbani H, Raghuveer TS. Craniosynostosis. Am Fam Physician. 2004;69:2863-2870.

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