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Hot Topic Commentary

Differentiating Neonatal Dubin Johnson Syndrome from Biliary Atresia: Start Simply

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Dubin Johnson syndrome usually appears in the second decade of life, making differentiation from biliary atresia (BA) relatively easy. However, there are rare cases of neonatal Dubin Johnson syndrome (nDJS) causing cholestasis in neonates that can be easily mistaken for other conditions, including BA. It is important to make a distinction between the two in neonates because nDJS is typically a benign condition and BA, if left untreated, has a high mortality rate.

nDJS is caused by a defect in the MRP2 protein, which transports conjugated bilirubin from hepatocytes into the bile duct system for excretion.[1] Clinical presentation is usually with jaundice, acholic stools, and choluria, similar to BA. Diagnosis can be made clinically with a combination of elevated total bilirubin (often >20 mg/dL),[1] high level of urine coproporphyrin excretion and (usually) normal aminotransferases, alkaline phosphatase, and gamma glutamyl transferase.[2]

BA has a similar clinical presentation to that of nDBS in neonates. BA is a rare disease that affects 1 in 5,000–9,000 live births.[3] It is an idiopathic and progressive disease characterized by obliteration of the extrahepatic biliary tree and is the number one indication for liver transplantation in children.[4] Survival without transplantation is around 30–55% at 5 years and 30–40% at 10 years.[5] The majority of patients will eventually need liver transplantation, but a hepatoportoenterostomy or Kasai procedure can restore bile flow into the small bowel. The important caveat is that success or prognosis of the Kasai procedure is negatively impacted by increased age at time of surgery, therefore a timely referral is crucial.[4,6]

In this issue of the journal, Liu *et al*.[7] investigate how to make the distinction between BA and nDJS using simple hepatic function tests, which is a noble effort to achieve timely and cost-effective care. The difficulty arises because there can be an overlap in the clinical presentation of both conditions, especially when all of the liver function tests are abnormal in nDJS. The one simple laboratory test often used in conjunction with the hepatic panel, the dry blood spot test for conjugated bile acids, lacks specificity. Essentially, there is no specific laboratory finding or universal screening test that can differentiate BA from nDBS.[4] Ultrasound can help diagnose BA, especially when there is an absent gallbladder or a triangular cord sign, which has a high specificity for BA,[3] but its sensitivity is low. A hepatobiliary iminodiacetic acid scan can exclude BA when there is excretion into the small bowel, but is often noncontributory.[4] Liu *et al*.[7] found that overall liver chemistries are lower in nDBS compared with BA. Using specific cutoffs for liver tests, they found that an AST level of <87 IU/L had a high sensitivity and specificity for nDBS, and therefore highlight its potential as a sensitive biomarker to differentiate nDBS from BA.[7]

Given its wide availability, applying this finding is a good starting point to reach a diagnosis in a neonate with jaundice. Complementing this with other tests can help guide the physicians for final diagnosis. Local expertise and test availability are also important factors. For example, the duodenal tube test consists of insertion of a nasoduodenal tube into the third portion of the duodenum in order to collect fluid for 24 hours and test for the presence of bile. Yoshii *et al*.[8] found that the sensitivity and specificity of this test were 98% and 100%, respectively for diagnosis of BA. In nDBS urine coproporphyrin excretion is high and has a specific pattern. Even though it can also be elevated in BA, the values are rarely above the diagnostic cut off established for nDJS.[2] Other laboratory tests currently being investigated such as interleukin-33 and matrix metalloprotein-7 may have diagnostic utility in the future.[9,10] Percutaneous gallbladder cholangiogram or endoscopic retrograde cholangiopancreatography can also be useful for diagnosis of BA in the neonatal period as they provide visualization of the biliary system.[11] Cholangiogram remains the gold standard for diagnosis, but is often not the first choice because of its invasive nature and need for radiation. In BA, branches of the hepatic artery become hypertrophic and hyperplastic, causing dilated blood vessels to appear on the liver surface.[12] These are also known as hepatic subcapsular spider-like telangiectasias, may be apparent on color Doppler or during laparoscopy/open surgery, and have a high sensitivity and specificity.[12,13] A liver biopsy will show histology changes consistent with obstruction (e.g. expanded portal tracts with bile duct proliferation, portal tract edema, fibrosis, and bile duct plugs) but those changes alone cannot help distinguish from other causes of obstruction. In conclusion, the astute physician should be very skilled in interpreting the hepatic panel as it can often guide toward the next steps of a focused diagnostic work-up.

Abbreviations: BA, biliary atresia; nDJS, neonatal Dubin Johnson syndrome.

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Conflict of interest

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Author contributions

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