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Case Report

Combined saposin deficiency: A rare occurrence

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ABSTRACT

Combined saposin deficiency (OMIM #611721), an exceedingly rare lysosomal storage disorder, is caused by a mutation in the gene *PSAP*. This gene encodes a protein, prosaposin, that cleaves into four constituent proteins, each of which has a role as a cofactor for the enzymes whose deficiency results in Krabbe disease, metachromatic leukodystrophy, Gaucher disease, and Farber disease, respectively. Intact prosaposin itself is essential for neuronal survival. The typical manifestation of combined saposin deficiency is of severe neurological features in the neonatal period, hepatosplenomegaly, thrombocytopenia, and early death. We report, to the best of our knowledge, the first Indian case with these clinical manifestations and confirmation by genetic and enzymatic testing.

Introduction

Combined saposin (Sap) deficiency (OMIM #611721) is an extremely rare lysosomal storage disorder[1] with less than 10 cases reported in worldwide literature till date.[2] The disease is caused by a mutation in *PSAP*, a gene located on chromosome 10q22.1, that encodes for a protein called prosaposin. The clinical features include early onset with severe neurological manifestations, hepatosplenomegaly, and early death.[1] We report a case of Sap probably the first, from India.

Case report

A 29-year-old primigravida delivered a male infant weighing 2620 g at term gestation by elective lower segment caesarean section indicated due to breech presentation. The infant was a product of non-consanguineous marriage. The infant did not require resuscitation. However, he was shifted to the neonatal intensive care unit (NICU) due to shallow respiratory efforts, poor sucking, and dysmorphic features in the form of microstomia, microtia, overlapping middle and ring fingers bilaterally, and moderate ectropion. A thin collodion membrane covering the entire skin, especially the torso, with fissuring in flexural areas of the groin was noted. Shedding of this membrane revealed generalized ichthyosis all over the body. Poor state-to-state variability (STSV) was noted on neurological examination at the NICU. Investigations including complete hemogram, liver, renal, and thyroid function tests, and serial bedside blood sugar estimations were within normal limits.

Minimal continuous positive airway pressure support was provided for 24 h. Emollients prescribed in consultation with a

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dermatologist resulted in significant improvement of ichthyosis. The poor STSV persisted for about four days and then resolved spontaneously. Magnetic resonance imaging (MRI) brain performed on day 25 of life was normal. Orogastric feeds combined with non-nutritive sucking using a pacifier were initiated on day 1. Gag reflex on day 3 of life was noted to be present but weak. A decision was made to attempt minimal oral feeds as feasible, if tolerated. The infant, however, developed microaspirations on day 12 of life, probably due to the persistence of poor suck-swallow-breathe coordination. This necessitated the institution of oxygen therapy through heated humidified high-flow nasal cannula for 24 h. Reports of tandem mass spectrometry and urine gas chromatography/mass spectrometry sent in view of poor STSV were normal. The karyotype was also normal (46, XY). The infant was discharged on day 31 of life while still on feeds by an orogastric tube. Transition to oral feeds could not be achieved due to persistent bulbar weakness and poor suck-swallow-breathe coordination. The STSV had improved with the infant spending most time in Brazelton state 3 reaching a maximum of state 6 very occasionally. Axial and appendicular tone were normal at this time.

The infant continued to be on follow-up at the high-risk clinic. Over the next eight weeks, he developed generalized axial and appendicular hypotonia, microcephaly, and massive hepatosplenomegaly. Deep tendon reflexes were not elicitable. Ichthyosis had completely regressed by this time.

The infant was readmitted at three months of age with history of fever, breathing difficulty, and loose stools for the previous three days. At admission, the infant had features of septic shock and respiratory failure which were corrected by fluid resuscitation, non-invasive ventilation, and broad-spectrum antibiotics. During this admission, lasting 38 days, the infant developed refractory seizures requiring administration of phenytoin, levetiracetam, and valproate. Fundus examination of the infant, performed by an ophthalmologist, was essentially normal. MRI brain planned at this point could not be carried out in view of clinical instability. Cranial sonography revealed severe cerebral atrophy. Electrocardiography and echocardiography were normal. The infant had progressive respiratory failure requiring non-invasive followed by invasive mechanical ventilation. At about 20 days of admission, the infant had developed thrombocytopenia (platelet count 75,000-95,000/cu mm) without clinical manifestations and not requiring platelet transfusion. The infant eventually succumbed to the illness in the fifth month of life due to sepsis with multiorgan dysfunction and progressive respiratory failure.

In view of high index of suspicion of genetic nature of the disease, clinical exome sequencing had been ordered during the second month of life, results of which were received a few days before demise of the infant. A homozygous pathogenic variation in *PSAP* gene at exon 12 (c.1419_1422 del CTTC, p. Phe474fster3) and another homozygous variation of unknown significance at exon 10 (c.1076A>C, p. Glu359Ala) of the same gene were reported. Both variations were confirmed by Sanger sequencing of the infant and both parents. Enzyme testing in skin fibroblasts reported low enzyme activity for β-glucosidase (28 nmol/h/mg; normal 120–510 nmol/h/mg) and β-galactocerebrosidase (1.8 nmol/h/mg, normal 8.4–40 nmol/17 h/mg). This confirmed the diagnosis of combined Sap deficiency. Genetic counseling of the family was performed to guide decision-making for future pregnancies.

The parents consented for reporting of the case but requested that the infant not be photographed or subjected to any tissue biopsy (other than skin biopsy) while alive and nor was permission for an autopsy granted.

Discussion

The first case of combined Sap deficiency was reported by Harzer et al[3] in 1989. After the condition was recognized, nine cases have been reported in medical literature.[2] Clinical features reported in this condition include neonatal apnea, insufficient sucking and swallowing, multifocal clonic seizures, hypotonia, arthrogryposis, microcephaly, and extrapyramidal findings. Neonatal onset of disease, hepatosplenomegaly, and death due to respiratory failure are consistent features.[2–5] Nearly all of these features were present in our patient. Systemic findings other than hepatosplenomegaly reported anecdotally include mitral insufficiency and abnormalities on electrocardiography.[2,6] These were absent in our patient, but he had a collodion membrane at birth. Collodion formation is not reported in combined Sap deficiency but may be a presenting feature of type 2 Gaucher disease,[7] which may be a part of spectrum of saponin C deficiency.[8]

Findings on neuroimaging include gray matter heterotopias, abnormal gyration, periventricular and subcortical white matter lesions, and cortical atrophy.[4–6] We were not able to perform MRI brain at a time when abnormal findings were expected. However, the findings of microcephaly and cortical atrophy on neurosonography were in keeping with previous description.

The gene *PSAP* encodes prosaposin, a 65–70 kDA glycoprotein with 524 amino acids. Prosaposin is cleaved into four Saps: A, B, C, and D. Each Sap is a small non-enzymatic glycoprotein that acts as an indispensable cofactor for the enzymatic degradation of a particular sphingolipid. Specifically, Sap A, B, C, and D are cofactors for the enzymes whose deficiency results in Krabbe disease, metachromic leukodystrophy, Gaucher disease, and Farber disease, respectively.[8] The loss of function of any cofactor of a Sap due to pathogenic variation in *PSAP* results in clinical features of the disease caused by deficiency of the specific enzyme for which the Sap is a cofactor. Table 1 summarizes the role of various Saps. In addition, intact prosaposin has a neuroprotective role related to neuron survival that is independent of lysosomal function.[9] Therefore, a homozygous truncating mutation in PSAP resulting in two null alleles can cause clinical features of all four lysosomal storage disorders mentioned earlier and in addition cause cerebral atrophy due to loss of this neuroprotective function.

Pathologically, complete Sap deficiency is characterized by storage of glycosphingolipids in the non-neuronal tissues and

Table 1 – Role of saposins (Saps).

Sap	Prosaposin amino acids	Cofactor for	Deficiency results in
A	195–273	Galactocerebrosidase	Krabbe disease
B	60–142	Arylsulfatase A Alpha galactosidase	Metachromic leukodystrophy
C	311–390	Beta glusosidase Galactosylceramidase	Gaucher disease
D	405–486	Acid ceramidase	Farber disease (mouse model only)

References: (8,11)

loss of neurons in the central as well as peripheral nervous system without glycosphingolipid accumulation, probably due to neuronal survival crisis.[10] Assays for sphingomyelin, sulfatide, globoside, and GM2 ganglioside in biopsy samples of extrarenal tissues,[5] urinary sphingolipid analysis by tandem mass spectrometry,[6] and quantification of plasma lysosphingolipids by liquid chromatography mass spectrometry[2] have been reported but are not universally available.

There is good genotype-phenotype correlation with pathogenic variations reported in *PSAP* so far. Variations in *PSAP* resulting in two null alleles have been reported in association with combined Sap deficiency. Compound heterozygous variations that result in a single null allele and a second allele causing deficiency of a specific Sap (A, B, or C) have also been reported. In such a situation, the patient's phenotype is dictated by the second allele.[8] In our patient, the homozygous pathogenic variation, that is, c.1419_1422 del CTTC, p. Phe474fster3 is a null allele. This variation in the homozygous state alone explains the phenotype. The role of the additional homozygous variation, that is, c.1076A>C, p. Glu359Ala, in causation of the disease in this infant is unclear.

Disclosure of competing interest

The authors have none to declare.

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