January

Question 1

You see an infant with an unusual facial appearance that is not typical of any of the described dysmorphic syndromes. Observation of family picture albums reveals infant pictures of older family members with similar features. Of note, all grew to adulthood, and other than having similar facial features, they have no matching health problems. You consider the genetic possibilities underlying this phenomenon and consider the variations in gene structure that could underlie this change.

Of the following, in the human genome, the MOST common modification in gene structure is:

- A. deletion
- B. duplication
- C. insert
- D. nucleotide variation
- E. wild type

Of the 25,000 genes comprising the human genome, gene sequencing among different people is identical 99% of the time. Although this is obviously a high concordance, the potential for considerable variation remains high because the human genome has 3.3 billion base pairs. There are estimated to be 12 million potential variations between any two persons' genomes. The most frequent or unmodified base pair sequence of a given segment of DNA or gene is termed the wild, or common, allele. Infrequently occurring differences in DNA structure, defined as being found in less than 1% of the population, are termed mutations. Differences occurring more frequently (>1%) are termed polymorphisms.

The most frequent type of polymorphism results from changes in single base pairs (nucleotide variation) and is known as single-nucleotide polymorphism (SNP). In the human genome, over 12 million SNPs have been catalogued. An SNP may occur anywhere along the DNA helix. If the SNP affects the amino acid coding portion of a gene, the resultant protein may be absent or dysfunctional. A change in noncoding segments of DNA may affect other aspects of transcription, such as the promoter or enhancer, or there may be no demonstrable adverse effect.

Single-nucleotide polymorphisms are relatively easy to detect, but the true relationship of a particular SNP to a disease state or condition is more difficult to ascertain. If the goal is to
use the presence/absence of an SNP as a marker of risk, the identified SNP among patients
could be either truly a part of the gene associated with the condition in question or located
nearby (closely linked) on the chromosome. On the other hand, if the goals are to use gene
function(s) to understand the biology of a condition and/or to devise a new treatment,
finding abnormalities directly affecting the gene controlling the condition in question is more
essential and difficult.

Polymorphisms of DNA that are less common than SNPs include deletions or insertions of
DNA segments into or from the wild DNA allele. Another variant of polymorphism involves
duplication of segments of DNA, often repeating several times (tandem repeats). As with
SNPs, some of these variants may occur in active genes or in DNA affecting gene expression
and thus be associated with a phenotype or with a disease; other variants may be silent.

For the case in the vignette, because no genetic marker has been previously identified, a
case control study of affected individuals’ DNA could be conducted to identify SNPs or other
polymorphisms associated with affected individuals and absent from the DNA of unaffected
family members. This process is called linkage analysis. If such an association were found,
the hypothesis that this variant truly is related to the facial features would then require
confirmatory studies. Whether these studies should be done can only be determined from the
impact of the condition on affected individuals and the ability of the genetic knowledge to
further desired health outcomes.

References:

Attia J, Ioannidis JPA, Thakkinstian A, et al. How to use an article about genetic association:
A, background concepts. JAMA. 2009;301:74-81

Attia J, Ioannidis JPA, Thakkinstian A, et al. How to use an article about genetic association:
B, are the results of the study valid. JAMA. 2009;301:191-197

Attia J, Ioannidis JPA, Thakkinstian A, et al. How to use an article about genetic association:
C, what are the results and will they help me in caring for my patients? JAMA. 2009;301:304-308

American Board of Pediatrics Content Specification(s):

05_Genetics_Dysmorphism: Know how linkage studies are used clinically
05_Genetics_Dysmorphism: Know the meaning of the terms point mutation, polymorphism,
and haplotype
05_Genetics_Dysmorphism: Know basic functional units of a gene, including intron, exon,
promoter, enhancer, and polyadenylation sequence
A full-term female infant with a late prenatal diagnosis of tetralogy of Fallot is admitted to the neonatal intensive care unit. Her examination reveals the following dysmorphic craniofacial features: cleft palate; prominent nose with squared nasal root and narrow alar base; narrow palpebral fissures; abundant scalp hair; vertical maxillary excess with a long face; and a retruded mandible with chin deficiency. The infant’s initial serum ionized calcium is 2.4 mg/dL (0.6 mmol/L).

Of the following, genetic testing for this infant is MOST likely to discover a:

- A. deletion
- B. duplication
- C. monosomy
- D. single gene mutation
- E. trisomy

Correct Answer: A

The infant in this vignette most likely has DiGeorge syndrome (DGS), also known as velocardiofacial, CATCH22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia), Shprintzen, or conotruncal anomaly face syndrome. In 1981, the deletion associated with DGS was identified on chromosome 22 at q11.2. Three megabases of DNA are lost from this site in 80% to 90% of people affected with DGS. This deletion corresponds to an insufficiency of approximately 40 contiguous genes, many of which have not been well characterized. The next most common omission arises proximal to this deletion; this smaller defect removes 25 genes.

DiGeorge syndrome is an autosomal dominant disorder and is the most common chromosomal deletion syndrome in humans, occurring in 1 in 4,000 live births. The pattern of organ malformations involving the heart, thymus gland, and parathyroid gland coincides with an abnormal migration of neural crest cells leading to abnormal development of the fourth branchial arch and third and fourth pharyngeal pouches.

Eighty-five percent of affected individuals have conotruncal defects,
including tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, or perimembranous ventricular septal defects. Characteristic craniofacial findings in this disorder include the following: secondary cleft palate; prominent nose with squared nasal root and narrow alar base; narrow palpebral fissures; abundant scalp hair; deficient malar area; vertical maxillary excess with a long face; retracted mandible with chin deficiency; and microcephaly (accessed May 20, 2009). Affected individuals may have slender and hyperextensible hands and fingers. Patients with DGS may have aplasia or hypoplasia of the thymus leading to abnormal T-cell function. Transient neonatal hypocalcemia resulting from primary hypoparathyroidism may occur in 70% to 80% of infants with DGS. Up to 90% of individuals affected with DGS have developmental delay and low intelligence quotient. Later in life, these individuals are at greater risk for mild to moderate learning problems, attention deficit disorder, autism spectrum disorder, and bipolar disorder.

Ninety percent of the chromosomal deletions associated with DGS arise de novo. Indeed, most affected individuals do not have a family history of this disorder. Only 7% of parents with affected infants have been found to carry the deletion. Parents who carry the deletion may not appear symptomatic as a result of variable expression. Thus, parental testing of this syndrome is critical to assess the recurrence risk in future pregnancies; while the commonly occurring de novo mutations carry a very low recurrence risk, identification of a parental deletion ensures a 50% risk of this disorder in future pregnancies because of the autosomal dominant nature of the deletion.

The variable clinical phenotype of individuals affected with DGS, even among affected members of the same family, highlights the variable expressivity of this disorder. Indeed, this syndrome has been previously described using five distinct names, emphasizing the variable clinical constellations of DGS. Some patients with DGS have mild learning disabilities and subtle craniofacial malformations, while others die in the neonatal period as a result of thymic aplasia and major cardiovascular abnormalities. The diversity of this syndrome is most likely related to the heterozygous microdeletion of approximately 25 to 40 genes on chromosome 22. In addition, environmental factors may also play a role in the diverse phenotype. As a result of variable clinical manifestations, DGS is probably underdiagnosed. Interestingly, the size of the missing DNA is not related to the extent or the severity of DGS. Rather, the deletion of multiple crucial genes spanning the deleted region correlates with disease expression. Thus, a small deletion of critical genes will lead to a more severe phenotype compared with the milder clinical manifestations of individuals who have a larger deletion of less significant genes. Similar phenotypes may occur in affected individuals with nonoverlapping deletions, emphasizing the complex molecular mechanisms underlying this syndrome.

Prenatal and postnatal chromosomal diagnosis of DGS requires a request for fluorescence in situ hybridization (FISH) of the targeted 22q11.2 site. Although FISH testing for this specific deletion can identify most patients with DGS, 7% of affected individuals with clinical features of DGS will have a negative FISH result. While a small percentage of these individuals may have a deletion affecting the short arm of chromosome 10, a chromosomal abnormality is not currently detectable in the remaining group. However, because the phenotype is consistent, these individuals are still considered to have DGS.

Of all the genes that are lost in the DiGeorge deletion, T-box transcription factor (Tbx1) is most responsible for the cardiovascular, craniofacial, thymic, thyroid, and parathyroid manifestations of the syndrome. Indeed, affected individuals with karyotypically normal DGS have been found to have mutations of this gene. The protein for the Tbx1 gene has an extremely dose-sensitive effect; deleterious DGS-like effects are observed with either quantitative or qualitative changes above as well as below its usual limit. Several other genes within the deleted region, such as COMT, CDC45L, HIRA, and UFD1L, may also contribute to the DiGeorge phenotype. DiGeorge phenotype is not associated with chromosomal duplications, monosomies, trisomies, or single gene mutations.

References:
Bishara N, Clericuzio CL. Common dysmorphic syndromes in the NICU. NeoReviews. 2008;9:e29
Dhamne C, Adesida R, Agrawal V. Index of suspicion in the nursery. NeoReviews. 2008:e301


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

03_Cardiovascular: Know the pathophysiology (including genetics) of a neonate with a right-sided cardiac lesion

09_Immunology: Recognize the clinical features and know the evaluation and management of disorders associated with T-cell dysfunction, including DiGeorge sequence and HIV infection

17_EENT_mouth_neck: Know the clinical and diagnostic features of the DiGeorge sequence ( velocardiofacial syndrome, 22q11 deletion)
June

A local pediatrician asks you to “check out a baby” in the newborn nursery. He has been called by the nurses because the infant had a single umbilical artery. The infant was delivered at 38 weeks’ gestation at a birthweight of 3,200 g. The woman’s prenatal course and family history were normal. Gestational age was confirmed on ultrasonography at 10 weeks and repeat ultrasonography findings at 24 weeks’ were normal. No abnormalities are detected on physical examination. You ask the resident to consider the association of congenital anomalies with a single umbilical artery and value of added testing.

Of the following, isolated single umbilical artery HAS BEEN shown to be associated with:

- A. Afro-Caribbean heritage
- B. cardiovascular anomalies
- C. macrosomy
- D. occult renal anomalies
- E. post-term birth

**Incorrect:**
Correct Answer: D

Single umbilical artery (SUA) often has been described in association with adverse perinatal outcomes, with morbidity or mortality in individual patients attributed to chromosomal or structural abnormalities. SUA occurs with persistence of the original artery of the embryonic body stalk, atrophy of a previously normal umbilical artery, or agenesis of one of the umbilical arteries.

The incidence of SUA is higher in infants of white women than in infants of African-American, Afro-Caribbean, or Japanese heritage. Infants of multiple gestations have higher risks also. Maternal diabetes also increases the risk. When a SUA is discovered prenatally, significant fetal anomalies are reported in about 20% of cases, and include cardiovascular, gastrointestinal, renal anomalies—alone or in combination. Chromosomal abnormalities affect 20% of cases, with trisomy 18 being the most frequent. Perinatal mortality ranges from 5% to 20%, with two thirds of the deaths occurring in utero. Neonatal mortality is highly correlated with the presence of multiple anomalies. Because of these aforementioned factors, the finding of SUA in a fetus is a call to action, which includes a...
detailed anatomic survey; fetal echocardiography; fetal karyotyping; and serial evaluation of fetal growth, even in the absence of structural or chromosomal abnormalities.

Of what significance is the finding of an isolated single umbilical artery in an otherwise normal-appearing infant? Of the factors listed, only occult renal anomalies is associated with isolated SUA.

In surveys of records of infants having isolated SUA, significant associations include the following:

- gestational age is lower (39 vs 40 weeks; \( P < .001 \)),
- mean birthweight is lower (3,160 vs 3,402 g; \( P < .001 \)),
- prematurity is more common (15% vs 7.4%) as is extreme prematurity (3.9% vs 1.2%; \( P = .019 \)),
- intrauterine growth restriction is more prevalent (5.4% vs 1.9%; \( P < .001 \))

When infants having chromosomal or multisystem anomalies are excluded, occult multisystem anomalies have not been reported in association with SUA.

Recent surveys of the literature and case studies have addressed the relationship between isolated SUA and occult or significant renal anomalies. The existing data are confusing and a bit conflicting. In a metaanalysis of 37 studies of SUA over a 40-year period, only seven studies contained data regarding isolated SUA. The investigators found significant renal or urinary abnormalities in 8% of cases, with the most common abnormality, vesicoureteral reflux (VUR) of grade 2 or higher, in 2.9% of cases. Although controls were not available in the studies in the metaanalysis, investigators made estimates from the reported incidence of renal anomalies in the general population and concluded that silent renal anomalies of any severity may be sixfold higher and severe malformations up to be threefold higher among infants with isolated SUA. Because VUR comprised the majority of the severe cases, and because VUR and associated urinary tract infection may precede reflux nephropathy, the authors of the metaanalysis recommended that infants having isolated SUA undergo renal ultrasonography and a micturating cystourethrogram. Renal ultrasonography alone has been associated with a positive predictive value of only 32.5% for suggesting VUR. Follow-up recommendations include having a low threshold for diagnosis of urinary tract infection in these patients.

In another analysis, isolated SUA was found in 129 of 33,067 sequential newborns at a single institution, an incidence of about four cases per 1,000 live births. The data confirmed the association with prematurity and fetal growth restriction. Of the 122 infants who underwent renal ultrasonography, two had clinically significant renal anomalies (absent kidney; unilateral hypodysplastic kidney with grade 2 VUR) and three had minor, transient abnormalities. The authors of the study also compared their data with data from the general population. Their data also found that occult renal anomalies occurred more often among infants with isolated SUA (4.1% vs 0.9%; \( P = .005 \)), but no significant differences were found in the prevalence of clinically significant renal anomalies (1.6% vs 0.4%, \( P = .74 \)), albeit the trend suggests the need for more data. The authors concluded that although the overall incidence of renal abnormality may be higher in association with SUA, the risk for significant abnormality is no greater than that in the general population. They believe that the incidence of significant renal anomalies in infants with isolated SUA does not warrant routine postnatal renal imaging. Their conclusion was supported in a second study of 52 cases of isolated SUA over 8 years at a single hospital in Europe. Although 10% of the infants were found to have abnormalities on renal ultrasonography, none was clinically significant and the authors do not recommend routine screening.

Prenatal ultrasonography may play a role in decision making about renal studies in cases of SUA. If the mother had undergone sophisticated ultrasonography, including examination of fetal anatomy, especially if the SUA was detected and the renal system was well visualized; further imaging may be avoided, as suggested in the vignette. Of note, if screening is desired, delay until the second month after birth may allow transient findings to resolve.

Although there is no consensus regarding screening for renal anomalies in infants having isolated SUA, screening has regularly revealed an increased prevalence of minor renal anomalies. Prenatal screening may play a role in making individual case decisions.

**References:**


Related readings from Neoreviews.org

American Board of Pediatrics Content Specification(s):

07_Water_Salt_Renal: Know how to diagnose specific anatomic abnormalities of the kidneys and urinary tract in infants

13_Skin: Know how to evaluate and manage disorders of the umbilical cord, including granulomas, persistent omphalomesenteric duct remnant, and patent urachus
July

Question 9

A 3-week-old male infant, born at 33 weeks' gestation with a normal head circumference and a birthweight at the 25th percentile for gestational age, has had persistent conjugated hyperbilirubinemia and poor weight gain. His total serum bilirubin concentration is 5.2 mg/dL (88.9 μmol/L) with a conjugated fraction of 2.1 mg/dL (35.9 μmol/L). During the past week he has gained less than 10 g/kg per day while receiving 150 mL/kg per day of fortified expressed breast milk. His stools are pale yellow. Physical examination reveals icteric sclera, a broad forehead, deeply set eyes, and a systolic heart murmur at the left upper sternal border, which radiates to the axilla and back. The liver is palpable at the right costal margin. He has a healthy sibling, but his father (Figure 1) has had a liver transplantation.

Figure 1: Photographs of neonate's father as an older adolescent. Note the broad forehead, deep set eyes, and pointed chin. (From Spinner [2007].)

Of the following, the infant is MOST likely to have additional findings of:

- A. abnormal vertebrae
- B. cataracts
- C. hepatic cysts
- D. intracranial calcifications
- E. renal cysts

Incorrect: Correct Answer: A

The infant in this vignette is most likely to have Alagille syndrome, as suggested by...
persistent cholestasis, poor weight gain, typical facial features, and family history of liver disease. Neonatal cholestasis is characterized by an accumulation of components of bile, most commonly conjugated bilirubin, in the bloodstream. A conjugated bilirubin concentration higher than 2 mg/dL (>34 μmol/L) or a conjugated bilirubin/total bilirubin ratio higher than 15% are measures commonly used to define neonatal cholestasis. Cholestasis results from decreased bile flow and/or excretion. The cholestasis in Alagille syndrome is the result of intrahepatic bile duct hypoplasia.

There are many ways to categorize the myriad causes of neonatal cholestasis. A simple practical method is to divide the disorders anatomically into three main categories (Table) that reflect the primary site of the disease:

- extrahepatic bile ducts
- intrahepatic bile ducts
- hepatocytes

### Table: Neonatal Cholestatic Disorders*

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<th>Extrahepatic bile ducts</th>
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<td>• Biliary atresia</td>
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<td>• Choledochal cyst and choledochocele</td>
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<td>• Biliary hypoplasia</td>
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<td>• Choledocholithiasis</td>
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<td>• Bile duct perforation</td>
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<td>• Neonatal sclerosing cholangitis</td>
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<th>Intrahepatic bile ducts</th>
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<tr>
<td>• Syndromic paucity (Alagille syndrome, mutation in JAG1)</td>
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<td>• Nonsyndromic paucity</td>
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<td>• Hypothyroidism</td>
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<td>• Panhypopituitarism</td>
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<td>• Bile duct dysgenesis</td>
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<td>• Congenital hepatic fibrosis</td>
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<td>• Ductal plate malformation</td>
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<td>• Polycystic kidney disease</td>
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<td>• Caroli disease</td>
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<td>• Hepatic cysts</td>
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<td>• Cystic fibrosis</td>
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<td>• Langerhans cell histiocytosis</td>
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<td>• Hyper-IgM syndrome</td>
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<th>Hepatocytes</th>
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<td>• Sepsis-associated cholestasis</td>
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<td>• Neonatal hepatitis</td>
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<td>• Viral infections</td>
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<td>• Toxoplasmosis</td>
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<td>• Syphilis</td>
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<td>• Progressive familial intrahepatic cholestasis syndromes</td>
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<td>• Bile acid synthetic defects</td>
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<td>• Tyrosinemia</td>
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<td>• Fatty acid oxidation disorders</td>
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<td>• Mitochondrial enzynopathies</td>
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<td>• Peroxisomal disorders (Zellweger syndrome)</td>
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<td>• Carbohydrate disorders</td>
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Lipid storage disorders
- $\alpha_1$-Antitrypsin deficiency
- Neonatal hemochromatosis
- Total parenteral nutrition-associated cholestasis

* Adapted from Karpen (2002).

Intrahepatic and extrahepatic bile ducts are lined by columnar epithelium that is derived from two embryologically distinct sources. The intrahepatic bile ducts arise from hepatoblasts in the liver parenchyma, whereas the extrahepatic bile ducts arise from invaginations of the embryonic foregut. This distinction may help to explain how certain biliary diseases reside exclusively in the intrahepatic or extrahepatic domain.

Paucity of intrahepatic bile ducts can be divided into syndromic and nonsyndromic forms. Alagille syndrome, the syndromic form, is an autosomal dominant disorder with variable penetrance. It is a multiorgan disorder that consists of:

- bile duct paucity
- posterior embryotoxon
- vertebral anomalies (butterfly vertebrae)
- cardiovascular abnormalities
- triangular facies (frontal bossing, deep-set eyes, narrow pointed chin)

Patients with Alagille syndrome present with poor weight gain, cholestasis, and peripheral pulmonic stenosis. In a series of 92 patients with Alagille syndrome, cholestasis was reported in 96% of cases, peripheral pulmonic stenosis in 90%, and a characteristic facies, noted in the father of this infant, in 96%. Posterior embryotoxon (Figures 2 and 3) occurred in 78% of cases. Osseous abnormalities can include shortening of the distal phalanges and vertebral arch defects (eg, hemivertebrae, butterfly vertebrae [Figure 4], and decreased interpedicular distance).

**Figure 2: Photograph of posterior embryotoxon which presents as a sharply defined concentric white line (see arrows) or opacity anterior to the limbus at edge of iris. The line is due to a thickened or hypertrophied Schwalbe ring. (From Dhir [2008].)**
Figure 3: Slit-lamp examination of the eye shown in Figure 2. Sharply defined white line (see arrows) can be seen at the edge of the iris. (From Dhir [2008].)

Figure 4: Radiograph of a butterfly vertebrae in older child with Alagille syndrome. (Radiograph courtesy of Robert Wells, MD, Pediatric Diagnostic Imaging.)
Hepatomegaly is not always present, and ultrasonographic findings of the abdomen are usually unremarkable. Laboratory analysis reveals an elevated serum bilirubin concentration, approximately 50% of which is conjugated. Serum alkaline phosphatase and gamma glutamyl transpeptidase may be extremely elevated, whereas serum aminotransferase concentrations are mildly to moderately increased.

The hallmark of Alagille syndrome is a decreased ratio of interlobular portal bile ducts to portal tracts (<0.5:1). Histologic features during the first months after birth may be similar to those of neonatal hepatitis. Ballooning hepatocytes, portal inflammation, and giant cell transformation may be present. Often the number of interlobular bile ducts is not diminished on initial biopsies, and bile duct proliferation may be present. However, paucity of interlobular bile ducts is usually apparent after 3 months of age. Extrahepatic bile ducts are open, but often narrowed or hypoplastic.

The mechanisms involved in the pathogenesis of bile duct paucity in Alagille syndrome are not established. A mutation in the JAG1 gene has been identified in approximately 70% of affected patients. JAG1 encodes Jagged1, a ligand in the notch signaling pathway that is involved in cell fate determination during development. The strong JAG1 expression during human embryogenesis in the vascular system and in other mesenchymal and epithelial tissues implicates abnormal angiogenesis in the pathogenesis of Alagille syndrome. Although a vascular basis for the anomalies in Alagille syndrome seems likely, the exact mechanism leading to bile duct paucity remains unknown.

The clinical course of Alagille syndrome is marked by varying severity of cholestasis, often worsened by intercurrent viral infections. Long-term prognosis depends on severity of liver disease and associated malformations. In a series of 168 patients with Alagille syndrome, survival rates with a native liver were 51% and 38% at 10 and 20 years of age, respectively. Liver transplantation increases the 10- and 20-year survival rates to 68% and 62%, respectively.

Galactosemia as well as a number of other inborn errors of metabolism or storage disorders can impair bile formation or flow (Table) at the level of the hepatocyte. Symptomatic
galactosemia (classic galactosemia) is caused by complete or near complete deficiency of galactose-1-phosphate uridyl transferase. Without the transferase enzyme, neonates are unable to metabolize galactose-1-phosphate, which subsequently accumulates to cause injury to the kidney, liver, and brain. Classic galactosemia is an autosomal recessive disorder that can cause bilateral nuclear cataracts. Neonates with classic galactosemia do not have dysmorphic facial features, and the infant in this vignette did not have a course that would be compatible with complete deficiency of galactose-1-phosphate uridyl transferase activity.

Viral, bacterial, and parasitic infections (Table) may cause cholestasis through sepsis-associated cytokines. Neonates with severe symptomatic congenital cytomegalovirus (CMV) infections may present with hepatosplenomegaly, elevated hepatic enzymes, and cholestasis. Intrauterine growth restriction, chorioretinitis, microcephaly, and periventricular calcifications also may be present. CMV is not familial and has not been associated with peripheral pulmonic stenosis; the neonate in this vignette had no other stigmata of congenital CMV infection.

Hepatic and renal cysts are seen in patients with Caroli syndrome, an autosomal recessive disorder that can impair bile flow and result in neonatal cholestasis. Congenital intrahepatic ductal dilation and features of hepatic fibrosis result in repeated episodes of acute cholangitis that cause conjugated hyperbilirubinemia and leukocytosis. Patients with Caroli syndrome may also have autosomal recessive polycystic kidney disease. Caroli syndrome is not associated with dysmorphic facial features or peripheral pulmonic stenosis.

References:


Related readings from Neoreviews.org

American Board of Pediatrics Content Specification(s):

11_Gastroenterology: Know the pathogenesis and clinical features, differential diagnosis, and treatment of intrahepatic biliary hypoplasia

11_Gastroenterology: Know the etiology, clinical manifestations, and differential diagnosis of metabolic and familial causes of cholestasis in the neonate

11_Gastroenterology: Know the laboratory and imaging features and management of metabolic and familial causes of cholestasis in the neonate