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Hepatology highlights

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El-Guindi MA et al. Hepatic immunohistochemistry of bile transporters in progressive familial intrahepatic cholestasis

El-Guindi MA *et al*. In this issue of *Annals of Hepatology*, investigators from the National Liver Institute at Menofiya University aimed to evaluate hepatic expression of proteins involved in bile acid export and homeostasis as a potential means to distinguish progressive familial intrahepatic cholestasis (PFIC) from other causes of neonatal cholestasis. The study included 50 pediatric patients (median age 86.5 days), of whom 25 were diagnosed phenotypically as PFIC (2 with PFIC1, 17 with PFIC2 and 6 with PFIC3) and 25 with a variety of non-PFIC cholestatic disorders. Expression of bile salt export pump (BSEP) and multidrug resistance 3 (MDR3) proteins was assayed in these 50 patients by immunohistochemistry on deparaffinized liver tissue sections from Tru-Cut needle biopsy specimens and compared between groups. As expected, expression of BSEP and MDR3 proteins was less frequent in PFIC patients compared to non-PFIC ($p = 0.077$ and $p = 0.048$, respectively), thus the absence of these proteins was suggestive of PFIC, although not exclusively specific. Interestingly, none of the patients in the PFIC group were positive for both BSEP and MDR3; therefore, positive staining for both proteins appears to rule-out PFIC with a negative predictive value of 100%. El-Guindi *et al*. concluded that MDR3 and BSEP immunostaining is a helpful tool in supporting the phenotypic diagnosis of PFIC and in differentiating it from other causes of neonatal cholestasis.

PFIC refers to a heterogeneous group of autosomal-recessive disorders, of which three types have been identified to date: PFIC1 (defect in adenosine triphosphate, type 8B, member 1 [ATP8B1] gene encoding the FIC1 protein), PFIC2 (defect in adenosine triphosphate-binding cassette, subfamily B, member 11 [ABCB11] gene encoding the BSEP protein), and PFIC3 (defect in ABCB 4 gene encoding the MDR3 protein).[1,2] Whereas the first two manifest with cholestasis within the first few months of life, the latter may present later in childhood or adolescence. The main clinical manifestations of PFIC include pruritus and jaundice; in addition, because the ATP8B1 gene is abundantly expressed in a variety of tissue aside from the liver, a multitude of extrahepatic manifestations such as hearing loss, pancreatitis, and diarrhea can be seen in patients with PFIC1. Irrespective of the genetic mutation and histopathological differences between the PFIC types, the majority of patients with PFIC develop hepatic fibrosis and end-stage cirrhotic liver disease and require liver transplantation (LT) prior to reaching adulthood.[1]

In summary, immunohistochemical assessment of hepatic BSEP and MDR3 protein expression appears to provide valuable clinical information to help support a diagnosis of PFIC, particularly when genotypic data are unavailable. While the absence of these proteins cannot definitively rule-in PFIC, the presence of both can be used to effectively rule it out. Further research is needed to validate these findings and determine if they may be readily applicable to other cholangiopathies.[3]

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Gaba RC et al.
What Constitutes Liver Failure after Transjugular Intrahepatic Portosystemic Shunt Creation? A Proposed Definition and Grading System

Gaba RC *et al.* It is well known that transjugular intrahepatic portosystemic shunt (TIPS) can decrease portal perfusion and lead to hepatic ischemia with resultant hepatic dysfunction; indeed, a major concern following TIPS creation is development of post-TIPS hepatic failure.[4] Although serum bilirubin and international normalized ratio (INR) levels following TIPS may correlate with impending hepatic failure, these are incomplete measures, and to date there are no practice guidelines by which to definitively diagnose post-TIPS hepatic failure, predict clinical outcomes, and guide management. In this issue of *Annals of Hepatology*, investigators from the University of Illinois Hospital and Health Sciences System aimed to thus develop and preliminarily evaluate a simple, objective, and TIPS-specific definition and grading system for post-TIPS hepatic failure.

The study cohort consisted of 268 patients who underwent TIPS at an academic medical center. The proposed classification scheme was based on post-TIPS peak INR and bilirubin levels (adapted from recent international study group definition of post-partial hepatectomy hepatic failure);[5] inclusion of other important clinical parameters such as serum, creatinine, and cardiac dysfunction were not taken into account in order to maintain simplicity. The highest risk level was considered to be among those with bilirubin ≥ 3x the upper limit of normal or INR ≥ 2x the upper limit of normal, and in fact such values were found to successfully stratify patients into the highest risk of adverse clinical outcomes.

Although the pathophysiological basis of the laboratory tests and cutoffs chosen by the investigators is uncertain, this is a valuable study which helps lay the groundwork for an important issue for patients undergoing TIPS, their hepatologists, and interventional radiologists. Further studies should evaluate these and other readily-available metrics (including continuous variables rather than subjective/discrete cutoffs) and their association with key clinical outcomes in the post-TIPS setting; this would help more precisely grade post-TIPS hepatic failure and thus guide optimal management.

ABBREVIATIONS

- **BSEP:** bile salt export pump.
- **INR:** international normalized ratio.
- **LT:** liver transplantation.
- **MDR3:** multidrug resistance 3.
- **PFIC:** progressive familial intrahepatic cholestasis.
- **PSG:** portosystemic gradient.
- **TIPS:** transjugular intrahepatic portosystemic shunt.

CONFLICTS OF INTEREST

None.

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