Paucity of biliary ducts:
A rare etiology of neonatal cholestasis

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ABSTRACT

We report a case of a newborn with cholestasis that was diagnosed as nonsyndromic Alagille syndrome. The main feature of the disease is a paucity of biliary ducts. There are two known types of the disease: the syndromic type which is associated with other congenital defects and the nonsyndromic type without other anomalies detected at birth. We describe the case and discuss its clinical and radiologic findings. We also discuss the various etiologies of cholestasis that are included in the differential diagnosis.

CASE REPORT

A 6-week-old term male was referred to our institution for evaluation of jaundice since birth. On admission, his total bilirubin was 7.4 mg/dL (normal range 0.3-1.2 mg/dL) with a direct bilirubin of 5.8 mg/dL (normal below 0.2 mg/dL). His serum gamma-glutamyl transferase was 831 U/L (normal range below 34 U/L). The patient was originally treated with phototherapy, which did not result in improvement and on admission he was treated with Phenobarbital, again with no improvement.

The initial working diagnosis was biliary atresia and the patient underwent hepatobiliary scintigraphy which demonstrated absence of excretion of the radiotracer during the initial 4 hours of imaging with bowel visualized only after 24 hours, consistent with delayed biliary excretion. Biliary atresia was excluded (figure 1). In abdominal sonography the gallbladder could not be visualized (figure 2). The patient underwent percutaneous cholangiogram which demonstrated normal hepatic ducts, common bile duct, and gallbladder with normal drainage of the contrast to the duodenum (figure 3).

A liver biopsy was performed and demonstrated a paucity of the interlobular biliary ducts (figure 4). The patient had no cardiac abnormalities. Ophthalmologic examination was normal and no osseous abnormalities were seen on skeletal radiography. The diagnosis of non-syndromic Alagille syndrome was made. The patient is being followed.

DISCUSSION

Alagille syndrome (AGS) is characterized by the paucity of interlobular biliary ducts and affects approximately one in 100,000 live births. The vast majority of patients present before six months of age with jaundice and failure to thrive or cardiovascular symptoms. Morbidity and mortality are linked to the severity of liver and/or cardiac involvement [1,2]. Currently no cure exists for AGS, and medical management is directed at treating disease in each affected organ system [3]. AGS is an autosomal dominant disease, with highly variable expression. Mutations in the JAG-1 gene on chromosome 20p12 are responsible for more than 90 percent of cases; others have mutations in NOTCH-2 [4].

Both syndromic and nonsyndromic forms of AGS have been differentiated from other causes of intrahepatic cholestasis in infancy. A liver biopsy often depicts bile duct paucity; however, this finding alone is not specific for AGS [5]. In the nonsyndromic form, the bile duct pathology is identical; however, there are no extrahepatic findings and currently there is no clinical, biochemical, radiological, or...
histological test specific for AGS and diagnosis is based solely on the clinical phenotype [8].

In the syndromic form of AGS, congenital heart disease has been reported in up to 90% of cases. The most common heart abnormalities involve the pulmonary valve, pulmonary artery, and its branches with the most common finding being peripheral pulmonary stenosis [9]. Ophthalmological findings include defects of the anterior chamber (posterior embryotoxon, Axenfeld's anomaly, or Rieger anomaly), and retinal pigmentary changes [10]. In addition, evaluation of the biliary anatomy using diagnostic modalities including hepatobiliary nuclear scintigraphy, magnetic resonance cholangiopancreatography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP) can aid in a proper diagnosis. Patency of the extrahepatic biliary tree can be assessed by cholescintigraphy and patients with AGS will often show delayed visualization of the gastrointestinal tract [11]. MRCP fails to demonstrate the absence of bile ducts because these are barely visible in normal subjects. However, MR sequences without and with gadolinium injection show clear structural abnormalities of the liver, with a combination of tumor-like nodules centered on a hypertrophic portal vessel and areas of major atrophy generating a bright signal on T1 images [6]. In the case of AGS, ERCP will display marked diffuse narrowing of the extrahepatic biliary ducts and uniform narrowing of the intrahepatic ducts with reduced arborization [12]. In addition, ultrasonography (US) can display evidence of portal hypertension and can help to establish indications for hepatic transplantation [8]. Although these findings alone are not specific for AGS, in a cholestatic child, they help in establishing a diagnosis of AGS [8]. Therefore, diagnostic testing is important to exclude other causes of neonatal cholestasis and to evaluate for associated malformations.

Diagnosis is further complicated by the fact that there are over a hundred specific causes of neonatal cholestasis. Cholestasis results from diminished biliary flow and/or excretion caused by obstruction, infection, metabolic and genetic abnormalities [13].

Causes of obstructive neonatal cholestasis include biliary atresia (BA) and choledochal cysts. BA is a progressive, idiopathic, destructive disease of the extrahepatic biliary tree that presents with biliary obstruction in the neonatal period and is the most common cause of neonatal jaundice for which surgery is indicated [14]. BA has characteristic findings on histology and cholangiogram. The histology typically shows inflammation, portal tract fibrosis, cholestasis, and bile duct proliferation. The cholangiogram demonstrates loss of patency of the extrahepatic bile ducts [14]. In infants with BA, the gallbladder is usually either absent or irregular in shape on ultrasound (US) examination. Additional features on US can be identified to support the diagnosis of BA, including abnormal gallbladder size and shape, the "triangular cord" sign, gallbladder contractility, absence of the common bile duct, and enlarged hepatic artery [15]. The triangular cord sign is a triangular echogenic focus seen just above the porta hepatis on US scan. Its presence is highly suggestive of biliary atresia [15]. Patency of the extrahepatic biliary tree can be further assessed by hepatobiliary scintigraphy. Failure of radiotracer excretion after 24 hrs suggests BA, but does not exclude other diseases. Conversely, if scintigraphy demonstrates definite excretion of the radiotracer from the liver to the small bowel, patency is established, and BA is very unlikely. In addition, if the diagnosis of BA is suspected an endoscopic retrograde cholangiopancreatography (ERCP) can be used to demonstrate biliary patency. ERCP findings suggestive of BA include: absence of the biliary tree and opacification of the distal common duct and gallbladder without visualization of the main hepatic duct [16]. Choledochal cysts are a rare but treatable cause of conjugated hyperbilirubinemia. Most affected infants have diffuse enlargement of the common bile duct, which can usually be detected by US. US findings suggestive of choledochal cysts include larger common bile duct, dilated intrahepatic bile ducts, and normal appearing gallbladder [17].

Bacterial, protozoal, and viral infections can result in cholestasis. Common congenitally acquired pathogens include toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis. Cranial imaging is performed on neonates with toxoplasmosis to assess focal brain lesions or hydrocephalus. Abnormalities on CT and MRI neuroimaging may include: intracranial calcifications, hydrocephalus, and cortical atrophy [18]. In regards to newborns with clinical findings compatible with intrauterine rubella infection, structural defects include hearing loss, cardiac and vascular anomalies, eye lesions, and central nervous system abnormalities [19]. Cytomegalovirus has emerged as the most common congenital viral infection. A wide range of abnormalities of the brain may be detected on cranial CT imaging. These abnormalities include periventricular leukomalacia and cystic abnormalities, periventricular calcifications, ventriculomegaly, vasculitis, neuronal migration abnormalities, and hydranencephaly. Brain imaging with enhanced computed tomography (CT) or magnetic resonance imaging (MR) is recommended to determine the location and extent of brain involvement [20]. Neonatal infection with herpes simplex virus (HSV) occurs in 1 out of every 3200 to 10,000 live births. The imaging findings of neonatal HSV central nervous system disease are variable. Neuroimaging may be normal early in the course of the disease. Several days to a week into illness, neuroimaging studies may show parenchymal attenuation abnormalities, parenchymal atrophy, parenchymal contrast enhancement, leptomeningeal contrast enhancement, extra-axial fluid collections, and parenchymal calcification. In addition to the classic temporal lobe destructive lesions, imaging abnormalities may be multifocal [21]. Chest radiographs may demonstrate bilateral, diffuse pneumonitis in neonates with primary HSV pneumonia or in infants with disseminated HSV disease. In addition, abdominal ultrasonography in neonates with HSV hepatitis and acute liver failure may demonstrate ascites and an enlarged liver [22]. Congenital syphilis may demonstrate abnormal long-bone radiographs. Findings may include metaphyseal lucent bands, symmetric localized demineralization and osseous destruction of the medial portion of the proximal tibial metaphysis (Wimberger sign), metaphyseal serratation ("sawtooth metaphysis," or Wegener sign), diaphyseal periostitis with new bone formation, and irregular areas of increased density and rarefaction ("moth-eaten" appearance) [23].
Neonatal excretion of conjugated bilirubin is impaired in a number of metabolic disorders including galactosemia, tyrosinemia, disorders of lipid metabolism (Niemann-Pick disease, Gaucher disease), Caroli’s disease, alpha-1-antitrypsin deficiency, neonatal hemochromatosis, and cystic fibrosis.

Galactosemia is a disorder of carbohydrate metabolism that causes neonatal cholestasis. Galactosemia is the result of deficiency of galactose-1-uridytransferase. Affected infants present with mixed hyperbilirubinemia after the onset of galactose-containing feedings. The diagnosis is suggested by the presence of reducing substances in the urine and is confirmed by an assay of galactose-1-phosphate uridytransferase activity in erythrocytes, leukocytes, or liver. However, ultrasound and CT findings such as a fatty liver and evidence of portosystemic shunt vessels are also indicative of galactosemia [24].

Tyrosinemia is disorder of amino acid metabolism and another potential source of neonatal cholestasis. It is caused by deficiency of fumarylacetoacetate hydrolase (FAH), and presents in infancy. It is characterized by progressive liver disease, renal tubular acidosis, and neurologic impairment [25].

Disorders of lipid metabolism, including Gaucher disease (GD) and Niemann-Pick disease (NPD), can occasionally present with cholestasis. GD is an inborn error of metabolism that affects the recycling of cellular glycolipids. Glucocerebrosidase and several related compounds that are ordinarily degraded to glucose and lipid components accumulate within lysosomes. GD involves the visceral organs, bone marrow, and bone in all affected patients. The initial radiology assessment should include various examinations to evaluate liver and spleen volume and the extent and severity of skeletal disease. Computed tomography (CT) or magnetic resonance imaging (MRI) of the liver and spleen can help determine the severity of hepatosplenomegaly, evaluate for cirrhosis and hepatic or splenic fibrosis. Ultrasound may also be used to measure organomegaly [26]. NPD is a group of autosomal recessive disorders associated with sphingomyelagly, variable neurologic deficits, and the storage of sphingomyelin. Storage of sphingomyelin in pulmonary macrophages leads to interstitial lung disease, which can be observed on chest radiographs or CT [27].

Caroli’s disease is a congenital disorder associated with multifocal, segmental dilatation of large intrahepatic bile ducts [28]. The condition is usually coupled with polycystic renal disease of varying severity. The diagnosis of Caroli’s disease is established by imaging studies that demonstrate bile duct ectasia and irregular, cystic dilation of the large proximal intrahepatic bile ducts with a normal common bile duct. These findings can be observed on ultrasound, ERCP, and MRCP [28].

Alpha-1-antitrypsin deficiency (ATT), can also produce neonatal cholestasis. AAT is an antiprotease and the natural inhibitor of the serine proteases released by activated neutrophils. Other clinical presentations among newborns consist of hepatomegaly with elevated aminotransferase levels and early evidence of moderate to severe liver disease with ascites and bleeding diathesis [29]. Diagnosis is based primarily on spirometry to test pulmonary function; however, it has been suggested that a chest CT may demonstrate decreased lung density in some cases of ATT [30].

Neonatal hemochromatosis is a rare disorder characterized by extrahepatic iron accumulation and liver failure [31]. The onset is prenatal, and newborns present with signs of severe liver failure, including coagulopathy, ascites, and hypoalbuminemia. Hyperbilirubinemia typically is both conjugated and unconjugated. The diagnosis may be suspected on the basis of the iron studies, but demonstration of extrahepatic iron on MRI is required for the diagnosis of neonatal hemochromatosis [31].

Cystic fibrosis (CF) is the most common fatal autosomal recessive disease among Caucasian populations, with a frequency of 1 in 2000 to 3000 live births. Signs and symptoms include persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels. However, many patients demonstrate mild or atypical symptoms including neonatal cholestasis. CT is the current "gold standard" for assessment of lung morphology. MR is comparable to CT with regard to the detection of most morphological changes in the CF lung. It is thought to be less sensitive to detect small airway disease. Radiologic findings on plain film, CT, and MRI include linear atelectasis, dilated and thickened airways, and irregular peripheral opacities that may represent mucusplurulent plugs. CT will also show airway dilatation, which can be detected as parallel lines or end-on ring shadows, bronchial wall thickening, mucusplurulent plugs with post-obstructive air trapping, and cysts off the bronchial wall [32]. Additionally, ERCP can be used to demonstrate biliary patency. Cystic fibrosis patients will demonstrate multiple irregular filling defects throughout the biliary tree on ERCP representing thickened bile and mucus as well as stones [33].

Other inherited syndromes that may produce neonatal cholestasis include Dubin-Johnson syndrome, benign recurrent intrahepatic cholestasis, and familial hepatocellular cholestasis.

Dubin-Johnson syndrome is characterized clinically by mild icterus. Otherwise, patients are asymptomatic, although mild constitutional complaints such as vague abdominal pains and weakness can occur. Icterus can be so mild as to be noted only during intercurrent illnesses, pregnancy, or use of oral contraceptives [34]. CT of the liver in patients with Dubin-Johnson syndrome shows a significantly higher attenuation of the parenchyma compared with that of normal subjects [35].

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of disorders characterized by defective secretion of bile acids or other components of bile. With the exception of benign recurrent cholestasis (BRIC), these disorders usually present during infancy or childhood, and are associated with growth failure and progressive liver disease. Ultrasonography of the liver and gallbladder is useful in...
Determining biliary tract anatomy and differentiating from extrahepatic causes of cholestasis [36].

Idiopathic neonatal hepatitis is defined as prolonged conjugated hyperbilirubinemia without an obvious etiology. Characteristic findings on liver biopsy are multinucleated giant cells, variable inflammation with infiltration of lymphocytes, neutrophils, and eosinophils, and little or no bile duct proliferation. However, these findings also are seen in other conditions, including AAT deficiency and progressive familial intrahepatic cholestasis, among others. With continued improved diagnostic advances and identification of other specific causes, this entity, which is a diagnosis of exclusion, will become increasingly rare [37].

In conclusion, AGS is an autosomal dominant disorder with variable expression. Associated abnormalities include those of the liver, heart, eye, and skeletal features. The specific diagnosis of AGS is based solely on the clinical phenotype [8]. Thus, diagnostic testing is important to exclude other causes of cholestasis and to evaluate for associated malformations.

TEACHING POINT

Paucity of biliary ducts is a rare entity that manifests in the neonatal period as cholestasis. Two types of this entity are known: Alagille syndrome that is associated with congenital anomalies and the nonsyndromic type. The radiologist should consider this entity in the differential diagnosis among the numerous other etiologies of cholestasis.

REFERENCES


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Figure 1: 6-week-old male with nonsyndromic Alagille syndrome. Hepatobiliary scintigraphy obtained following the intravenous administration of 0.2 mCi Tc-99m-mebrofenin. (A) Image obtained 2 minutes after the administration of the radiotracer demonstrates normal appearance of the liver (red arrow) and the heart (red asterisk). (B) At 60 minutes the radiotracer is still in the liver (red arrow). There is no excretion to the bowel. The bladder is visualized (green arrow). (C) Delayed image at 24-hours following the administration of the radiotracer demonstrates visualization of bowel loops.

Figure 2: 6-week-old male with nonsyndromic Alagille syndrome. Sonogram of the right upper quadrant of the abdomen performed with multi-frequency probe (GE sector 4-10) demonstrates normal appearance of the liver. The gallbladder not visualized. The gallbladder fossa appears to be empty (red arrow).

Figure 3: 6-week-old male with nonsyndromic alagille syndrome. Percutaneous cholangiogram performed following with 63 kVp and 0.48 mA and the administration of 8 cc of Omnipaque 350 into the gallbladder demonstrates normal visualization of the gallbladder (white arrow). Common bile duct is visualized (red arrow) with normal drainage of the administered contrast into the duodenum (green arrow).
**Figure 4:** 6-week-old male with nonsyndromic Alagille syndrome. Pathologic appearance.  A: Portal tract without an interlobular bile duct. A normal hepatic artery (arrow) and portal vein segment (arrowhead) are identified. H&E x 100.  B: Portal area with cuffing of inflammation around the hepatic artery (arrow) and portal vein (arrowheads). Extramedullary hematopoiesis H&E x 200.  C: Scanning view of CK 19 immunohistochemical stain (antibody specific for biliary epithelium) demonstrating multiple portal areas with peripherally placed regenerative bile ducts (arrowheads). CK 19 immuno x 40.  D: Appearance of a portal triad with hepatic artery segment without a normal bile duct (arrow). Note the peripherally placed regenerative bile ductules stained with CK 19 (arrowhead). CK 19 immuno x 400.  E: Scanning view of the solitary portal area with a normal bile duct. CK19 immuno x 100.  F: Portal triad with normal bile duct. CK 19 immuno x 400.

**Table 1:** Summary table of syndromic Alagille syndrome

| Etiology | Autosomal dominant genetic disease  
| Incidence | Mutations in the JAG-1 gene on chromosome 20p12 are responsible for AGS in more than 90 percent of patients; others have mutations in NOTCH-2  
| Gender Ratio | Approximately 1/100,000 live births  
| Age Predilection | There is equal gender distribution  
| Risk Factors | The majority of patients present before six months of age  
| Treatment | Mutation in the Jagged1 (JAG1) or NOTCH2 gene  
| Prognosis | Currently no curable treatment exists and medical management depends on diagnosing and treating disease in each affected organ system  
| Findings on Imaging | Predicting prognosis is difficult; however, it is dependent on the severity of liver damage and cardiac complications  
| ERCP: Narrowing of the extrahepatic biliary ducts and uniform narrowing of the intrahepatic ducts with reduced arborization  
| Cholescintigraphy: Delayed visualization of gastrointestinal tract  
| MR: Peripheral pulmonary stenosis. Structural abnormalities of the liver, with a combination of tumor-like nodules centered on a hypertrophic portal vessel and areas of major atrophy  
| CT: Peripheral pulmonary stenosis; Butterfly vertebrae  

**Table 1:** Summary table of syndromic Alagille syndrome
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<th>X-Ray</th>
<th>Cholangio-gram</th>
<th>Chole-scintigraphy</th>
<th>MRCP</th>
<th>ERCP</th>
<th>US</th>
<th>MR</th>
<th>CT</th>
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<td>Butterfly vertebral</td>
<td>Delayed visualization of GI tract</td>
<td>Narrowing of the extrahepatic biliary ducts with reduced arborization</td>
<td>Portal hypertension</td>
<td>-Peripheral pulmonary stenosis</td>
<td>-Structural abnormalities of the liver, with a combination of tumor-like nodules centered on a hypertrophic portal vessel and areas of major atrophy</td>
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<td>Narrowing of the extrahepatic biliary ducts</td>
<td>Narrowing of the extrahepatic biliary ducts</td>
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<td>Gallbladder is usually either absent or irregular in shape</td>
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Table 2: Differential table for cholestasis
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**Table 2:** Differential table for cholestasis (continued 1)
### Table 2: Differential table for cholestasis (continued 2)

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<td>Multiple irregular filling defects throughout the biliary tree</td>
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### Abbreviations

AGS - Alagille syndrome  
ATT - Alpha-1-antitrypsin deficiency  
BA - Biliary atresia  
BRIC - Benign recurrent cholestasis  
CMV - Cytomegalic virus  
CNS - Central nervous system  
CT - Computerized tomography  
ERCP - Endoscopic retrograde cholangiopancreatography  
FAH - Fumarylacetoacetate hydrolase  
GD - Gaucher disease  
HSV - Human simplex virus  
MRCP - Magnetic resonance cholangiopancreatography  
MRI - Magnetic resonance imaging  
NPD - Niemann–Pick disease  
PFIC - Progressive familial intrahepatic cholestasis  
US - Ultrasound

### Keywords

Alagille syndrome; Cholestasis; Biliary ducts