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CASE REPORT

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Resolution of recurrent pediatric acute liver failure with liver transplantation in a patient with *NBAS* mutation

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Abstract

Background: Pediatric acute liver failure (PALF) remains an enigmatic process of rapid end-organ dysfunction associated with a variety of pathologic conditions though the predominant cause is indeterminate. A growing body of research has identified mutations in the *NBAS* gene to be associated with recurrent acute liver failure and multi-systemic disease including short stature, skeletal dysplasia, facial dysmorphism, immunologic abnormalities, and Pelger-Huët anomaly.

Methods and Results: Here, we describe a 4-year-old girl who presented with dehydration in the setting of acute gastroenteritis and fever but went on to develop PALF on day 2 of hospitalization. She clinically recovered with supportive measures, but after discharge, had at least 2 additional episodes of PALF. Ultimately, she underwent liver transplant and her recurrent episodes of PALF did not recur throughout a 6-year follow-up period. Whole-exome sequencing post-liver transplant initially revealed two variants of uncertain significance in the *NBAS* gene. Parental studies confirmed the c.1549C > T(p.R517C; now likely pathogenic) variant from her mother and a novel c.4646T > C(p.L1549P) variant from her father. In silico analyses predicted these variants to have a deleterious effect on protein function. Consistent with previously characterized NBAS mutation-associated disease (NMAD), our patient demonstrated the following features: progeroid facial features, hypoplasia of the 12th ribs, Pelger-Huët anomaly on peripheral blood smear, and abnormal B and NK cell function.

Conclusion: Altogether, we describe a novel pathogenic variant in the *NBAS* gene of a patient with NMAD and report the resolution of recurrent PALF secondary to NMAD following liver transplantation.

KEYWORDS
acute liver failure, immunocompromised host, liver transplantation, NBAS, pediatric, pediatric liver, transplantation

Abbreviations: ALF, acute liver failure; CPK, creatine phosphokinase; HLH, hemophagocytic lymphohistiocytosis; INR, international normalized ratio; iPALF, indeterminate pediatric acute liver failure; NBAS, neuroblastoma amplified sequence; NK, natural killer; NMAD, *NBAS* mutation-associated disease; PALF, pediatric acute liver failure; PALFSG, pediatric acute liver failure study group; PT, prothrombin time; VUS, variant of uncertain significance.

1 | INTRODUCTION

Pediatric acute liver failure remains an enigmatic process of rapid end-organ dysfunction associated with a variety of pathologic conditions. The multi-center PALF study group (PALFSG) set-forth a study level criteria for PALF to include biochemical evidence of acute liver injury in the absence of chronic liver disease, coagulopathy not corrected by phytonadione administration (prothrombin time [PT] ≥15 or international normalized ratio [INR] ≥ 1.5) with clinical evidence of hepatic encephalopathy (HE), or severe coagulopathy (PT ≥ 20 or INR ≥ 2.0) in the absence of HE.[1] The pathogenesis of PALF is broadly associated with age-dependent infectious, immunologic, metabolic, toxic, and drug-induced insults, with indeterminate PALF (iPALF) comprising 45% of all cases.[1,2] Indeed, iPALF is associated with worse clinical outcomes[3] and the underlying immune dysregulation is characterized by increased activation and expansion of the CD8+ T-cell compartment along with CD103+CD8+ T-cell infiltration of the liver.[4,5]

The treatment of PALF is centered on supportive measures and liver transplantation.[6,7] Reliable tools to prognosticate a patient's spontaneous survival versus those who will progress to death without liver transplantation are lacking.[3] Contributing to the uncertainty of PALF progression is the heterogeneity of the disease processes that lead to the common pathway of acute liver failure and the ever-expanding catalogue of novel genetic mutations implicated in PALF.

There has been a growing body of research identifying various mutations in the neuroblastoma amplified sequence (NBAS) gene being associated with recurrent acute liver failure and varying degrees of multi-systemic involvement.[8,9] The NBAS protein is broadly expressed in various organs including liver, heart, skeletal muscle, and leukocytes (Source: https://source-search.princeton.edu/). Its function is postulated to be involved in Golgi-to-endoplasmic reticulum (ER) retrograde vesicular trafficking and to regulate nonsense-mediated mRNA decay.[10,11] Phenotypic abnormalities associated with mutations in the *NBAS* gene include short stature, skeletal dysplasia, facial dysmorphism, immunologic abnormalities, optic nerve atrophy, and Pelger-Huët anomaly, which is a leukocyte anomaly characterized by coarse, bell-shaped nuclei.[8,12,13] Here, we describe a 4-year-old girl with a novel genetic variant in the *NBAS* gene along with phenotypic manifestations of NBAS mutation-associated disease (NMAD)—including recurrent PALF—and demonstrate resolution of recurrent PALF following liver transplantation that includes 6-year post-transplant follow-up period.

2 | CASE PRESENTATION

The patient on initial presentation was a 4-year-old Caucasian girl with a longstanding history of failure-to-thrive and persistent elevation in transaminases who presented with several days of non-bloody, non-bilious emesis, anorexia, and fever. In the emergency department, she was noted to have clinical signs of dehydration and metabolic acidosis with a HCO3 of 10mmol/L and elevated lactic acid (21.5 mg/dl). Past medical history was notable for a growth curve with weights and heights consistently below the 5th and 3rd percentiles, respectively. The Z-scores for weight were −2.69, and height was −3.32 on admission. A liver biopsy obtained two years prior to her PALF presentation to evaluate for persistently elevated transaminases yielded no evidence of cholestasis, inflammation, or fibrosis (data not shown). Family ancestry was reported to be of Scottish/European descent, and there was no family history of metabolic or genetic conditions nor familial liver disease. With no other remarkable history, she was presumed to have a viral illness and admitted for IV fluids and close observation. Though her metabolic acidosis was corrected with IV fluids, her liver indices increased over the course of two days with AST 219 IU/L and ALT 185 IU/L rising to >7500 and >10 000 IU/L, respectively. Total bilirubin on admission was not only 0.8 mg/dl but also increased to 3.7 mg/dl. The INR was 6.3 on day 2 of hospitalization indicative of coagulopathy secondary to hepatic synthetic dysfunction as it was unresponsive to IV vitamin K repletion. Subsequently, she was transferred to our institution for further PALF management and liver transplant evaluation. Her neurologic examination was remarkable for hepatic encephalopathy ranging from grade 1 to 2.

Her liver injury tests, coagulopathy, and mental status normalized with supportive measures but she subsequently had at least 2 additional episodes of marked hepatic dysfunction in a stereotypic pattern following discharge including vitamin K unresponsive coagulopathy, marked transaminase elevation, relatively mild elevation of bilirubin, no hyperammonemia, low-to-normal creatine phosphokinase (CPK), and mildly elevated aldolase. As she presented with recurrent PALF, an underlying metabolic disorder was suspected. In briefly summarizing her PALF work-up prior to liver transplantation, abdominal ultrasound was normal with normal flow of the hepatic and splenic vasculature on Doppler. There was no evidence of chronic liver disease or vascular abnormalities. For infectious work-up, the hepatitis viral serologic panel was negative along with negative serum EBV, CMV, and HSV PCRs. Undetectable acetaminophen and salicylate levels and no history of ingestion were reassuring against drug-induced liver injury. Her metabolic work-up was overall normal and included both urine (amino acid, organic acid, and acylglycine) and plasma (amino acids, acylcarnitine profile, and pyruvic acid) studies. Immunologic evaluation was only remarkable for low immunoglobulin A (10 mg/dl) and G (419 mg/dl). Anti-nuclear antibody, total IgG, anti-smooth muscle antibody, and liver-kidney-microsomal type 1 antibody were not detected—inconsistent with autoimmune hepatitis. Ferritin was elevated (4880 ng/ml), but she did not have any cytopenias concerning for hemophagocytic lymphohistiocytosis (HLH). Pelger-Huët anomaly was noted on peripheral blood smear, but cell counts and differential were within normal limits. The patient had a repeat liver biopsy with the histology revealing an absence of inflammatory infiltrate, periportal fibrosis, and diffuse microvesicular steatosis (Figure 1A). Evaluation for a mitochondrial hepatopathy revealed a normal electron microscopy of the mitochondria, and a mitochondrial DNA depletion panel (Baylor

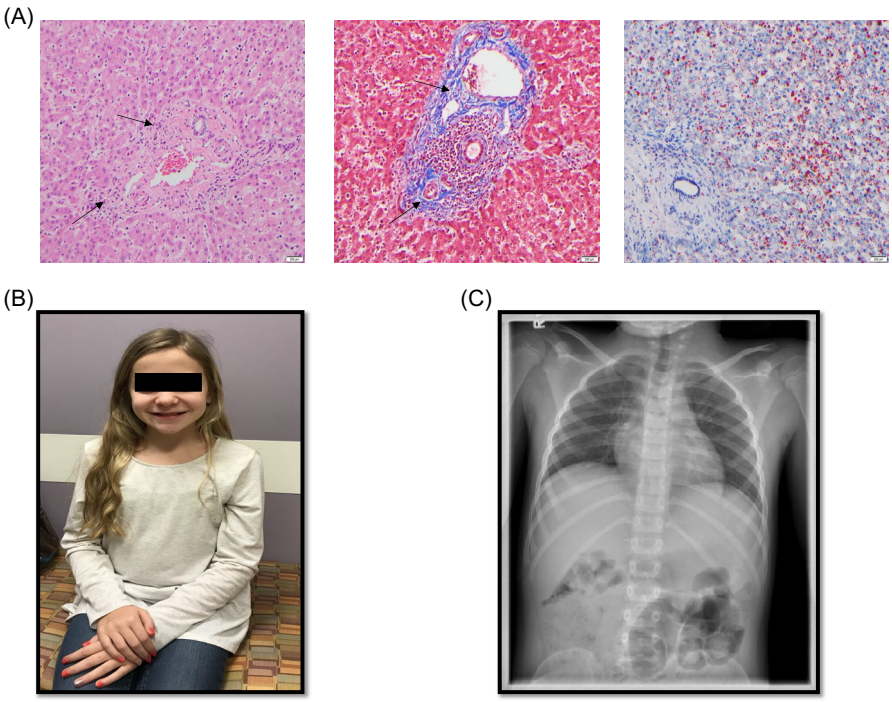

FIGURE 1 Histologic and clinical findings of NBAS mutation-associated disease. (A) The liver architecture is preserved with only mild abnormalities on routine hematoxylin-eosin (H&E; left panel) and trichrome stains (middle panel) including rare acidophil bodies (left panel; black arrows), and mild periportal fibrosis (middle panel; black arrows). Oil red O stain (right panel) confirms diffuse microvesicular steatosis as the main pathology in the native liver. (B) Progeroid facial features and (C) skeletal survey remarkable for hypoplasia of the 12th ribs

MTDNA Depletion panel, hepatocerebral form) was negative for deleterious mutations.

The patient underwent liver transplantation 7 months after initial presentation to our institution at 5 years of age following another admission for PALF in context of fever, rhinorrhea, and anorexia. She was listed for liver transplant with a PELD of 30 by exception for suspected metabolic disease. She underwent whole-organ liver transplant with duct-to-duct anastomosis. She had an uncomplicated surgery and post-operative course and was discharged on post-operative day 7. Her immunosuppressive regimen on discharge was prednisolone daily and tacrolimus every 12 hours with trough goal of 10-12ng/mL.

Her clinical course after discharge was notable for a single episode of severe acute cellular rejection diagnosed by liver biopsy at 2 weeks post-transplant that was treated with pulse steroids and maintaining higher tacrolimus trough levels of 15–18 ng/ml. Five months post-transplant, she had another liver biopsy for elevated liver enzymes, but histology was normal (not shown). She did not have any additional episodes of synthetic liver dysfunction (ie, coagulopathy or lactic acidosis) but did have intermittent episodes of elevated transaminases in context of minor illnesses with normal GGT and histologically normal liver biopsies.

Post-transplant whole-exome sequencing revealed that the patient initially had two variants of uncertain significance (VUS) in the *NBAS* gene (NM_015909.3). Parental studies confirmed that each parent carries one of these variants. Her mother carries a c.1549C > T(p.R517C) variant, which recently has been revised from VUS to likely pathogenic. Her father carries a novel c.4646T > C(p.L1549P) variant. Indeed, there are 109 supposedly disease-causing variants listed in the Human Gene Mutation Database for NBAS, and 78 of these are associated with hepatopathy. The c.1549C > T variant is cataloged in gnomADv2.1.1 database as a missense mutation with an allele frequency of 0.00001591, and no homozygotes have been reported. The c.4646T>6 is a novel variant that has never been reported in referencing the gnomADv2.1.1 and ClinVar databases. In assessing the effects of these genetic variations on protein function, the Protein Variation Effect Analyzer (PROVEAN) software revealed each parental variant to have a deleterious effect on the protein function. Based on a threshold of deleterious effect for score < −2.5, the PROVEAN scores were −5.743 for the p.R517C maternal variant and −5.369 for the p.L1549P paternal variant. The Polyphen-2 program v2.2.2r398 predicted the p.R517C variant as possibly damaging (score 0.890 with sensitivity 0.82 and specificity 0.94) and p.L1549P variant as probably damaging score 1.000 (with sensitivity 0.00; specificity 1.00). Taken together, the in silico analyses of the patient's allelic variants indicate a deleterious effect on NBAS protein function.

Subsequently, she was evaluated for other phenotypic abnormalities associated with NBAS deficiency. Indeed, she has the progeroid facial features noted in other patients with NBAS deficiency including beaked nose, thin lips, pointed chin, prominent eyes, and triangular faces (Figure 1B). Her skeletal survey showed hypoplasia of the 12th ribs (Figure 1C), but the long bones and cervical vertebrae were normal. Further immunologic work-up revealed several abnormalities in the natural killer (NK) cell population and humoral response. NK cell number was normal in the peripheral blood but NK cell cytotoxicity profile demonstrated essentially absent spontaneous NK cell cytotoxicity. Telomere length analysis of blood leukocytes revealed very low telomere length in CD57+NK cells of 4.2kb relative to a normal median telomere length of 8.6kb in her age group. Additionally, the humoral compartment had low IgA and IgG levels despite normal B cell numbers—including normal memory

pool and class-switch function. To assess the humoral response to vaccine challenge, Strep pneumoniae serotype IgG and tetanus anti-toxoid IgG titers were measured prior to immunization and at approximately 6 weeks afterward. The IgG titers appropriately increased after vaccination, but the titers were undetectable when rechecked approximately 31 months post-immunization (Figure 2A, B). Consequently, she receives 4g of subcutaneous immunoglobulin every 2 weeks for her humoral deficiency. Collectively, the phenotypic abnormalities in facial features, stature, skeletal anatomy, NK cell, and humoral immunity along with a history of recurrent PALF were all consistent with NMAD.

3 | DISCUSSION

The *NBAS* gene was initially identified through its co-amplification with the *MYCN* gene in neuroblastoma cell lines.[14] The function of NBAS is postulated to be involved in Golgi-to-ER transport as a subunit of the syntaxin-18 complex.[10] Additionally, NBAS is a component of an evolutionarily conserved nonsense-mediated mRNA decay pathway regulating the expression of genes involved in a variety of processes including cholesterol biosynthesis, bone development, cytokine signaling, and cellular stress.[15] The clinical manifestations of deleterious mutations in the *NBAS* gene were initially identified in the isolated Yakut population, which has a high prevalence of hereditary short stature syndrome, and this led to the characterization of the novel short stature with optic atrophy and Pelger-Huët anomaly (SOPH) syndrome.[13] Subsequently, a growing body of literature discovered *NBAS* mutations to be associated with the pathogenesis of multi-systemic diseases involving recurrent acute liver failure.[8,9,12,16-20] Mutations resulting in NBAS deficiency are implicated in the development of NMAD, but the mechanism is unknown.

Our patient demonstrated clinical features consistent with NBAS mutation described in the literature. She had short stature, progeroid facial features, and hypoplasia of the 12th ribs (skeletal dysplasia), which are all features noted in SOPH and NMAD.[12,13] However, the absence of ocular disease and recurrent acute liver failure suggests NMAD to be more likely. These morphologic abnormalities are indeed consistent with the role of NBAS regulating genes involved in bone growth and organogenesis. Furthermore, hematologic evaluation revealed Pelger-Huët anomaly on peripheral blood smear and several immunologic abnormalities. Segarra et al. in their case series reported two pediatric patients with NMAD—one having hypogammaglobulinemia, absent response to vaccinations, and reduced NK cell number while the other patient demonstrated only low NK cell count.[9] Consistent with these findings, immunodeficiencies were noted in our patient. Evaluation of NK cell function revealed essentially absent cytotoxicity responses. This may be due to the significantly decreased telomere length noted in our patient's NK cell population as shortened telomere length has been associated with immune cell dysfunction and senescence.[21] In the humoral compartment, low IgA and IgG levels requiring subcutaneous immunoglobulin every two weeks, and poor vaccination responses were noted. Interestingly, the most common immunologic abnormality reported for NMAD is hypogammaglobulinemia,[20] but the underlying mechanism by which NBAS deficiency affects the humoral immune compartment remains to be elucidated. Altogether, our patient encompassed both physical and immunologic features described in the growing literature for NMAD.

In contrast to iPALF, the induction of a catabolic state by fever is speculated to induce robust ER-stress and acute-phase responses resulting in metabolic decompensation and systemic inflammation in NMAD.[8] There are notable differences between the immune dysregulation noted in our patient relative to those with iPALF. In contrast, the dense CD8+ T-cell infiltration of the liver noted in iPALF,[4] native liver histology of our patient demonstrated no inflammatory infiltrate. Although not shown, our patient did not exhibit the decreased CD4:CD8 T-cell ratio, increased absolute CD8+ T-cell number, cytopenias, or elevations in serum soluble IL-2 receptor or ferritin to the magnitude noted in iPALF or HLH whereby the CD8+ T-cell compartment is activated in the context of NK cell dysfunction.[5,7,22] Taken together, these findings suggest that the immune dysfunction and pathogenesis of PALF in NMAD may be distinct from iPALF.

Conceivably, the immunodeficiencies observed in patients with NMAD may increase their susceptibility to microbial infections, and consequently, fevers that trigger recurrent episodes of liver failure. Indeed, the episodes of acute liver dysfunction in our patient were preceded by febrile viral illnesses not only highlighting the potential importance of anti-pyretics in the management of these patients but also demonstrating intolerance of global inflammatory stressors. As corticosteroids and immunomodulators have been shown to be

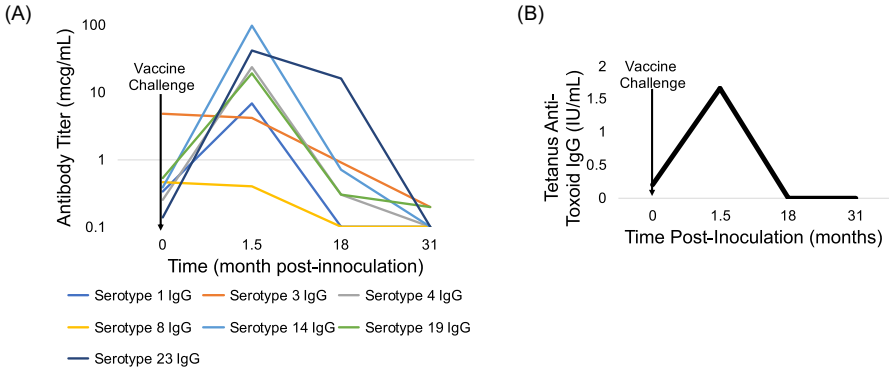

FIGURE 2 Impaired humoral response to vaccination in NBAS mutation-associated disease. (A) Pneumococcal and (B) tetanus anti-toxoid vaccine challenge induces IgG titers to various pneumococcal serotypes and tetanus anti-toxoid IgG, respectively, that subsequently wanes and becomes undetectable as early as 30 months post-inoculation

efficacious in iPALF, and anti-pyretics may not be enough control the thermal and cytokine stress on the liver, there may also be a role for immunosuppressive medications to dampen the systemic inflammation in NMAD. However in absence of lymphocytic infiltration noted in our patient, their efficacy is unclear. Future studies investigating the role of NBAS in immunity and NMAD response to immunosuppressive therapies are warranted.

In the absence of protein assays demonstrating impaired NBAS expression or function, the clinical observations noted above together with whole-exome sequencing and in silico analyses of her *NBAS* gene indicate that each variant inherited from her parents to be deleterious resulting in the phenotypic expression of NMAD. The p.R517C maternal variant is now classified as likely pathogenic, and accordingly, this variant is a rare allele with no known homozygotes and predicted to have a highly deleterious effect on protein function. Interestingly, the paternal p.L1549P is a novel variant that has never been reported but similarly predicted to be highly deleterious for NBAS function. This variant is likely pathogenic since it is absent in control populations, yields NMAD in trans with the likely pathogenic maternal variant, and is predicted to have deleterious effects on protein function based on in silico analyses. As neither parent have any signs or symptoms of NMAD, our patient's multi-systemic, phenotypic expression of NMAD appears to be autosomal recessive as previously published.[8]

Lastly, the treatment for pediatric acute liver failure in NMAD has centered on supportive measures despite the heterogeneity of disease. One case series reported 2 patients who died due to ALF, and though these patients did not have a confirmatory diagnosis at the time, both had younger siblings who presented with confirmed NMAD-associated ALF.[5] Another patient developed a hemorrhagic cerebral insult due to coagulopathy during an ALF episode.[9] Patients may have a less severe presentation when they are older with only mild liver abnormalities without synthetic dysfunction.[9] Our patient presented with recurrent ALF suspicious for a metabolic disorder. The decision was made to proceed with liver transplant without a confirmatory diagnosis given the cumulative morbidity of recurrent ALF and the absence of any contraindications to transplant.

Notably, NMAD-associated recurrent ALF was first described in 2015,[8] which was after our patient's liver transplant. Her recurrent episodes of acute liver failure resolved after transplant, and despite her underlying immune dysregulation, she continues to tolerate her allogeneic liver and remains healthy without additional episodes of acute liver failure even at 6 years post-transplant. Thus, allogeneic liver transplantation remains a feasible treatment option for recurrent acute liver failure in NMAD. Indeed, a recent case series by Chavany et al. have also described two patients who had resolution of recurrent PALF following liver transplantation.[23] However, given the phenotypic variability of NBAS deficiency, liver transplantation must be assessed on a case-by-case basis.

In summary, we report a novel likely pathogenic *NBAS* allelic variant, which together with a maternally inherited likely pathogenic variant, yielded clinical features consistent with NBAS deficiency and autosomal recessive NMAD in a pediatric patient. We also report the resolution of recurrent acute liver failure episodes after allogeneic liver transplantation, and she continues to be healthy even after 6 years of regular post-transplant follow-up. Thus, despite being a multi-systemic disease, patients with NBAS deficiency and associated acute liver failure should be assessed for transplant candidacy as it may not only prevent subsequent episodes of acute liver failure but may also be life-saving.

ETHICS STATEMENT

Written consent was obtained from the parents of the patient to utilize the case details and images for publication.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to disclose.

AUTHOR CONTRIBUTION

DG, DSR, RR, SJK, and JFM conceived the case report. DSR and RR helped recruit patient and draft article. DG gathered data. WJ analyzed genetic data and helped draft article. HBR provided histologic data and helped draft article. SC helped interpret immunologic data and revise article. DG, AS, and JPS drafted and revised the article.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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