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Case Report

Infantile Gaucher Disease Due to a Novel Variant in the *PSAP* Gene

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Abstract Prosaposin deficiency is a rapidly progressive fatal neurovisceral lysosomal storage disorder (LSD) caused by pathogenic variation in the *PSAP* gene. The phenotype overlaps with LSDs and the short lifespan of patients has led to misdiagnosis of these complex and rare diseases. A 2-month-old girl presented with encephalopathy, resistant tonic-clonic seizures, giant hepatosplenomegaly, hypotonia, and delay in head control with lack of sucking reflex. Due to persistent respiratory distress and resistant seizures, the child succumbed in the fourth month of her life. Although clinical findings suggest Gaucher disease, the diagnosis was rejected because of normal β-glucosidase activity. Whole exome sequencing identified a previously unidentified homozygous, frameshift, clearly pathogenic variant of p.Arg186Profs*9 (c.551dupG) in the *PSAP* gene. This frameshift variation has been classified as "likely pathogenic," according to the ACMG Guidelines. As a result of homozygous variation in *PSAP* gene our case was accepted as combined prosaposin deficiency with early infantile onset and severe neurological involvement. Detected frameshift variation that leading protein length changes has not been previously reported.

Key words *Encephalopathy; Hepatosplenomegaly; Hypotonia; Infant; Seizures*

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Introduction

Prosaposin (pSap) deficiency is a rapidly progressive fatal neurovisceral lysosomal storage disorder caused by mutations in the *PSAP* gene.[1] It is characterised by the absence of pSap and pSap proteolytic processing products. These polypeptide products, called saposins (Saps, sphingolipidhydrolase activating proteins), are activators of a number of lysosomal sphingolipid hydrolases. In the absence of Saps, sphingolipid substrates remain intact. Substrates accumulating in visceral cells lead to swelling of lysosomes. It results in organ failure similar to classical lipid storage disorders.[2]

Inherited deficiency of the major Saps proteins Sap A, Sap B or Sap C causes sphingolipidoses, which are noted

as late-onset Krabbe disease, metachromatic leukodystrophy (MLD), and Gaucher disease (GD), respectively. A mutation in the Sap D domain of another pSap causes Farber's disease.[3]

Our patient is an ultra rare case in the literature with a homozygous variation in the *PSAP* gene that causes combined saposin deficiency. The detected variation has not been previously reported. Our patient provides new information concerning of combinated saposin deficiency. With our case, we wanted to emphasize the importance of genetic diagnosis in rare diseases.

Case

A 2-month-old girl, the fourth child of consanguineous parents, presented with encephalopathy, resistant tonic-clonic seizures, giant hepatosplenomegaly, hypotonia, and failure to thrive (delay in head control with lack of sucking reflex). The child was born with normal delivery and the birth weight was 3 kg. At birth, the baby presented with respiratory distress. In the first month, tonic-clonic seizures, abdominal distension, hepatosplenomegaly, hypotonia in all extremities and deep tendon reflexes were evident. Response to antiepileptic drug was poor and the patient continued to be in encephalopathic condition. Ventilator support was given to the child due to recurrent respiratory distress. Brain magnetic resonance imaging showed signal changes in hypointense myelin foci with corticomedullary enlargement in the hyperintense demyelinating area of the white matter on both sides suggesting MLD. Biochemically, the child had leukopenia, anaemia, thrombocytopenia, and abnormal liver transaminases. Acid sphingomyelinase and β-glucosidase activity were normal, plasma chitothriosidase level was elevated, and galactosylceramidase activity was low. Gaucher cells were not found in the bone marrow biopsy and smear. Liver biopsy was consistent with lysosomal storage disease (LSD) (Figure 1). Due to persistent respiratory distress and resistant seizures, the child succumbed in the fourth month of her life. Although clinical findings suggest Gaucher disease, the diagnosis was dismissed due to normal β-glucosidase activity and absence of Gaucher cells in the bone marrow. In whole-exome sequencing, a previously unidentified homozygous, clearly pathogenic p.Arg186Profs*9 (c.551dupG) variant was identified in the *PSAP* gene (Figure 2). This variation has been classified as "likely pathogenic" according to the ACMG.[4] As a result of homozygous frameshift variation in the *PSAP* gene in genetic examination, our case was accepted as combined pSap deficiency with early infantile onset and severe neurological involvement. Written consent was obtained from the patient's parents for publication.

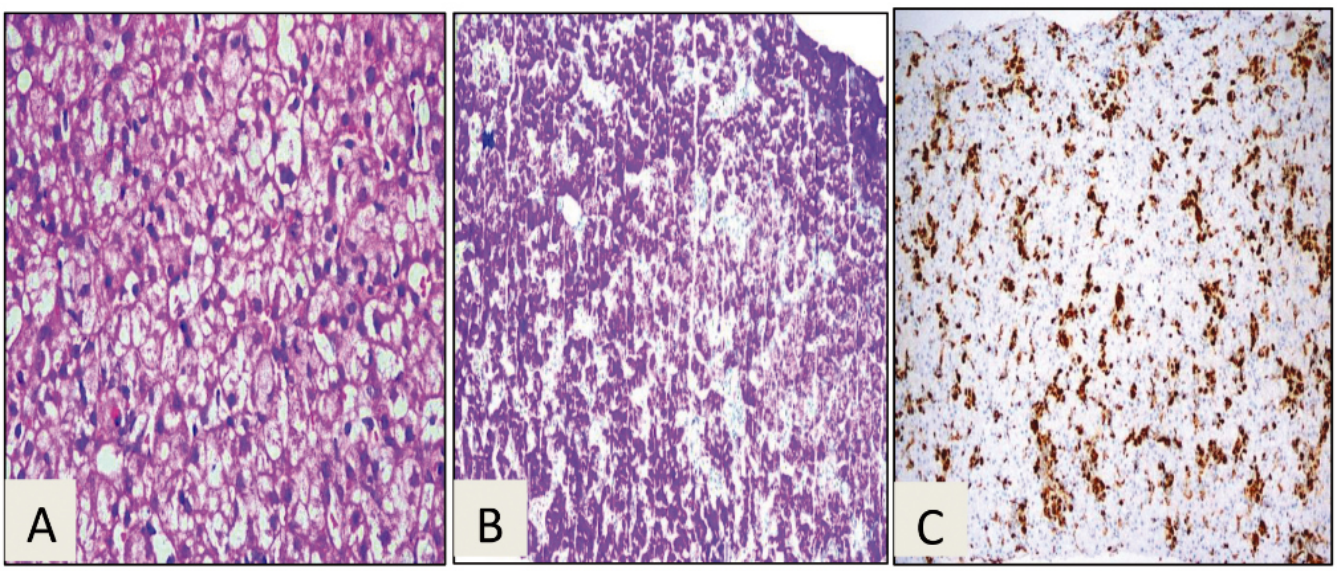

Figure 1 Liver biopsy. A. Swelling and vacuolar-foamy appearance in hepatocytes (H&E 400x), B. No staining with histochemical PAS-Ab (PAS-Ab 100x), C. Staining in foamy histiocytes with CD68 (CD68, DAB 100x).

Discussion

LSDs are congenital metabolic diseases characterised by excessive accumulation of substrates in cells of various organs due to defective functioning of lysosomes. They cause dysfunction in the organs where they accumulate and as a result, morbidity and mortality.[5] GD is one of the most common lysosomal storage diseases. GD type 2 (also called acute neuronopathic GD) has an estimated incidence of 1 in 150,000.[6]

The phenotypic overlap with LSDs and the short life span of patients has led to misdiagnosis of this complex and rare disease. The initial clinical of our patient suggested GD. It included dismyelination of cerebral white matter with a very rapid neurological deterioration that resulted in death at four months. This diagnosis was abandoned because the glucocerebrosidase enzyme was normal in our patient and Gaucher cells were not observed in the bone marrow. Krabbe disease was also considered in the diagnosis due to the low level of galactoseramidase enzyme, but it was excluded because the clinical findings were not compatible. In order to find out the final diagnosis, whole exome sequencing was performed. A homozygous variation in the *PSAP* gene, p.Arg186Profs*9 (c.551dupG) was discovered. Apart from genetic examination, a specific and rapid method is needed for rapid diagnosis. Molecular analysis and plasma lysoSL profiling resulting in increased amounts of LysoGb3 and GlSph can be performed for early diagnosis of pSap deficiency.[7] Motta et al[8] screened plasma lysoSLs and the diagnosis of pSap deficiency was confirmed by molecular analysis. They showed that the quantitative analysis of plasma lysoSLs is a very informative tool in the early diagnosis of pSap deficiency and can be used to screen for different sphingolipids such as GD, Fabry disease, Niemann-Pick type A/B and type.[8] Because the clinical course of our patient was rapidly progressive and resulted in death in the early period, these examinations could not be performed.

In summary, plasma lysoSL profiling can be used as a rapid and informative pre-test that can be used to guide diagnostic genetic analysis in metabolic disorders with complex phenotypes lacking pathognomonic features. We also wanted to draw attention to the necessity of genetic examination to clarify the diagnosis of pSap deficiency in infants with early-onset severe neurological involvement, hepatosplenomegaly, and failure to thrive.

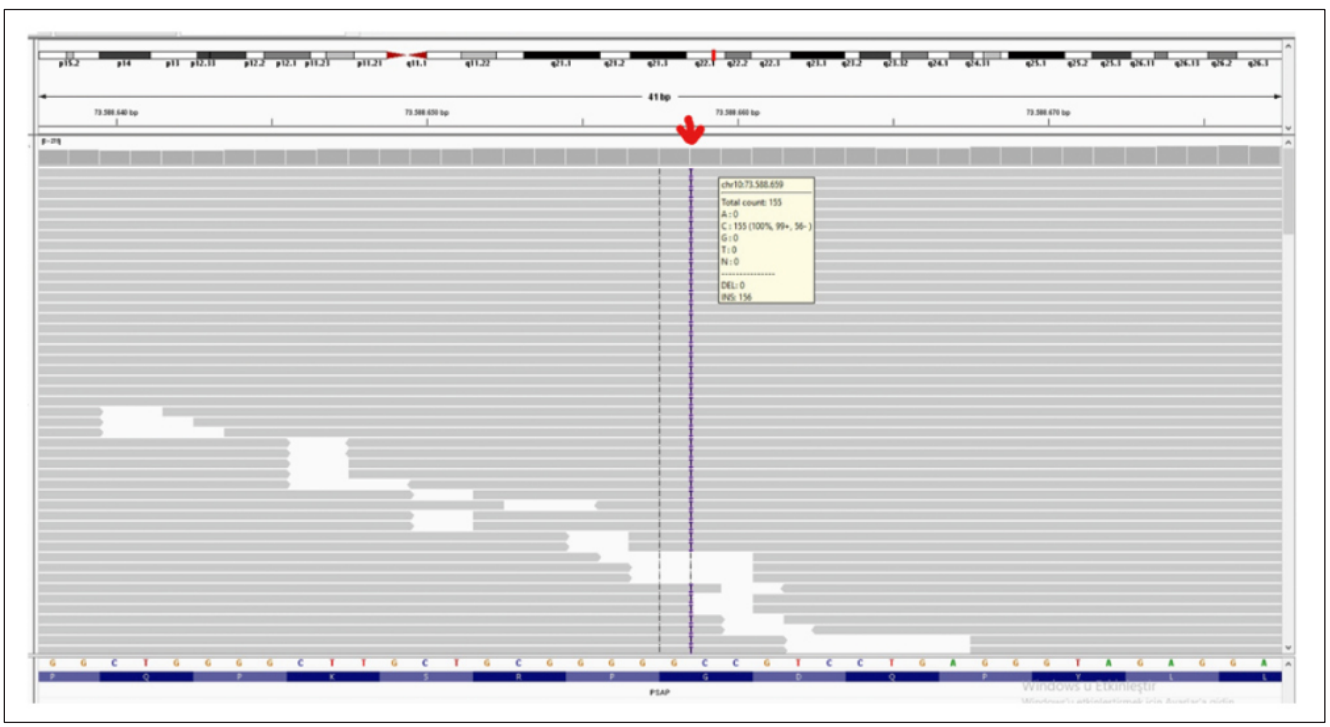

Figure 2 The homozygous p.Arg186Profs*9 (c.551dupG) variation discovered in the patient.

Declaration of Interest

The author(s) indicated no potential conflicts of interest. No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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