



NBAS deficiency due to biallelic c.2809C > G variant presenting with recurrent acute liver failure with severe hyperammonemia, acquired microcephaly and progressive brain atrophy

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Abstract

Biallelic pathogenic variants in the neuroblastoma amplified sequence (*NBAS*) gene were firstly (2015) identified as a cause of fever-triggered recurrent acute liver failure (RALF). Since then, some patients with *NBAS* deficiency presenting with neurologic features, including a motor delay, intellectual disability, muscular hypotonia and a mild brain atrophy, have been reported. Here, we describe a case of pediatric patient diagnosed with *NBAS* deficiency due to a homozygous c.2809C > G, p.(Pro937Ala) variant presenting with RALF with severe hyperammonemia, acquired microcephaly and progressive brain atrophy. Not reported in the literature findings include severe hyperammonemia during ALF episode, and neurologic features in the form of acquired progressive microcephaly with brain atrophy. The latter raises the hypothesis about a primary neurologic phenotype in *NBAS* deficiency.

Keywords *NBAS* deficiency · Recurrent acute liver failure · Acquired microcephaly · Brain atrophy · Reye syndrome

Introduction

In 2015, biallelic pathogenic variants in the neuroblastoma amplified sequence (*NBAS*) gene were identified as a cause of fever-triggered recurrent acute liver failure (RALF) (Haack et al. 2015). Staufner et al. (2020) have recently reported results of an international, multicenter study involving 110 patients, including novel and previously published patients. This study had shed a new light on the pathomechanism and expression of *NBAS* deficiency. Not only liver but also other organs and systems, including the skeletal, immunological

and central nervous system, could be affected. Regarding neurologic features, a motor delay, intellectual disability, and muscular hypotonia were observed in some patients (Balasubramanian et al. 2017; Capo-Chichi et al. 2015; Haack et al. 2015; Li et al. 2017; Staufner et al. 2016, 2020; Suzuki et al. 2020). MRI of the brain was normal in the majority of patients while a mild brain atrophy in some of them was reported. Hepatic encephalopathy with hyperammonemia were also transiently observed in some patients secondarily during ALF. However, the natural history of *NBAS* deficiency, especially regarding the neurologic phenotype, is not known.

Here, we describe a case of a pediatric patient diagnosed with *NBAS* deficiency due to a homozygous c.2809C > G, p.(Pro937Ala) variant presenting with recurrent acute liver failure with severe hyperammonemia, acquired microcephaly and progressive brain atrophy.

Case report

The patient was the third child of nonconsanguineous Polish parents born at 39 weeks of gestation by a spontaneous delivery with a birth weight of 3,000 g and head

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circumference 33 cm (10–25 pc). At 2 months of age head circumference was 37 cm (10 pc). A psychomotor development was normal till 10 months of age. At this age, she underwent the respiratory tract infection with high fever. Recurrent vomiting and increasing apathy within 2 days after the onset of fever were observed and the child was admitted to hospital. At baseline, laboratory results revealed the presence of anemia (Hgb 6.2 g/dl), thrombocytopenia (PLT $60 \times 10^3/\mu\text{L}$), elevated serum transaminases (ALT 7725 IU/L, AST 3024 IU/L), hyperbilirubinemia (total serum bilirubin 1.8 mg/dl, direct serum bilirubin not tested), coagulopathy (INR 3.4) and hyperammonemia (serum ammonia 572 $\mu\text{mol/l}$). She was transferred to the pediatric intensive care unit because of hepatic encephalopathy and acute kidney injury.

The greatest degree of elevation of serum transaminases (ALT 7259 IU/L and AST 12,246 IU/L) was noted on the 2nd day of hospitalization. Severe coagulopathy (INR 9.0) and increasing parameters of cholestasis reaching up to total serum bilirubin 6.0 mg/dl with direct serum bilirubin 5.1 mg/dl were noted on the 3rd day of hospitalization. Serum ammonia concentrations were observed elevated

(range 572–662 $\mu\text{mol/L}$) during first six days of hospitalization (no ammonia scavengers were administered).

A fully recover of liver function was noted on the 20th day of hospitalization. Brain MR at that time revealed the presence of extensive symmetrical atrophic cortico-subcortical changes of both hemispheres of the brain (Fig. 1). The patient was discharged home on the 70th day of hospitalization because ALF was complicated by sepsis.

At the age of 3 years, the patient developed the 2nd episode of respiratory tract infection with fever. She was hospitalized within 6 days after the onset of fever due to apathy and weakness in our Institute; no antipyretics were administered ambulatory because of Reye syndrome suspicion. The patient's head circumference was 44,5 cm (below 3rd pc), height was 94,5 cm (25th pc) and body weight was 12,5 kg (10th pc). Neurological examination revealed the psychomotor retardation and muscle hypotonia. At baseline, laboratory results revealed the presence of elevated serum transaminases (AST 3300 IU/L, AST 1520 IU/L), cholestasis (total serum bilirubin 2.0 mg/dl and direct serum bilirubin 1.0 mg/dl), coagulopathy (INR 1.8). Normal serum ammonia concentration was noted. The patient received parenteral 10%

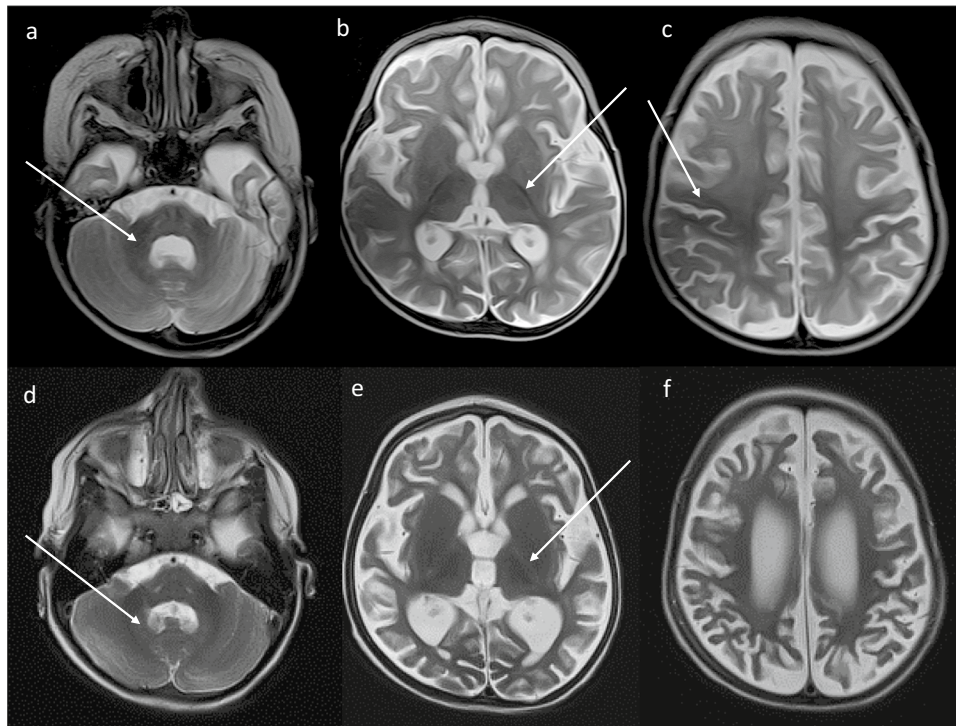


Fig. 1 Upper row – MR brain examination at the age of 11 months, axial T2-weighted images. Hypointensity of the pons and cerebellar peduncles (a), posterior limbs of internal capsules (b), corpus callosum (not shown), perirolandic cortex (c) are visible, indicated myelination. Diffuse hyperintensity of the cerebral white matter of both hemispheres is seen. Mild enlargement of the ventricular system, enlargement of Sylvian fissures, subarachnoid spaces along the con-

vexities and anterior interhemispheric falx are demonstrated. Bottom row – MR brain examination at the age of 3 years, axial T2-weighted images. Hyperintensive signal of hilum of dentate nuclei (d) and posterior limbs of internal capsules (e) suggested degeneration of myelin. Progression of the atrophy of the cerebral hemispheres with severe cortical and subcortical atrophy (e, f)

glucose infusion during all hospitalization. The follow-up brain MR examination showed progression of the atrophy of the cerebral hemispheres with severe cortical and subcortical atrophy (Fig. 1). A fully recover of liver function was noted on the 8th day of hospitalization.

All known causes of pediatric ALF, including inborn errors of metabolism, were ruled out. TruSightOne NGS panel containing 5000 genes (including 33 genes associated with acute liver failure development) was commenced. There have been found *NBAS* (RefSeq: NM_015909.3, NP_056993.2) c.2809C > G p.(Pro937Ala) variant, in a homozygous state. The variant was confirmed by Sanger sequencing to be inherited by biparental transmission.

During control visit in the Outpatient Clinic, at 4 years of age, she was able to sit independently, walk with help, speak simple words. Ophthalmologic examination revealed no abnormalities; visual evoked potentials test is planned. Normal serum concentration of immunoglobulins G, A, M was noted. Echocardiography revealed normal structure of the heart.

Discussion

In the study we reported an additional patient with fever-triggered recurrent ALF associated with *NBAS* deficiency. Not reported findings include severe hyperammonemia during ALF episode, and neurologic features in the form of acquired microcephaly and progressive brain atrophy.

Staufner et al. (2020) have recently published results of an international, multicenter study defining clinical subgroups and genotype–phenotype correlations in *NBAS*-associated disease across 110 patients. Three subgroups related to the affected region of the *NBAS* protein that differed significantly regarding main clinical features were explored, including Sec39 (predominant liver phenotype with recurrent acute liver failure), C-terminal (multisystemic phenotype with the presence of short stature, skeletal dysplasia, immunological abnormalities, Pelger-Huët anomaly and optic nerve atrophy), and β -propeller (combined phenotype with RALF and multisystemic phenotype). The c.2809C > G (p.Pro937Ala) variant identified in our patient, was located in the region coding for the Sec39 domain, thus *NBAS* deficiency should have a predominant liver phenotype. However, the presence of an acquired microcephaly and progressive brain atrophy questions this hypothesis.

What's more, there have been reported only 1 patient, found to be compound heterozygous for c.2809C > G, p.(Pro937Ala) and c.([5138 + 1_5139-1]_7116del), p.(?) but no abnormalities of the central nervous system were observed (Staufner et al. 2020).

Motor and cognitive development was normal in the most of reported patients with *NBAS* deficiency

(Balasubramanian et al. 2017; Capo-Chichi et al. 2015; Haack et al. 2015; Li et al. 2017; Staufner et al. 2016, 2020; Suzuki et al. 2020). Neurologic features, including a mild hyperammonemia, encephalopathy and mild MRI abnormalities (non-progressive brain atrophy with normal results of ¹H-MRS studies) observed in some reported patients could be explained as a sequelae of ALF, however a primary neurological phenotype cannot be ruled out (Balasubramanian et al. 2017; Capo-Chichi et al. 2015; Haack et al. 2015; Li et al. 2017; Staufner et al. 2016, 2020; Suzuki et al. 2020). The presence of an acquired and progressive microcephaly with brain atrophy in our patient raises the hypothesis about a primary neurologic phenotype in *NBAS* deficiency. On the other hand, brain atrophy could be secondarily to acute hepatic hyperammonemic encephalopathy (HE), however this phenomenon is reversible in the course of HE while the progression of brain MR suggests a primary central nervous system (CNS) involvement.

Liver involvement in *NBAS* deficiency is characterized by recurrent episodes of acute liver failure (liver crises) with normalization of liver function between crises Balasubramanian et al. 2017; Capo-Chichi et al. 2015; Haack et al. 2015; Li et al. 2017; Staufner et al. 2016, 2020; Suzuki et al. 2020). Based on our case report, we could speculate that the CNS involvement is independent of the liver dysfunction.

An early and consequent administration of antipyretics together with an anabolic energy management (high glucose and lipids) proved to be highly beneficial on liver function recovery but it seems to have no effect on the course of CNS involvement.

The long-term outcome in *NBAS* deficiency is unknown. Suzuki et al. have recently reported the oldest patient (34-year-old) showing a progressive course of disease (Suzuki et al. 2020). The patient presented with RALF until an early childhood, epilepsy diagnosed at 12 years of age, progressive intellectual disability and liver fibrosis with portal hypertension at 20 years of age.

Giving the similarities between the clinical presentation of *NBAS* deficiency and Reye syndrome (defined as an acute non-inflammatory encephalopathy with acute liver failure) we could speculate about the classification of *NBAS* deficiency as a Reye-like syndrome (Schrör 2007). It is obvious that a primarily genetic background as the cause of Reye syndrome, was not identified or even considered in the 1960s and 1970s when the majority of cases were reported (Schrör 2007). Nowadays, such a genetic background is an explanation for recurrent Reye-like symptoms triggered by infections/fever and should be considered. Thus, every patient presenting with Reye-like symptoms should undergo molecular analysis, especially including *NBAS* gene.

Author contribution The specific contributions made by each author: a) Conception and design of study – PL, ATS, b) Acquisition of data – PL, MG, c) Analysis and/or interpretation of data – PL, MG, DPA, EJ, AB, IJ, PS, DR, ATS. d) Drafting the manuscript – PL. e) Revising the manuscript critically for important intellectual content – MG, DPA, IJ, PS, ATS. f) Approval of the version of the manuscript to be published – PL, MG, DPA, EJ, AB, IJ, PS, DR, ATS.

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Data availability All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval Ethical approval was obtained from the Children's Memorial Health Institute Bioethical Committee, Warsaw, Poland.

Conflicts of interest All authors declare no conflict of interest.

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