One of many tasks charged to the primary care pediatrician during the newborn period is the surveillance and management of hyperbilirubinemia. Among the minority of those infants who are cholestatic, prompt diagnosis and treatment can prolong health, as in the case of biliary atresia, and even be life-saving, as is the case for certain metabolic derangements. This disease may soon join the list of medically treatable diseases is Niemann-Pick disease type C (NPC-C).

We present a patient with neonatal cholestasis who was found to have NPC-C. Prompt recognition of abnormal bilirubin levels and physical exam findings by the primary hospitalist team directly facilitated making a definitive diagnosis at the early age of two months. With her diagnosis of NPC-C, her primary care pediatrician and subspecialists are now aware to chronicle her neurological milestones and growth which are both at-risk. In addition, we still potential be enrolled into a clinical study with potential be enrolled into a clinical study with characteristic of Niemann-Pick disease type C.

History of Present Illness and Hospital Course

A five-week-old, ex-35 week female, was transferred to the emergency department due to vomiting and liver. Upon arrival, she received fluid resuscitation, initial pediatric work up, and administered empiric broad-spectrum antibiotics.

Examinations revealed failure-to-thrive: weight 8.4 kg, length 21" and birth circumference 5.8 kg, hepatosplenomegaly was present. Congenital bilirubin was 2.5 mg/dL. ALT 224 U/L, AST 135 U/L, and GGT 110 U/L. Tests for congenitally acquired infections (toxoplasmosis, syphilis, CMV, EBV, and HIV) were normal. Metabolic screening tests were obtained for alpha-1 antitrypsin deficiency, urine catecholamines, and tyrosinemia; all were non-diagnostic.

The hospitalist team was appropriately concerned for obstructive jaundice and ordered an abdominal ultrasound which revealed a connatal gallbladder, no intraperitoneal bile duct dilatation, and homogenous liver parenchyma. HDH scan was subsequently performed. Radiotracer activity was promptly detected in the bowel, arguing against biliary obstruction. A liver biopsy (Fig. A) was next performed; the findings were suggestive of tyrosinemia disease type C. Radiotracer activity was promptly detected in the bowel, arguing against biliary obstruction. A liver biopsy (Fig. A) was next performed; the findings were suggestive of tyrosinemia disease type C.

Liver Biopsy Results

• Glucosylceramide and sphingomyelin
• Cytoplasmic inclusion of NPC1

Figure A. Diffuse Giant cell transformation and fibro Sarco degeneration of hepatocytes. Hematoxylin-eosin x 40.

Figure B. Portal tracts and focal wall inflammation composed of mononuclear cells, neutrophils, and scattered eosinophils. Interlobular bile ducts surrounded by inflammatory cells bile plugs. Hematoxylin-eosin x 100.

Electron Microscopy Results

Figure C. Electron Microscopy of Liver Biopsy. Multiple cytoplasmic (lysosomal) vacuoles in all the hepatocytes display prominent phospholipid accumulation. These findings are characteristic of Niemann-Pick disease type C.

Niemann-Pick Disease Type C

Niemann-Pick disease type C is autosomal recessive lipid storage disorder that presently with cholestasis jaundice in the neonatal period and spleno- or hepatosplenomegaly in infancy or childhood.

Niemann-Pick disease was first described in the 1920’s by Albert Niemann and Ludwig Pick as an autosomal recessive inherited disease with hepatosplenomegaly and sphingomyelin storage in reticuloendothelial and parenchymal tissues. Later, Crocker and Farber noted Niemann-Pick disease has variable phenotypic expression in regard to age of onset and clinical expression and separately designated them A-D Type. C, which turned out to be distinct from Type A and B, is characterized by nervous system involvement with a slow-to-moderate disease course and milder visceral storage. The estimated incidence of NPC is conservatively 1/120,000 live births. Afflicted individuals can present with dysostasia, dysphagia, and vertical supranuclear gaze palsy.

NPC-C is attributed to genetic mutations in two genes, NPC1 and NPC2, which are thought to be responsible for processing and utilization of endocytosed, unesterified cholesterol in the cell’s late endosome/lysosome (Fig. D).

Case Outcome

Confirmatory genetic testing of NPC was performed at Baylor College of Medicine. She was found to harbor two different mutations c.1456G>A and c.2094C>T which are both known to cause NPC- independently.

Her cholestasis resolved over two months, however, she has continued to gain weight slowly. No neurological signs are yet present. She was referred for consideration of nilvadipine in the context of a clinical trial but has not started medical therapy yet. This medication looks promising as it has been shown to stabilize swallow function and improve and stabilize cognitive function in pediatric NPC patients.

References


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