Neonatal multiple sulfatase deficiency with a novel mutation and review of the literature

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Multiple sulfatase deficiency is a rare autosomal recessive disorder in which affected individuals present a complex phenotype due to the impaired activity of all sulfatases. There are different types of multiple sulfatase deficiency; among them, the neonatal form is the most severe, with a broad range of mucopolysaccharidosis-like symptoms and death within the first year of life. The disorder is caused by homozygous or compound heterozygous mutations in the sulfatase-modifying factor-1 (SUMF1) gene. In this article, we describe a non-ichthyotic neonatal multiple sulfatase deficiency patient with a novel mutation in the SUMF1 gene. The missense mutation c.777C>G, for which the patient was homozygous, had been caused by a p.N259K amino acid substitution. We evaluated the patient using clinical findings, neuroimaging studies and molecular analysis via the literature; we also wanted to note the difficulties in the diagnosis of this rare disease.

Key words: lysosomal storage disease, multiple sulfatase deficiency, ichthyosis, neonatal

Multiple sulfatase deficiency (MSD, OMIM #272200) is a very rare autosomal recessive inherited disorder characterized by the accumulation of sulfated lipids and acid mucopolysaccharides. Its estimated prevalence is <1:1 million births[1]. Sulfatases are rendered catalytically active through post-translation modification of a highly conserved cysteine to formyglycine within their active catalytic site. In MSD, all sulfatases are inactive due to a defect in the post-translational activation that impairs activities of sulfatases. The enzymatic defect in MSD affects the whole family of sulfatase enzymes; thus, the disorder combines the features of metachromatic leukodystrophy, X-linked ichthyosis and various mucopolysaccharidoses. Affected individuals show neurologic deterioration, mental retardation, skeletal anomalies, organomegaly and ichthyosis.

Multiple sulfatase deficiency can be classified into three clinical phenotypes according to the time of onset of the disease: neonatal, late-infantile and juvenile types[2]. Neonatal MSD is the most severe form, with a broad range of mucopolysaccharidosis-like symptoms and death within the first year of life[3,4]. Late-infantile MSD (0 to 2 years), which includes the majority of cases, resembles late-infantile metachromatic leukodystrophy, with progressive loss of mental and motor skills and skeletal changes. Rare cases of juvenile-onset MSD (2 to 4 years) have been reported, with onset of symptoms in late childhood and a slower progression[5].

Multiple sulfatase deficiency is caused by homozygous or compound heterozygous mutation in the sulfatase-modifying factor-1 gene (*SUMF1*) on chromosome 3p26, which encodes the formylglycine-generating enzyme[6]. Here, we present a non-ichthyotic MSD patient with a novel mutation in the *SUMF1* gene.

Case Report

A female infant was born at 36 weeks of gestation as the second child of a first-degree cousin marriage. Fetal ultrasound in the third trimester of gestation revealed congenital ascites and oligohydramnios. Amniocenthesis showed a normal female karyotype 46,XX. The baby was delivered by caesarean section. The Apgar score was 5 at the 1st minute and 8 at the 5th minute. Her parents and an older sister were healthy. Her cousin was being followed up with a diagnosis of Tay-Sachs disease.

On physical examination, birth length was 46 cm (25th-50th percentile), birth weight was 2650 g (50th percentile) and head circumference was 33 cm (50-75th percentile). Muscular hypotonia, a coarse face, thick eyebrows, long eyelashes, a depressed nasal bridge and broad nasal tip, hypertelorism, low-set ears, gingival hypertrophy, pectus carinatus, a short neck, abdominal distention, hepatosplenomegaly, generalized tonic-clonic convulsions and limitation of joint mobility were the positive findings on her first examination. Facial dysmorphism at 8 month of age is shown in Fig. 1.

A skeletal survey done in the second day of life showed an ovoid spine, beaked vertebrae and scoliosis (Fig. 2). The long bones and the pelvis appeared normal. Abdominal ultrasonography showed hepatosplenomegaly and ascites. Renal ultrasonography showed bilateral grade 2 echogenicity and three areas of 4-5 mm hyperechoic appearance (nephrocalcinosis). Ophthalmologic examination showed cloudy corneas. The brainstem auditory evoked response demonstrated sensorineural hearing loss. Patent ductus arteriosus and muscular ventricular septal defects were noted on echocardiography. The electroencephalogram showed multifocal epileptiform abnormalities. Cranial magnetic resonance imaging detected bilateral frontotemporal subarachnoidal dilatation, corpus callosum hypoplasia and delayed myelination, and J-shaped sella turcica (Fig. 3). Newborn metabolic screening, including tandem mass spectrometry, showed no abnormalities.

The blood smear showed leukocyte granulation abnormalities. The urine tests for mucopolysaccharides detected elevated glucosaminoglycans (3.37 mg/dl, normal range: 0-3 mg/dl). The patient's leukocyte enzyme activities are presented in Table I.

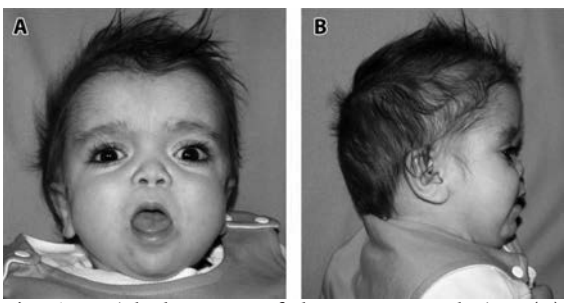

Fig. 1. Facial phenotype of the case. Frontal view (A) and lateral view (B) of the patient at 8 months of age, showing coarse facies, thick eyebrows, long eyelashes, depressed nasal bridge, broad nasal tip, hypertelorism, low-set ears, and short neck.

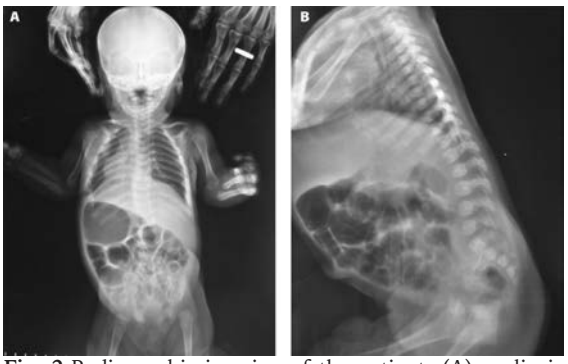

Fig. 2. Radiographic imaging of the patient: (A) scoliosis on anteroposterior vertebrae radiography and (B) ovoid spine and beaked vertebrae on lateral vertebrae radiography.

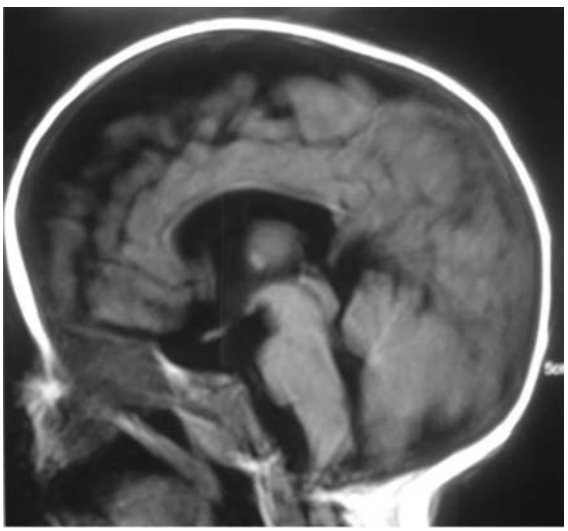

Fig. 3. Bilateral frontotemporal subarachnoidal dilatation, corpus callosum hypoplasia and delayed myelination, and J-shaped sella turcica seen on cranial magnetic resonance imaging of brain.

Table I. Leukocyte enzyme activities of the patient

Leukocyte enzyme	Patient	Control values
Arylsulfatase B	0 nmol/h/mg protein	Control (mean±SD): 209.9±96 nmol/h/mg protein
Alpha-N-acetyl-glucosamine-6-sulfatase	0.25 nmol/24h/mg protein	Control 1: 9.06 nmol/24h/mg protein Control 2: 13.87 nmol/24h/mg protein
Iduronate-2-sulfatase	0.35 nmol/24h/mg protein	Control 1: 25.5 nmol/24h/mg protein Control 2: 53.7 nmol/24h/mg protein

At the 6-month follow-up, her psychomotor development and growth were delayed. Her length and weight were below the 3rd percentile, while her head circumference was in the 50th percentile. The width of the fontanel was abnormal, and the patient suffered from convulsions. A cranial ultrasound detected hydrocephaly (ventriculocephalic index 45%), and lateral and third ventricle dilatation.

She was admitted several times to our hospital because of pneumonia and convulsions. At 20 months of age, her psychomotor development was mildly retarded, especially in the areas of speech and gross motor skills. On her last admission, she presented with pneumonia and died due to sepsis and heart failure.

Mutation analysis was carried out by PCR amplification and direct sequencing of the genomic DNA isolated from the peripheral blood of the patient and 50 control individuals (100 alleles) using a kit (QIAGEN, www.qiagen.com), to exclude the presence of sequence polymorphisms. Oligonucleotides spanning intron/exon junctions to amplify all the *SUMF1* exons were used. In the cDNA reference sequence for *SUMF1* (GenBank: AY323910), the nucleotide numbering uses the A of the ATG translation initiation start site as nucleotide +1. We found that the patient was homozygous for the novel missense mutation c.777C>G,

Table II. Clinical findings and mutations detected in unrelated patients with the neonatal form of multiple sulfatase deficiency

	Vamos[15], 1981	Burch[18], 1986	Busche[12], 2009	Schotawa[6], 2011	Our patient
Prenatal findings	Placental insufficiency	n.d.	Fetal ascites/ mild hydrops	n.d.	Congenital ascites and oligohydramnios
Age at onset	Neonatal	Neonatal	Neonatal	Neonatal	Neonatal
Birth length <10. centile	+	+	+	n.d.	+
Birth weight <10. centile	+	+	+	n.d.	
Normal head circumference	+	+	-	n.d.	+
Facial dysmorphic features	+	+	+	+	+
Corneal clouding	+	+	-	+	+
Ichthyosis	+	n.d.	+	+	-
Hepatomegaly	+	+	+	+	+
Nephrocalcinosis	-	-	-	-	+
Skeletal changes	+	+	+	n.d.	+
Limited joint mobility	+	n.d.	+	n.d.	+
Hydrocephalus	+	+	+	+	+
Muscular hypotonia	+	+	+	n.d.	+
Death	n.d.	3.5 months	3 months	n.d.	20 months
Mutations in SUMF1	unknown	661 delG 2nd mutation unknown	unknown	c.979C>T p.R327X	c.777C>G p.N259K

causing a p.N259K amino acid substitution.

Discussion

Lysosomal storage disorders (LSD) are a group of more than 45 genetic diseases, with MSD being a subgroup thereof. Both the clinical and biochemical findings of MSD are variable. The lack of sulfatase activities in MSD patients leads to the accumulation of sulfated lipids and mucopolysaccharides, resulting in a clinical phenotype that combines the features of at least six diseases due to individual sulfatase deficiencies: metachromatic leukodystrophy (MLD), X-linked ichthyosis and mucopolysacccharidoses type II, IIIA, IIID, IVA and VI. Coarse facial features, sparse hair, edema (including hidrops), macrocephaly, deafness, cloudy cornea, gibbus, hepatosplenomegaly, seizures and cardiomyopathy are some of the clinical features of MSD[7]. Ichthyosis is a common feature. It can be seen in all types of MSD, but is most often seen in the neonatal and severe late-infantile types. It is undoubtedly caused by steroid sulfatase (arylsulfatase C) deficiency, as an isolated deficiency of this enzyme is responsible for X-linked ichthyosis[8]. In MSD, scaly skin may be milder than in X-linked ichthyosis. This could be a consequence of variation in the residual activity of steroid sulfatase for metabolizing cholesterol sulfate in the skin. In addition, environmental factors such as warm weather and humidity can reduce the cutaneous symptoms in X-linked ichthyosis[9]. Our patient showed the majority of the features of neonatal-onset MSD, but did not have ichthyotic skin lesions. In the literature, all MSD patients diagnosed in the neonatal period have ichthyosis. In our patient, lack of ichthyosis may be due to a level of steroid sulfatase activity in the skin that is high enough to prevent the skin manifestations.

Nephrolithiasis is a very rare condition associated with some inborn metabolic diseases, such as cystinuria, adenine phosphoribosyl-transferase deficiency, and xanthine deficiency, or inborn errors of metabolism leading to renal tubular acidosis (glycogen storage disease type I, tyrosinaemia type I, hereditary fructose intolerance, Wilson disease, respiratory chain disorders, etc.)[10]. In our patient, nephrolithiasis was confirmed by repeated ultrasonographies. To our knowledge, there are no other reports in the literature that describe nephrocalcinosis in patients affected by lysosomal storage diseases.

Diagnosis of this disorder is often difficult due to clinical variety, phenotypic overlap and the fact that more than one enzyme analysis is required[11,12]. Multiple sulfatase deficiency can be diagnosed by detecting the relevant sulfatides and mucopolysaccharides in the urine, and reduced sulfatase enzyme levels in the leukocyte and fibroblast assays[13]. Our patient displayed coarse facial features, a depressed nasal bridge, gingival hypertrophy, a short neck, hepatosplenomegaly, and limitation of the joints on her physical examination in the second day of life, which led us to the suspicion of LSD, and more specifically a type of mucopolysaccharidosis. The presence of cloudy cornea, along with the radiological findings, the electroencephalography and cranial MRI abnormalities, and the results of the urine screening tests for mucopolysaccharidosis confirmed the diagnosis. Definitive diagnosis was made by measurement of leukocyte enzyme activities for mucopolysaccharidosis and molecular analysis in the related gene. In the Turkish population, the first MSD cases to be described were reported by Yiş et al.[14]; these were two members of the same family, with a homozygous novel missense mutation. In the first index case (a 4-year-old girl), the rate of neurological impairment, degree of spasticity, frequency of seizures and amount of ichthyosis became relevant after two years of age. The second case (a 18-month-old girl) had less ichthyosis, hypertrichosis and spasticity, with no seizures. Vamos et al.[15] were the first to report early-onset MSD, in the case of a newborn male with clinical and radiological evidence of multiple bone deformities. The clinical findings and mutations detected in the cases of several unrelated patients with the neonatal form of MSD that appear in the literature are presented in Table II.

Multiple sulfatase deficiency occurs due to mutations in the *SUMF1* gene. The molecular defect is in a co- or post-translational mechanism that is common to all sulfatases and is required for their catalytic activity. *SUMF1* encodes the formylglycine-generating enzyme (FGE) that carries out a unique post-translational modification of cysteine residue to 2-amino-3-oxopropanoic acid in the active site of the sulfatases. Impaired FGE function

leads to reduced sulfatase activities[16]. The human *SUMF1* gene has nine exons, spans 105 kb and maps to chromosome 3p26[17]. We detected a novel homozygous missense mutation, c.777C>G, which caused a p.N259K amino acid substitution in our patient. The parents were heterozygous for this mutation. When a subsequent pregnancy occurred, the family was given a prenatal molecular genetic diagnosis.

In conclusion, a few cases with MSD have been reported in the literature. Our case is particularly interesting because of its presentation with all the typical features of neonatal MSD except icthyosis. When a mucopolysaccharidosis-like appearance and early neurological deterioration are detected in a newborn or infant, MSD should be considered in the differential diagnosis. Also, in order to not miss a possible diagnosis of MSD, analysis of at least two sulfatases is necessary. Early diagnosis will allow for more effective treatment, and, in the case of future pregnancies, genetic counseling and prenatal diagnosis.

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