Routine Cholestasis Genetic Testing in Patients with Intrahepatic Cholestasis of Pregnancy Reveals High Prevalence of Genetic Variants of Bile Acid Transport Defects.

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Background and Aims: Intrahepatic cholestasis of pregnancy (ICP) is a condition unique to pregnancy causing pruritus, elevated liver enzymes, and elevated serum bile acids. It has been associated with complications including stillbirth and preterm delivery. Some women continue to experience cholestasis often with pruritus that occurs outside of pregnancy.
Genetic predisposition is often implicated in ICP specifically with mutations in the ATP8B1, ABCB11, and ABCB4 genes that are associated with progressive familial intrahepatic cholestasis (PFIC). The aim of this study was to assess the utility of routine cholestasis genetic testing in patients with ICP.

Method: Consecutive patients that presented to a tertiary hepatology clinic for history of cholestasis and ICP were tested prospectively for causes of genetic cholestasis with the cholestasis panel that tests for 77 genes. Routine clinical and laboratory parameters were collected. The severity of liver disease was assessed with vibration controlled transient elastography (VCTE). Descriptive statistics were used to characterize the cohort.

Results: Seven patients with history of ICP were tested. The mean age was 41.3 ± 13.9 years and the mean BMI was 28 ± 3.6 kg/m2. Laboratory parameters were as follows: ALT 45 ± 20.7 U/L, AST 35 ± 18.5, alkaline phosphatase 120.4 ± 51, GGT 59.4 ± 54, bilirubin 0.44 ± 0.11, and platelet count 326.7 ± 57.4 k/uL. The mean liver stiffness on VCTE was 4.9 ± 1.0 kPa and the mean controlled attenuation parameter was 243.4 ± 62 dB/m indicating no significant liver fibrosis. Genetic testing revealed that 5/7 (71.4%) of patients were heterozygote for a genetic variant in the ABCB4 gene typically associated with PFIC type 3. One patient was heterozygote for a genetic variant of MYO5B associated with PFIC 10. One patient was heterozygote for 3 genetic variants including CC2D2A, NPHP3, and UGT1A1. 6/7 (85.7%) of patients had recurrent episodes of pruritus that continued to occur outside of pregnancy. 4/7 (57.1%) were on ursodeoxycholic acid.

Conclusion: Cholestasis genetic testing in patients presenting to hepatology clinic for history of cholestasis and ICP revealed high prevalence of ABCB4 variants. To our knowledge, the association between MYO5B and ICP is novel. The role of other genetic variants for cholestasis other than PFIC genes needs to be better understood.