**Synergistic Heterozygosity of Multiple Genes is Associated with Neonatal Cholestasis**

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Causes of neonatal cholestasis are very diverse and amongst them are several genes that have been implicated in the etiology.

In this case report, we describe a 5 months old female infant, a former 29 week preterm baby, who was transferred to Cleveland Clinic Children’s with severe cholestasis. Since birth, her course was complicated by multiple infections requiring antibiotics and prolonged course of TPN. Direct hyperbilirubinemia progressively worsened on day 175 of life with total/direct bilirubin of 39.1/25, mild elevation in liver enzymes AST 319 (normal 13-35 U/L) , ALT 171 (normal 7-38 U/L), GGT 126 (normal 0-35 U/L) and mild prolongation of INR 1.29 (normal 0.8 - 1.2). Patient underwent extensive work up which excluded biliary atresia, alpha-1- antitrypsin deficiency, infectious etiology, Alagille syndrome and chromosomal aberrations. A genetic cholestasis panel from Emory University was done and showed heterozygosity for variants of the following genes: AKR1D1, ATP8B1/PFIC1, ABCC2 and NPHP1. In the homozygous form, these gene variants are associated with the following diseases which manifest with neonatal cholestasis: congenital bile acid synthesis defect (type 2), progressive familial intrahepatic cholestasis type 1, Dubin-Johnson syndrome and nephronophthosis, nephrotic syndrome, respectively. Patient was started on Ursodiol, Phenobarbital and fat-soluble vitamins. Cholestasis and liver enzymes eventually normalized as patient clinical status stabilized over the next few weeks.

To our knowledge, this is the first report of potential role of synergistic heterozygosity in neonatal cholestasis. Although cholestasis in our patient is likely multifactorial and is related to prematurity, prolonged TPN course and multiple infections, the presence of variants of genes involved in neonatal cholestasis in the heterozygous form highlights the possibility of synergistic heterozygosity as another contributor. With the increased use of different genetic cholestasis panels, clinicians will likely be able to further uncover the possible role of synergistic heterozygosity in the etiology of neonatal cholestasis in some patients.