Was it Always in the Genes? ABCB4 and its Variable Presentations

Andre Khazak, DO[1], Carolina Villarroel, MD[1], Silpa Yarra, MD[1], Ilan Weisberg, MD, MSc[2]
[1]Department of Medicine, Mount Sinai Beth Israel Medical Center. Icahn School of Medicine at Mount Sinai. New York, NY.
[2]Division of Gastroenterology, New York - Presbyterian Brooklyn Methodist Hospital

Introduction

Progressive familial intrahepatic cholestasis (PFIC), low phospholipid-associated cholestasis (LPAC), and autosomal dominant intrahepatic cholestasis of pregnancy (ICP) are rare genetic disorders that should be considered in patients with elevated alkaline phosphatase (ALP) and unrevealing primary work ups.

We present a case of a 36-year-old female with a history of ICP who presented with elevated ALP, eventually found to have a nonspecific variant in the ABCB4 gene, concerning for Type 3 PFIC.

Case

A 36-year-old female with a history of ICP treated with Ursodiol, current oral contraceptive use (OCP), and remote cholecystectomy presented to a gastroenterologist for asymptomatic ALP elevation.

Case Continued

Initial labs revealed ALP 279 U/L, bile acids 9.9 µmol/L, and gamma-glutamyl transferase (GGT) 283U/L.

Magnetic resonance cholangiopancreatography (MRCP) was unrevealing. Given no signs of hepatic dysfunction, portal hypertension, or steatosis on fibroscan, liver biopsy was obtained, which was unremarkable.

Due to persistent elevation in ALP without a clear etiology and history of ICP, genetic testing was pursued. Genetic testing revealed a heterozygous variant of uncertain significance in the ABCB4 gene that is associated with PFIC type 3. OCPs were discontinued due to an association of ICP and OCP induced cholestasis. Ursodiol was restarted given high rates of recurrent cholelithiasis in patients with PFIC.

Discussion

Type 3 PFIC, LPAC, and ICP are rare genetic disorders linked to unique mutations in the ABCB4 gene responsible for ALP elevation.

Discussion Continued

The ABCB4 gene may manifest later in life as cholestasis, jaundice, or pruritus. Mutations in the ABCB4 gene can cause a reduction in biliary phospholipid concentration, leading to sludge, cholesterol stones, and microlithiasis.

Type 3 PFIC has a unique presentation associated with elevated GGT, unseen in type 1 PFIC or 2 PFIC.

LPAC should be considered in patients presenting with cholelithiasis before the age of 40, recurrent cholelithiasis after cholecystectomy, ICP, and family history of cholelithiasis.

Conclusion

The variant of uncertain significance in our patient's ABCB4 gene appeared to be a unifying diagnostic factor given her history of ICP, cholelithiasis at age 18 years requiring cholecystectomy, and persistent new elevation in ALP. She ultimately met criteria for Type 3 PFIC, LPAC and ICP. Given the rapidly evolving nature of medical genetics, reclassification and evaluation of genetic mutations requires follow up.