Are you willing to implicate villin in progressive cholestasis of childhood?

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ARTICLE

Over 30 years ago, Dr MJ Phillips first described the fatal intrahepatic cholestatic liver disease known as Byler’s syndrome (1). More recently, genetic defects in the bile salt excretory pump and the MDR3 phospholipid transporter have been described as causes of progressive familial intrahepatic cholestasis (2,3). Nevertheless, the exact pathophysiological basis underlying the development of most cholestatic liver diseases in both children and adults remains unknown. Recently, Phillips et al (4) from the University of Toronto, Toronto, Ontario published their findings implicating a defect in the expression of the villin gene as a cause of a biliary atresia-like disorder in three pediatric patients. Villin is a protein that is involved in the binding, bundling and severing of actin, thereby playing an important role in maintaining the structure of the bile duct canalicular microvilli (5). Although these three patients had progressive cholestasis and liver failure resembling biliary atresia, they exhibited unique ultrastructural abnormalities within microvilli of their bile duct canalculi as well as a lack of villin messenger RNA and protein expression (4).

In this study, Phillips et al used electron microscopy to examine the explanted livers of 50 patients who underwent liver transplantation at The Hospital for Sick Children, Toronto, Ontario for biliary atresia. Three of the patients were noted to have unusual ultrastructural abnormalities of the canalicular microvilli on electron microscopy. All three patients had persistent jaundice that was originally attributed to biliary atresia and all required liver transplantation at a young age. Immunohistochemistry demonstrated the absence of staining for villin in these three patients, in contrast to its presence in heptectomy specimens from cases of classic biliary atresia, other cholestatic liver diseases and in normal livers. In all three cases, Western blot analysis demonstrated the lack of a villin band and there was abnormal villin messenger RNA expression by reverse transcriptase-polymerase chain reaction. Although the three villin-deficient patients eventually developed liver failure that was clinically indistinguishable from classical biliary atresia, their early liver biopsies revealed distinctive abnormalities, including giant cell hepatitis, portal inflammation and mild cholestasis with mild fibrosis despite significant ductopenia (4).

Based on their eloquent study, the authors proposed a new mechanism of progressive cholestasis, involving biliary canalicular microvillus structural defects that result from the loss of villin function (4). Because genetic studies were not performed in these patients, it is not clear if the loss of villin function represents a primary genetic defect in villin synthesis, or if it is an acquired defect resulting from an environmental attack (perhaps by a virus) or as a consequence of cholestasis itself (6). Nonetheless, it is an intriguing and important finding from a group of Canadian researchers, and we are likely to hear more about the role of villin in other cholestatic disorders in the future.

REFERENCES

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The authors respond:

Thank you for writing a commentary on our *Lancet* (2003) paper. I must mention that I have always considered the paper by Clayton et al (1) to be the original report on Byler’s disease. We recognized the abnormal chunky appearance of the bile ultrastructurally and termed it “Byler Bile”, which is a useful canalicular marker of the condition to this day. I think this abnormality is seen only in Byler’s disease and familial benign recurrent cholestasis; interestingly, the same gene on chromosome 18q 21-22 is involved in these two conditions but the mutations are different (2).

Since publishing this report, I have heard from others (from Ireland and elsewhere) who tell me they have cases that are similar to the ones we described. We continue to work on molecular aspects of the villin gene. To me, ‘biliary atresia’ is not a single clinical pathological entity, as there are subsets or new disorders that mimic the disorder. The three villin-related cases we described form a distinct group, and are clearly different from the usual biliary atresia cases I have seen. Hence, I consider these villin cases to be in the category of new disorders. I also regard the zinc-related intrahepatic cholestasis found in Canadian First Nations children (3) as another condition that closely resembles biliary atresia. Defects in the genes that encode, for example, the canalicular bile acid transporter or the phospholipids transporter can also cause severe progressive cholestasis in infancy, as mentioned in the report by Dr Burak. There is still much to learn about the types and mechanisms of progressive intrahepatic cholestasis.

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REFERENCES