

# A Case of Type I Sialidosis With Osteonecrosis Revealing a New Mutation in *NEU1*

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## Abstract

Sialidosis is a rare lysosomal storage disease. The 2 forms described are as follows: the early-onset form, or type II, presents with dysostosis multiplex, while the late-onset form, or type I, does not involve bone in the literature. We report the case of a 42-year-old woman with type I sialidosis who presents with osteonecrosis of both humeral and femoral heads. Molecular study reveals a never listed mutation of *NEU1* in exon 5, p.Gly273Asp (c.818G>A), and a second known missense mutation.

## Keywords

sialidosis, bone involvement, *NEU1*

## Introduction

Sialidosis (Online Mendelian Inheritance in Man [OMIM] 256550) is a rare lysosomal storage disease,<sup>1</sup> with an estimated incidence of 1 in 4 200 000 live births, and it belongs to the group of oligosaccharidoses. Sialidosis is caused by to the recessively inherited deficiency of N-acetyl- $\alpha$ -neuraminidase, an acid hydrolase expressed from the gene *NEU1*, which is located in 6p21 and cleaves terminal  $\alpha 2 > 3$  and  $\alpha 2 > 6$  sialyl linkages of oligosaccharides. This deficiency results in an accumulation of sialyloligosaccharides in tissues. Two groups of the disease are distinguished. Type II sialidosis has an early onset and is more severe with dysmorphic aspects, such as coarse facies and dysostosis multiplex, statural and mental retardation, visceromegaly, myoclonus, seizure, and cherry red spots in the macula. This type is divided into congenital, neonatal, and infantile forms. Type I sialidosis has a later onset and is more progressive. Type I, often diagnosed during the third or fourth decade, is less severe without physical changes (normosomatic) nor dysostosis multiplex and is essentially characterized by ocular and cerebral involvement. We report the case of a patient with type I sialidosis who presents with unusual multiple osteonecrosis and a nonpreviously reported mutation of *NEU1*.

## Case Report

A 42-year-old woman with a history of myoclonus, seizure, and blindness presented with pain in the left hip and left leg. She

developed, at the age of 18 years, a rapidly progressive severe bilateral visual defect leading to blindness. At that time, the ophthalmologic examination revealed bilateral cherry red spot in the macula, evolving to macular and optic atrophy associated with bilateral cataract. At the age of 32 years, she developed myoclonus and epilepsy as grand mal seizure. Myoclonus affected all 4 limbs, but prevailed in the upper limbs, and increased with menstrual cycle and anxiety. Neurologic examination showed diffuse hyperreflexia with left Hoffmann sign and cerebellar ataxia. No mental retardation was found. Magnetic resonance imaging (MRI) showed corticosubcortical atrophy prevailing in frontal lobes. Electroencephalography showed salvo of slow waves in the frontal lobes. The patient was successively treated with valproate, lamotrigine, levetiracetam associated with clobazam, and piracetam. Treatments were effective on for the seizures but were less effective for the myoclonus.

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Metabolic assessment of urine samples found an accumulation of complex sugars rich in sialic acid, with 4% and 14% strips on the thin-layer chromatography (Humbel technics), which evoked a neuraminidase deficiency. The diagnosis was confirmed with evidence of absence of neuraminidase activity on fibroblast cultures (Supplementary Table 1). Beta-galactosidase activity was normal, excluding galactosialidosis. Hexosaminidase activity was also normal.

Molecular study of *NEUI* gene (NM\_000434.2) helped in the identification of 2 missense mutations. The first mutation was found in exon 3, p.Gly136Glu (c.407G>A), and was already reported.<sup>2</sup> The second mutation was found in exon 5, p.Gly273Asp (c.818G>A), and resulted in the substitution of the acidic residue aspartic acid for the neutral wild-type residue glycine at codon 273. This dramatic change in charge is consistent with the presence of biochemical and clinical phenotypes. In addition, the concerned amino acid residue and nucleotide are highly conserved through evolution. This mutation has not been reported yet.

At the age of 41 years, the patient felt pain in the left hip and leg and developed progressive walking difficulties. The x-rays revealed an advanced-stage bilateral osteonecrosis of the humeral (Supplementary Figure 1) and femoral heads (Supplementary Figure 2). Bone scintigraphy showed hyperfixation of both femoral and humeral heads. Femoral x-rays also showed lytic lesions on the diaphysis. The MRI confirmed osteonecrosis of both femoral and humeral heads and femoral diaphysis infarcts. An exhaustive research excluded the usual causes of osteonecrosis. Osteomedullary biopsy showed an important infiltration of foamy macrophages and histiocytes as described in storage diseases. Bone biopsy did not reveal Gaucher cells. Activities of tartrate-resistant acid phosphatases, chitotriosidase, and glucocerebrosidase were normal (Supplementary Table 1), excluding Gaucher disease.

## Discussion

Avascular osteonecrosis is well described in the lysosomal storage diseases spectrum, such as Gaucher disease, and rarely described in Fabry and Niemann-Pick type B diseases. Here, we excluded Gaucher disease with the normality of several biological parameters. The clinical presentation of this patient was not compatible with Fabry and Niemann-Pick type B diseases. Fabry disease is related to X-linked alpha-galactosidase A deficiency and presents with acral paresthesias; angiokeratomas; and renal, cerebral, and cardiac involvement. Niemann-Pick type B disease presents with hepatomegaly, splenomegaly, and interstitial lung involvement without any neurologic symptoms. Apart from sphingolipidosis, other lysosomal storage diseases of the mucopolysaccharidosis group are associated with dysostosis multiplex, although rare cases of bone necrosis have been described in I, II, III, and IV forms.<sup>3-6</sup> In the oligosaccharidosis family, cases of avascular osteonecrosis or bone infarct have only been reported in alpha-mannosidosis.<sup>7</sup>

Considering the severity of bone disease, the young age, and the presence of foamy macrophages on osteomedullary biopsy,

multiple osteonecrosis could be related to sialidosis in this patient. Sialidosis can involve bones in the early-onset form, that is, type II, with dysostosis multiplex phenotype, but bone abnormalities have never been described in type I. Nevertheless, this disease is extremely rare and the initial description could be partial.

Two missense mutations were identified in *NEUI* gene, p.Gly136Glu (c.407G>A) and p.Gly273Asp (c.818G>A). This last mutation is novel. It is worth noting that not all missense mutations are deleterious. Because of the ambiguity of missense mutations, accurate tools that predict the effect of a given point mutation on protein function are mandatory, and the use of more than 1 algorithm is recommended.<sup>8</sup> The 3 algorithms used (SIFT,<sup>9</sup> MutationTaster,<sup>10</sup> and Polyphen-2<sup>11</sup>) enabled us to conclude that this novel variant alters the protein function. Another hint associated with the pathogenic effect of this mutation is its low frequency or absence in the general population. We checked for the presence of the identified variant in the Exome Variant Server<sup>12</sup>; these mutations were not found among at least 8400 analyzed alleles.

We report here the case of a 42-year-old patient with type I sialidosis who presents with severe bone involvement, such as multiple osteonecrosis, and in whom the DNA sequencing reveals an unknown mutation in the fifth exon of *NEUI*, c.818G>A.

## Declaration of Conflicting Interests

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## Supplemental Material

The online [supplements] are available at <http://iem.sagepub.com/supplemental>.

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