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Reloading Against Rare Liver Diseases

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Much of pediatric gastroenterology and hepatology practice involves considering rare diseases in the differential diagnosis of children presenting with both common and uncommon clinical symptoms. No condition demonstrates this better than the infant with jaundice, a common entity, who is found to have cholestasis (conjugated hyperbilirubinemia), an uncommon condition, for which the diagnostic considerations now exceed 100 disorders (1), all regarded as rare disorders. Although biliary atresia and idiopathic neonatal hepatitis are responsible for at least 50%-60% of cases, a growing inventory of genetic and metabolic diseases have this clinical presentation. Among these, the most common is alpha-1 antitrypsin deficiency found to be causative in up to 17% of cholestatic infants in Northern European populations (2), but very rare in Asian countries (3). Alagille syndrome, progressive familial intrahepatic cholestasis (types 1, 2, and 3), Niemann-Pick type C (especially in Hispanic infants in the U.S.), citrin deficiency (in Asian infants), cystic fibrosis, and galactosemia (in countries that do not employ newborn screening) are among the other more common genetic causes of neonatal cholestasis. A long list of even rarer etiologies includes the expanding catalogue of defects in bile acid synthesis and metabolism (4).

In this issue of the Journal, Subramaniam et al. (5) provide important natural history data on 18 patients with the most common bile acid synthesis defect (3 β -HSD deficiency) who have been followed at King's College and Great Ormond Street Hospitals in London. A defect in this enzyme results in accumulation of both 7 α -hydroxycholesterol and abnormal C24 bile acids that retain the 3 β -hydroxy Δ^5 structure. Hepatic injury occurs as a consequence of inadequate synthesis of the normal bile acids necessary to stimulate bile flow and the accumulation of abnormal toxic bile acids. The resulting impairment in normal bile acid secretion can lead to profound malabsorption of fat-soluble vitamins as well as dietary fat. The importance of this rare disorder is that it responds to oral bile acid therapy, mandating the clinician to establish this diagnosis in a timely fashion, using reference laboratories capable of technologies such as urine or plasma fast atom bombardment, gas chromatography or electrospray ionization combined with mass spectrometry. It should be pointed out that these 18 3 β -HSD deficiency patients represent the total combined experience over 16 years at these two busy centers, attesting to the rarity of bile acid defects.

Although proposed decades ago as potential causes of cholestatic liver disease, defects in bile acid synthesis and metabolism are relative newcomers to the long list of causes of neonatal cholestasis. There are now nine known defects that share three clinical features that should raise clinical suspicion. These include the unusual finding of normal or low total serum bile acid concentrations (considering the degree of cholestasis), low or normal serum γ -glutamyl transpeptidase (GGT), and the absence of pruritus in most patients. Interestingly, three patients reported by Subramaniam et al. (5) had evidence of pruritus and no other skin condition.

Primary bile acid defects present with two primary clinical scenarios: clinical findings attributable to fat-soluble vitamin deficiency of unknown cause (particularly vitamin D and Vitamin K deficiencies) as the predominant finding or more typical symptoms of neonatal cholestatic liver disease (jaundice, hepatomegaly, failure to thrive). There is also a subset that presents with more gradual development of hepatomegaly and portal fibrosis without a history of neonatal liver disease. Meticulous correction of fat-soluble vitamin deficiency needs to be attended to in these patients, using appropriate individual vitamin supplements in escalating doses followed closely by serum levels. With appropriate oral bile acid therapy and nutritional rehabilitation, patients with some of the bile acid defects, especially 3 β -HSD deficiency, may avoid progression to cirrhosis and maintain a healthy life with their native liver. Indeed, 12 of 13 surviving patients reported by Subramaniam et al. (5) were thriving without evidence of chronic liver disease or vitamin deficiency. Other bile acid defects, such as oxysterol 7 α hydroxylase deficiency, do not respond to bile acid therapy and the option of liver transplantation must be considered early in their course (4). The true nature of the spectrum of bile acid defects is unknown, as well as modifying environmental and genetic factors that may influence the disease phenotype and outcome. Moreover, the ability to diagnose these rare diseases is not uniformly available, despite a proven effective therapy for most patients.

The United States National Institutes of Health (NIH) Action Plan for Liver Disease Research lists as one of its high priorities the need to develop definitions and diagnostic criteria as well as to delineate the molecular pathogenesis of neonatal cholestatic conditions (6). The target seems to be clear but the actions to achieve these goals have been for the most part random, not well organized, and under funded. Much of the reason for this lies in the rarity itself of these diseases, precluding all but a few centers from access to adequately sized clinical populations and the ability to obtain meaningful funding to support their efforts. In this revolutionary era of genomics, stem cell biology, innovative biotechnology and interdisciplinary research initiatives, the potential is within reach to use these tools to advance our fundamental understanding of disease etiology and pathogenesis, to improve and make available diagnostic capabilities, and to translate these findings into therapeutic targets for novel treatments. The means to this end is clear - we must bring together the global community of pediatric hepatologists to collaborate without restraint or constraints and to mount convincing campaigns to achieve funding for these important translational opportunities.

For some rare liver diseases, successfully funded collaborations have been achieved in recent years. EuroWilson (<http://212.99.52.2/eurowilson>), supported by the European Union's FP6 program under the direction of Stuart Tanner, maintains a registry and database on Wilson disease patients across European countries. The Biliary Atresia Research Consortium (<http://www.barcnetwork.org>) and the Cholestatic Liver Disease Consortium (<http://rarediseasesnetwork.org/clic>), soon to be merged to form the Childhood Liver Disease Research and Education Network or ChiLDREN, are supported by the NIH with additional funding from the Alpha-1 Foundation and Cystic Fibrosis Foundation. These consortia investigate biliary atresia, idiopathic neonatal hepatitis, five genetic causes of intrahepatic cholestasis (including bile acid defects) and cystic fibrosis liver disease at 14 centers in the United States, Canada and United Kingdom, and maintain tissue and DNA repositories. Each of these initiatives has generated a better understanding of the natural history, etiology, genotype-phenotype relationships and pathogenesis of these disorders and has provided the infrastructure for conducting much needed clinical trials. Collaboration with patient advocacy groups, foundations and the pharmaceutical industry is vital for translation of discoveries into new diagnostics and treatments.

In order to fully address critical needs in rare liver diseases, strategies are now needed to expand the international collaboration. For example, a genome wide association study to detect modifier genes in any of these rare genetic diseases may require several sets of many hundreds

of affected patients and genetically similar controls. This can only be achieved through international efforts. To facilitate a wider reach, efforts should be made to clearly and collaboratively define the research needs and objectives, and to establish goals and timetables for deliverables to maximize efficiency and transparency. A similar collaborative research network methodology could be replicated to tackle other pediatric digestive diseases, both rare and more common. Such efforts are underway in pediatric intestinal failure, eosinophilic diseases of the GI tract and inflammatory bowel disease, among others. The challenges ahead will be to obtain sustainable resources and funding, to develop robust national and international registries and annotated tissue/DNA repositories for rare diseases, to capitalize on the implementation of electronic medical records, and to formulate and disseminate best practices to practitioners. It is also essential that these collaborative networks align and cooperate with parallel quality improvement initiatives to leverage scarce resources and personal capital. Increased involvement of our national pediatric GI and hepatology professional societies could be instrumental in taking the leadership to promote these initiatives.

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