Acute Liver Failure Secondary to Neuroblastoma Amplified Sequence Deficiency

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Case Description

A 2-year-old boy presented to a local emergency department with a 3-day history of fever, cough, congestion, and 24 hours of vomiting. Initial laboratory tests revealed hypoglycemia (31 mg/dL), markedly elevated aspartate aminotransferase (27 630 IU/L) and alanine aminotransferase (14 500 IU/L) levels, and elevated total bilirubin (3.0 mg/dL) and alkaline phosphatase (360 IU/L) levels; his γ-glutamyl transpeptidase level was normal at 44 IU/L. He was noted to have lactic acidosis (6.5 mmol/L). He also had severe coagulopathy with an international normalized ratio of 4.5 and hyperammonemia (282 μmol/L). He was admitted, and shortly thereafter developed altered mental status requiring endotracheal intubation and mechanical ventilation. He was then transferred to our institution, a tertiary care center, for further evaluation and management.

Upon arrival, he was admitted to the critical care unit and initiated on continuous renal replacement therapy due to third-spacing of fluids and persistent hyperammonemia. His physical examination was notable for weight and length less than the third percentile, an open anterior fontanelle, and hepatomegaly. Listing for liver transplantation was considered during the first 48 hours of admission due to persistently elevated aminotransferase levels, ongoing severe coagulopathy despite vitamin K administration, and critical illness. He also received vasopressor support and empiric antibiotic coverage. Additional therapy while hospitalized included maintaining a high glucose infusion rate of 8-10 mg/kg/min, based on the differential diagnosis including metabolic disease. After the first 48 hours, his aminotransferase levels began to steadily decline, and his coagulopathy resolved spontaneously. His total bilirubin and direct bilirubin levels peaked at 11.5 mg/dL and 7.4 mg/dL, respectively, on hospital day 4. His clinical status improved, he was safely extubated, and subsequently weaned off of continuous renal replacement therapy. He was discharged from the hospital after 18 days in good clinical status with aminotransferases and bilirubin levels significantly improved.

A broad evaluation for etiologies of acute liver failure (ALF) performed while hospitalized was negative, including an extensive evaluation for infectious etiologies, viral testing, assessment of medication history, serum acetaminophen level, serum autoantibodies (antinuclear antibody, anti–smooth muscle antibody, anti–liver/kidney microsomal antibody), investigation for metabolic etiologies (plasma amino acids, urine organic acids, acylcarnitine profile, ceruloplasmin, alpha fetoprotein), mitochondrial disorders (serum lactate and pyruvate), and alpha-1 antitrypsin deficiency (phenotype MM). He had an unrevealing immunodeficiency workup, including a normal natural killer cell activity, laboratory screening for hemophagocytic lymphohistiocytosis and normal levels of immunoglobulins (IgG, IgM, and IgA). His echocardiogram was normal. Given his presentation, and unrevealing workup for other etiologies of ALF, genetic testing for neuroblastoma amplified sequence (NBAS) deficiency was sent based on recent case reports of pediatric patients presenting with ALF after a febrile illness.[1-4]

Genetic testing reported 2 variants in the NBAS gene, inherited in trans. The first variant, c.409C>T (p.Arg137Trp), has been identified previously in other reported patients with a similar phenotype, including ALF.[1-4] The second variant, c.758T>G (p.Val253Gly), is novel, but alters a highly conserved valine residue, and is predicted to be deleterious with an estimated allele frequency of <0.01%. These findings, in the setting of our patient's clinical picture, are most consistent with NBAS deficiency.

Review of his past medical history revealed a history of failure to thrive despite high calorie intake and mildly delayed early gross motor skills, but otherwise normal development. He had previously been evaluated in a local genetics clinic and had a normal chromosomal microarray. Notably, 1 year before presentation he was hospitalized for fever and symptoms of viral upper respiratory infection, and was found to have elevated aspartate aminotransferase (2721 IU/L) and alanine aminotransferase (1785 IU/L) levels; liver synthetic function testing such as an international normalized ratio was not available to review. His aminotransferase levels gradually normalized. There is no family history of liver disease or consanguinity.

After discharge, the patient returned to the University of Michigan Pediatric Genetic Clinic. Findings on detailed examination for dysmorphology are elaborated in the **Figure**. Aminotransferase levels and international normalized ratio were within normal limits at this visit. Given concern for optic

ALF	Acute liver failure
ER	Endoplasmic reticulum
NBAS	Neuroblastoma amplified sequence
SNARE	Soluble *N*-ethylmaleimide-sensitive factor attachment receptor

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The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.03.040

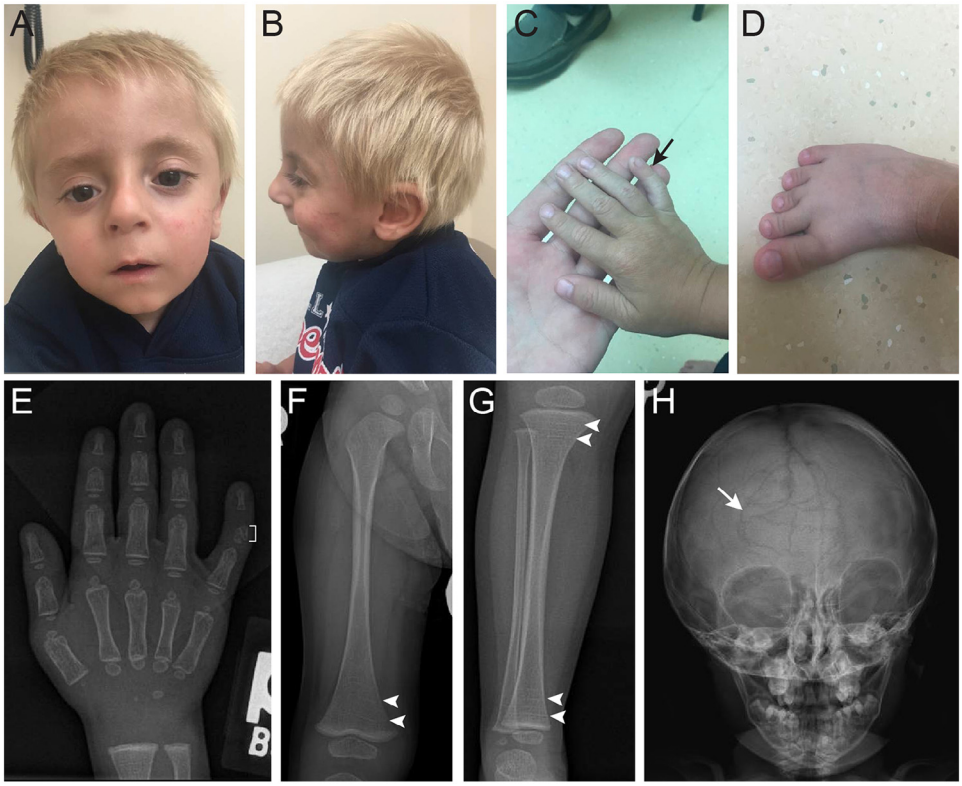

Figure. Morphologic findings in a 2-year-old boy with compound heterozygous mutations in NBAS. **A-D,** Physical features of NBAS deficient patient. Note deep set eyes (**A**), retrognathia (**B**), 5th finger clinodactyly (**C**, *arrow*) and brachydactyly of the 3rd-5th toes (**D**). **E-H,** Representative radiographs from skeletal survey. Brackets (**E**) demonstrate 5th-finger clinodactyly. Arrowheads (**F-G**) denote metaphyseal growth arrest lines. Arrow in (**H**) delineates significant wormian/intrasutural bone formation. Note diffuse osteopenia.

atrophy in patients who are NBAS deficient, he was referred for ophthalmologic evaluation, which has not been completed yet. An emergency management protocol was established for treatment and management during febrile illness that includes actively preventing a fever and avoiding catabolism, with dextrose containing intravenous fluids and intralipids.

Since that visit, the patient has been readmitted twice with fever in the setting of acute upper respiratory viral infection (rhino/enterovirus) with highly elevated aminotransferase levels (**Table**), including 1 episode with coagulopathy and mild encephalopathy consistent with ALF, which reversed with aggressive measures to control fever and reverse catabolism.

Discussion

ALF in infancy and childhood is a life-threatening emergency; however, in about 50% of cases the etiology remains unknown.[5] Failure to identify the etiology can significantly

Table. Peak aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and international normalized ratio values*

	Laboratory studies during and after febrile illnesses			
	Before diagnosis	Follow-up	After diagnosis	Follow-up
Variables (normal values)	Admission 05/10/16-05/28/16	6/16/2016	Admission 08/12/16-08/16/16	10/6/2016
Aspartate aminotransferase (5-60 IU/L)	27 630	42	6194	45
Alanine aminotransferase (≤35 IU/L)	14 500	42	4084	37
Alkaline phosphatase (70-350 IU/L)	357	250	434	237
Total bilirubin (0.1-1.0 mg/dL)	11.5	0.2	1.3	0.2
International normalized ratio	5.9	1	1.3	1

*Values were taken during the patient's initial prediagnosis admission and during his subsequent admission after a diagnosis of NBAS deficiency, demonstrating successful prevention of hepatic failure with appropriate recognition and treatment. Note that laboratory values return to baseline in between admissions.