PIGA Mutations Can Mimic Neonatal Hemochromatosis

Jaime Flores-Torres, MD, Jane D. Carver, PhD, Amarilis Sanchez-Valle, MD

Neonatal hemochromatosis (NH), one of the most common causes of liver failure in the neonate, often causes fetal loss or death during the neonatal period. Most cases are thought to be due to gestational alloimmune disease; however, other rare causes have been reported. NH is generally considered congenital and familial but not heritable. We present an infant diagnosed with NH whose clinical course differed significantly from that of most NH cases: at 11 months of age he had normal levels of liver enzymes, ferritin, and bilirubin, and normal neurodevelopment. This term male infant was born with a history of intrauterine growth restriction, oligohydramnios, and pericardial effusion. On day of life 1, he had hyperbilirubinemia and transaminitis; on day of life 3, ferritin was elevated; and on day of life 9, an MRI revealed iron deposits in the liver and renal cortex. Phenotypic features prompted a genetics consult. Whole-exome sequencing revealed a variant in the phosphatidylinositol glycan biosynthesis class A protein (*PIGA*) gene. Germ-line *PIGA* mutations are generally thought to be lethal in utero; however, there are reports of infants with *PIGA* mutations associated with dysmorphic features, neurologic manifestations, biochemical perturbations, and systemic iron overload; development can be normal up to 6 months of age. Because of the differences between infants with NH versus *PIGA* germ-line mutations in inheritance, prognosis, and natural history of disease, we propose that *PIGA* gene testing should be considered when evaluating newborns who present with NH.

CASE REPORT

The male infant was born at 37 weeks gestational age to a 22-year-old primigravida woman who had no remarkable medical history. The mother's prenatal laboratory results were within the normal ranges. Prenatal ultrasound revealed intrauterine growth restriction, oligohydramnios, and pericardial effusion. The infant's birth weight was 2070 g (lower than fifth percentile), with 1- and 5-minute Apgar scores of 6 and 8, respectively. On day of life (DOL) 1, an echocardiogram revealed a large patent ductus arteriosus and a trivial anterior pericardial effusion, and laboratory results revealed hyperbilirubinemia (conjugated bilirubin 5.9 mg/dL, reference range 0.0–0.5) and transaminitis (AST 163 U/L, reference range 5–34). The infectious disease workup was negative, and included blood and cerebrospinal fluid cultures, herpes simplex virus (polymerase chain reaction), respiratory viral panel and parvovirus B19 polymerase chain reaction, urine cytomegalovirus, and toxoplasma immunoglobulin M. Bilirubin, liver enzymes and ferritin levels remained elevated during hospitalization, with ferritin levels reaching 3229 ng/mL on DOL 20. Because of the elevated levels of bilirubin and ferritin, the patient was given a dose of intravenous immunoglobulin on DOL 2 and DOL 17.

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Drs Flores-Torres and Sanchez-Valle conceptualized and designed the report and reviewed and revised it for intellectual content; Dr Carver made substantial contributions to the conception and design of the study, drafted the article, and revised it for intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2020-0918

Accepted for publication Jul 13, 2020

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Flores-Torres J, Carver JD, Sanchez-Valle A. *PIGA* Mutations Can Mimic Neonatal Hemochromatosis. *Pediatrics*. 2021;147(3): e20200918

Ferritin levels on DOL 144, 266, and 357 were 109, 41, and 27 ng/mL, respectively.

A genetics consult, ordered on DOL 3 because of intrauterine growth restriction, cholestasis, and dysmorphic facial features, revealed an infant who was small for gestational age with overriding sutures, prominent forehead, receding hairline, and anteverted nares. The metabolic workup, karyotype, and chromosomal microarray analysis (2.67 million probes) were normal. An abdominal MRI on DOL 9 indicated iron deposition in the liver and renal cortex (Fig 1 A and B). A liver biopsy specimen revealed hepatocellular iron, cholestasis, and extramedullary hematopoiesis. The result of a salivary gland biopsy was negative for iron deposits. At this point of the evaluation, he met criteria for a diagnosis of neonatal hemochromatosis (NH) because of having extrahepatic siderosis and liver disease.

The phenotypic features of our patient prompted us to perform whole-exome sequencing, which revealed a variant in the gene for phosphatidylinositol glycan biosynthesis class A protein (*PIGA*) (hemizygous c.307 G>Z p. Ala 103Thr, X-linked). This mutation was recently reported to be associated with systemic iron overload.[1] Our patient's clinical course differed significantly from that reported for most patients with NH. The genetics team has continued to follow the infant, who, at 11 months, had normal liver enzymes, ferritin, and bilirubin, in addition to normal neurodevelopment.

DISCUSSION

NH, one of the most common causes of liver failure in neonates, often causes fetal loss or death during the neonatal period.[2] Most cases are thought to be due to gestational alloimmune liver disease, with the fetal liver injury being mediated by activation of the complement cascade.[2,3] The diagnosis is based on severe liver disease and extrahepatic siderosis, and most infants present with liver failure soon after birth. They often have hypoglycemia, coagulopathy, hypoalbuminemia, jaundice, and edema, and they may be oliguric. Intrauterine growth restriction, oligohydramnios, prematurity, and patent ductus arteriosus are common. Laboratory abnormalities include significant hyperbilirubinemia, high α-fetoprotein and serum ferritin levels, low transferrin levels, and high iron saturation.[2]

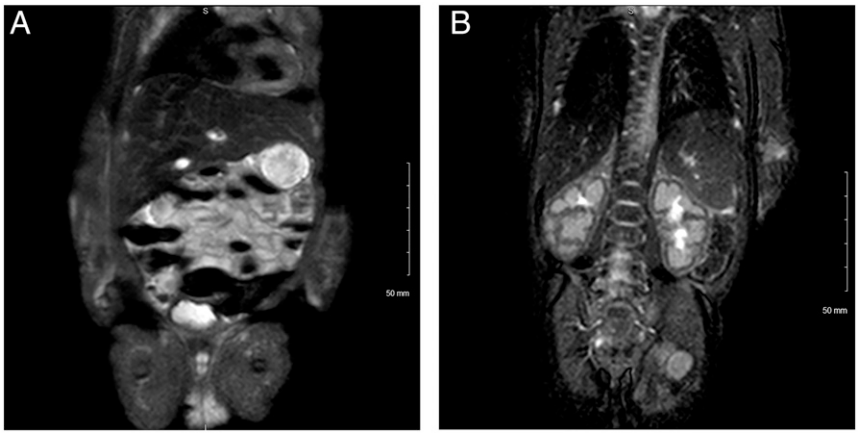

FIGURE 1
A and B, Abdominal MRI indicating iron deposition in the liver (A) and renal cortex (B) of our patient on DOL 9.

Observations that NH affects siblings has led to suspicions of a genetic defect; however, no gene locus has been identified. It is generally considered congenital and familial, but not heritable.[2,4]

Somatic mutations in the *PIGA* gene have been associated with paroxysmal nocturnal hematuria, which presents later in life and is life-threatening. Germ-line mutations in *PIGA* are generally believed to be lethal in utero.[5] However, there are reports of germ-line mutations in *PIGA* that can cause a phenotype of dysmorphic features, neurologic manifestations, and biochemical perturbations.[6] In addition, hypomorphic germ-line *PIGA* mutations can cause a spectrum of neurodevelopmental disorders, including the multiple congenital anomalies-hypotonia-seizures syndrome.[7] This X-linked recessive disorder is characterized by clinical heterogeneity, including hypotonia, anteverted nares, receding hairline, prominent metopic suture, iron deposits, and sutures. Development can be normal until the onset of intractable seizures after 6 months of age, with severe cases leading to early death.[1,7,8]

Our patient's facial features are similar to those described above; however, at 11 months of age he did not have any neurodevelopmental symptoms. His variant is classified as unknown clinical significance, and we speculate that it could result in partial function of the protein and mild symptoms. The finding that our patient's clinical course differed significantly from that reported for most patients with NH has significant implications for the treatment and expected outcomes for infants who present with NH but have a germ-line *PIGA* mutation. Because of the differences in inheritance, prognosis, and natural history of disease between NH and *PIGA* germ-line mutations, we propose that *PIGA* gene testing should be considered when evaluating newborns who present with NH, especially if they have

dysmorphic features or other congenital anomalies.

Our study reinforces the concept that NH, although often lethal or resulting in liver transplant, has different etiologies that can significantly alter the prognosis and management plan; this was demonstrated in our case by identification of a *PIGA* mutation. Although our understanding of this particular condition is limited, a recent study of multiple congenital anomalies-hypotonia-seizures syndrome revealed that patients with *PIGA* mutations may have a less severe phenotype than is typically expected.[9] Ethically, our findings reinforce the concept that NH is not uniformly fatal, which should prompt practitioners to perform a thorough investigation to rule out nonlethal causes. Our findings may also encourage the development of different approaches to the management of patients with NH.

ACKNOWLEDGMENTS

We thank the family of our patient for allowing us to share his case with the medical community, and Dr Thora Steffensen for the histology pictures.

ABBREVIATIONS

DOL: day of life
NH: neonatal hemochromatosis
PIGA: phosphatidylinositol glycan biosynthesis class A protein

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Pediatrics 2021;147;
DOI: 10.1542/peds.2020-0918 originally published online February 25, 2021;

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DOI: 10.1542/peds.2020-0918 originally published online February 25, 2021;