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Valproic Acid–Associated Vanishing Bile Duct Syndrome

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Abstract

Hepatotoxicity as a result of valproic acid therapy is well documented. Elevation in aminotransferase activities is rarely associated with symptoms. It sometimes manifests as acute liver failure. Here, we report a 8-year-old girl who was referred for unresolving jaundice and itching for 3 months. Past history revealed afebrile convulsion 5 months previously and beginning of valproic acid treatment. Valproic acid was discontinued after the development of jaundice. Physical examination revealed ichterus, xanthomas on extensor surfaces of extremities, and hepatomegaly without any sign of chronic liver disease. Total and direct bilirubin levels were 20.2 and 12.9 mg/dL, respectively. Enzyme activities indicating cholestasis were increased together with blood cholesterol. Tests for infectious and autoimmune, metabolic, and genetic disorders were not informative. Liver biopsy revealed portal inflammation, severe bile duct loss, and cholestasis. The patient was considered to have valproic acid–associated vanishing bile duct syndrome, which has not been reported previously.

Keywords

valproic acid, jaundice, bile duct loss

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Hepatotoxicity as a result of valproic acid therapy, a widely used antiepileptic drug in pediatric epilepsy, is well documented, although the mechanism for this toxicity remains unknown. In children, it is hypothesized that the causes of valproic acid–induced hepatotoxicity include valproic acid–induced hypocarnitinemia and/or the formation of toxic metabolites, 2-propyl-4-pentenoic acid, or 4-ene-valproic acid through a hepatic P450 function.[1,2]

Elevation in aminotransferase activities can occur but is rarely associated with symptoms. Greatest risk of hepatotoxicity is in children in the first 3 years of life. It manifests as acute liver failure due to hepatocellular necrosis, usually macrovesicular and sometimes extensive microvesicular fatty change in the liver.[3,4]

Unlike the classical hepatotoxic pattern, we present a case of valproic acid hepatotoxicity manifesting as vanishing bile duct syndrome, which has not been reported previously.

Case

An 8-year-old girl was referred for unresolving jaundice and itching for 3 months. Past history revealed afebrile convulsion 5 months previously and beginning of valproic acid treatment. Valproic acid had been discontinued after appearance of jaundice. Family history was unremarkable for a similar disease including any viral, genetic, or metabolic liver disease. Physical examination revealed ichterus, xanthomas on extensor surfaces of extremities, and hepatomegaly without any sign of chronic liver disease. Her growth and development were normal. Total and direct bilirubin levels were 20.2 and 12.9 mg/dL, respectively. Enzyme activities indicating cholestasis were increased together with blood cholesterol: gamma glutamyl transferase, 1531 IU/L (normal, 0-23); alkaline phosphatase, 2787 IU/L (normal, 100-320); and total cholesterol, 1398 mg/dL (normal, <170). Aminotransferase activities were slightly elevated: aspartate aminotransferase, 209 IU/L (normal, 20-45) and alanine aminotransferase, 118 IU/L (normal, 8-35). Prothrombin time and international normalized ratio were within normal limits. Tests for hepatitis A, B, and C, Epstein-Barr virus, cytomegalovirus, herpes simplex virus 6, and parvovirus B19 were negative. Metabolic and genetic disorders, namely, α1-antitrypsin deficiency, cystic fibrosis, and

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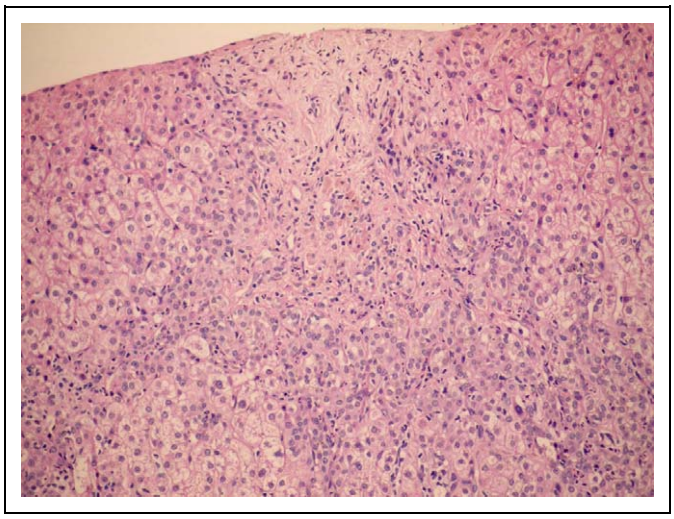

Figure 1. The portal tract displaying severe ductular reaction and no interlobular bile duct (hematoxylin & eosin, original magnification ×200).

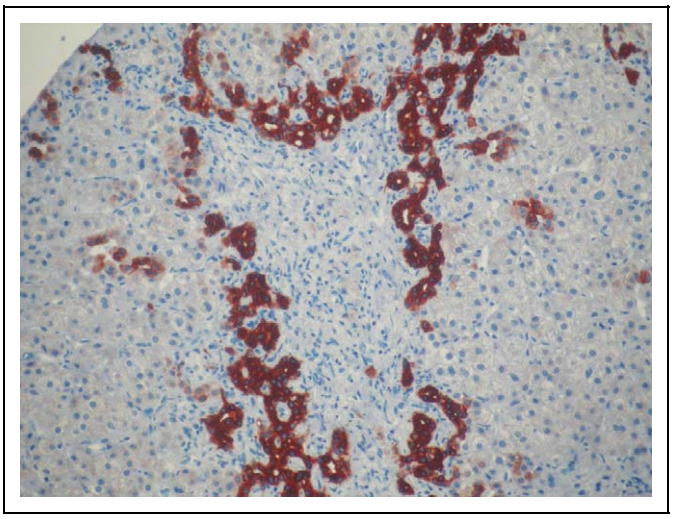

Figure 2. The portal area contains no interlobular bile ducts immunoreactive in cytokeratin 7 immunohistochemistry, which was used to highlight the biliary epithelial cells. The immunoreactive biliary interface activity displaying immunopositivity was seen (cytokeratin 7, Mayer hematoxylin as counterstain, original magnification ×200).

Wilson disease were excluded. Smooth muscle antibodies, antinuclear antibodies, type 1 liver/kidney microsomal antibodies, and antimicrosomal antibodies were all negative. Ultrasound scanning of the liver showed slight hepatomegaly and splenomegaly without dilatation of biliary tree. In the microscopic examination of the liver biopsy, eosinophil-dominant mixed inflammatory infiltration and severe interlobular bile duct loss in the portal areas were detected. There were severe biliary ductular reaction in the interface between the portal and lobular areas (Figure 1), and canalicular and hepatocellular cholestasis in the lobular area. Cytokeratin 7 and cytokeratin 19 immunohistochemical evaluations were performed to highlight the biliary epithelial cells. No interlobular bile ducts were seen in the portal areas. Cytokeratin 7 immunohistochemistry revealed immunopositivity on the ductular reaction in the interface areas (Figure 2). These histopathological findings were found to be consistent with vanishing bile duct syndrome that is presumed to be caused by valproic acid. Ursodeoxycholic acid therapy was commenced. Her bilirubin and blood cholesterol levels returned to normal within 8 months of presentation, together with near normalization of transaminase activities and significant decrease in gamma glutamyl transferase and alkaline phosphatase activities.

Discussion

Hepatotoxicity due to valproic acid is a known event, but the etiology and risk factors are poorly understood.[1] A review of pediatric hepatotoxicity due to valproic acid[4] found the patients at greatest risk for fatalities were males with neurological illnesses and seizures and on polytherapy with cytochrome P450-inducing agents such as phenobarbital or carbamazepine. Our patient did not possess those risk factors.

Asymptomatic increase in aminotransferases may rarely occur, but the most important and terrifying clinical picture is acute liver failure due to hepatocellular necrosis, usually macrovesicular and sometimes extensive microvesicular fatty change in the liver.[3-5] Modest increase in transaminase activities without liver failure was observed in our patient. However, the most striking feature was huge increase in gamma glutamyl transferase, alkaline phosphatase and cholesterol levels, together with direct hyperbilirubinemia. Liver biopsy that was performed after excluding the possible viral, metabolic, genetic, and obstructive causes demonstrated severe ductopenia, and the diagnosis was established as vanishing bile duct syndrome. We cannot definitely exclude an epiphenomena in this case with a paucicanalicular liver picture related to another yet-to-identify liver disease; viral, metabolic, or genetic. However, vanishing bile duct syndrome may be reasonably ascribed to valproic acid because (1) there was no history of preexisting liver or biliary tract disease; (2) liver and biliary tract were normal on ultrasonography; (3) there was a close temporal relation between valproic acid administration and the appearance of cholestasis; (4) eosinophil-dominant portal inflammation was present on liver biopsy; (5) other potential causes of vanishing bile duct syndrome were excluded including drugs known to induce cholestasis; and (6) jaundice resolved after exclusion of the offending drug.

Vanishing bile duct syndrome is a rare cause of progressive cholestasis. Although vanishing bile duct syndrome is observed in liver diseases such as allograft rejection, graft-versus-host disease, primary biliary cirrhosis, and primary sclerosing cholangitis, it is mostly related to drugs. Drugs act as a hapten and produce autoantibodies against cytokeratin in the bile duct.[6] Autoantibodies destroy biliary apparatus, which results in the disappearance of intrahepatic bile ducts.[7] The mechanism of biliary epithelial cell injury and interlobular duct loss in the vanishing bile duct syndrome is not yet fully understood.[6]

Toxic, idiosyncratic, metabolic, and immune etiologies have been suggested.[6,8] More than 30 drugs have been described as causing the vanishing bile duct syndrome, which has features resembling primary biliary cirrhosis including xanthomas, malabsorption, etc.[9] Although cholestasis was previously reported with valproic acid use,[10,11] this case is the first valproic acid–induced vanishing bile duct syndrome in both adults and children.

Drug-induced vanishing bile duct syndrome usually has a good prognosis; however, with jaundice resolving within several months (although rarely it can take several years before full resolution), a few instances of biliary cirrhosis have been reported.[12] There is no proven effective therapy for vanishing bile duct syndrome, but authors mostly agree that treatment modalities for vanishing bile duct syndrome include withdrawal of the offending agent, supportive care, and usage of immunosuppressants. Steroids, choleretic agents, and immunosuppressants have been tried with variable success.[13-15] There is evidence that ursodeoxycholic acid may have potential therapeutic effect through multiple mechanisms, including choleresis, protection of the hepatocellular lipid membranes against hydrophobic cytotoxic bile acids, and suppression of bile acid–induced apoptosis of the liver.[13,16] It improves canalicular transport by restoring bile flow and promotes excretion of toxic hydrophobic bile salts from the hepatocyte, preventing hepatocyte necrosis and apoptosis.[16] So, we tried ursodeoxycholic acid therapy. Clinical improvement was obtained and jaundice was resolved together with near normalization of transaminase activities within 8 months of presentation. Although still high, significant decreases in gamma glutamyl transferase and alkaline phosphatase activities were observed. Here, we cannot state that ursodeoxycholic acid is an effective therapeutic modality in vanishing bile duct syndrome. However, it may at least have contributed to improvement.

Here, we would like to report a pediatric case of valproic acid–associated vanishing bile duct syndrome. There was no published case of vanishing bile duct syndrome induced by this drug, although cholestasis was rarely reported. It might be important to search for underlying mechanism if similar cases are observed.

Declaration of Conflicting Interests

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