Superoxide Dismutase Deficiency due to Biallelic *SOD1* Variants

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Abstract

Gain-of-function mutations in superoxide dismutase 1 (*SOD1*) are typically associated with familial Amyotrophic lateral sclerosis (ALS). Recently a distinct neurodegenerative disorder has been described, occurring due to biallelic loss of function in *SOD1*, manifesting as spastic tetraplegia with axial hypotonia in childhood. Debate exists regarding its classification, as to whether it is a distinct disorder or a part of the ALS spectrum.

Keywords: *SOD1*, Amyotrophic lateral sclerosis, biallelic *SOD1* variant, childhood-onset neurodegenerative disorder

Introduction

Superoxide dismutase (SOD) facilitates the transformation of the superoxide anion into hydrogen peroxide and oxygen and plays an important role in the cellular antioxidant defense. In humans there are three different isoforms of SODs: human Cu–Zn SOD (SOD1), the mitochondrial MnSOD (SOD2) and the extracellular Cu–Zn SOD (SOD3). Impairment of their antioxidant function or overactivity due to gain-of-function molecular mechanisms, represents a major pathophysiological role in the development of human neurodegenerative disorders (primarily, Amyotrophic Lateral Sclerosis) and cancer linked to SOD1 abnormalities (Eleutherio et al., 2021).

Mutations in *SOD1* are known to be associated with familial autosomal dominant Amyotrophic Lateral Sclerosis (ALS) mainly due to gain-of-function mechanism. Recently, Andersen et al. (2019), Park et al. (2019) and de Souza et al. (2021) reported paediatric patients with a severe neuromuscular disorder characterized by progressive motor neuron disease with hypotonia, spastic tetraplegia and loss of motor function due to homozygous biallelic pathogenic variants in *SOD1*. With no family history of ALS conforming to autosomal dominant inheritance, it was concluded that this disorder is distinct from *SOD1*- related ALS and constitutes a new clinical entity.

We present the clinical and genetic findings of a patient with biallelic pathogenic variant in *SOD1* associate with an early neurodegenerative phenotype.

Patient Details

A 1-year-old male child, third born to consanguineous parents from Uzbekistan, was referred for genetic evaluation. He was born at term gestation, by lower segment Cesarean section (LSCS), with a birth weight of 3.7 kg. The neonatal period was uneventful. He achieved all developmental milestones at an appropriate age until the age of 7 months after which he was noted to develop a gradual motor decline, with tightness of lower limbs being noted at around nine months of age. At 12 months of age, there was further motor regression with loss of ability to crawl or sit with support. There were no concerns regarding social, communication and emotional responses. There was no history of seizures, and visual or hearing impairment.

The proband's elder sister, who is 10 years old, was reported to be similarly affected (**Figure 1**). Parents noted a gradual motor decline for her, after 5-6 months of age. Currently, she was

bedridden and was not brought for evaluation. There was absence of speech in her. Social and communication domains were seemingly preserved. Magnetic resonance imaging (MRI) of her brain showed evidence of cerebellar atrophy.

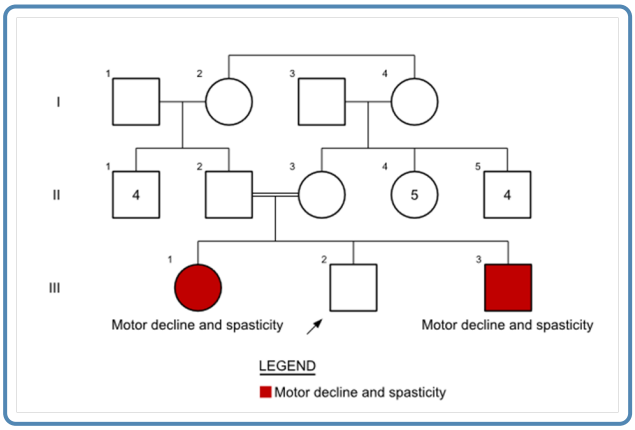

Figure 1 **Figure 1:** Pedigree of the family showing consanguinity and similar affected status of the elder sibling.

The parents were first cousins and were healthy and asymptomatic. There was no history of similar occurrence in the extended family. Paternal grandparents, who had passed away, had no neurological symptoms. The maternal grandparents were symptom free at the age of 70 years.

On examination, his growth parameters were within normal limits; weight: 10 kg (+0.33 Z), length: 75 cm (-0.32 Z), and head circumference: 46cm (-0.05 Z). The general physical examination was unremarkable. On neurological examination, the child was noted to be irritable and had appendicular hypertonia with axial hypotonia. Deep tendon reflexes were brisk in all four limbs. Bilateral plantar response was extensor. No fasciculations, myokymia or hyperekplexia were observed. Eye examination including fundus was unremarkable.

MRI brain was normal with no evidence of cerebral or cerebellar atrophy. In view of the progressive neurological symptoms in the child as well as his elder sibling with history of consanguinity, an autosomal recessive genetic condition was suspected and investigated for. Initial work up including hematological parameters, liver function tests, kidney function tests and serum creatine phosphokinase (CPK) were normal. Metabolic work up, including plasma lactate, homocysteine, acyl-carnitine, and amino acid profile by tandem mass spectrometry were also normal.

Whole exome sequencing revealed a homozygous pathogenic variant in the *SOD1* gene which is consistent with a diagnosis of autosomal recessive spastic tetraplegia and axial hypotonia, progressive type (**Table 1**).

This variant creates a shift in the reading frame starting at codon 112. The new reading frame introduces a premature stop codon 10 positions downstream. This variant has previously been reported as disease-causing (Andersen et al., 2019).

Discussion

The link between SOD1 variants and familial ALS is well-established, attributed to a gain of function in the *SOD1* gene. This leads to heightened oxidative activity, causing an overproduction of hydrogen peroxide. The mutated SOD1 also promotes increased protein–protein interaction, fostering aggregation, dimer destabilization, and oligomerization. These alterations contribute to abnormal axonal transport, microglia activation, heightened apoptosis, mitochondrial dysfunction, and oxidative stress, ultimately playing a critical role in motor dysfunction (de Souza et al., 2021; Kaur et al., 2016).

Biallelic truncating variants in *SOD1* result in spastic tetraplegia with axial hypotonia. There are very few cases reported in literature till now with the first case being reported in 2019 (Andersen et al., 2019). It is hypothesized that complete loss of function of SOD1 enzyme activity can produce an increased vulnerability to oxidative stress with mitochondrial dysfunction. It is characterized by onset of severe and progressive motor dysfunction in the first year of life. There is severe axial hypotonia combined with spastic tetraplegia, hyperekplexia, hypertonia, extensor plantar response and myokymia, reflecting upper motor neuron involvement. Cognitive development may be affected with absence of speech**.** Andersen et al. (2019) described the autosomal recessive *SOD1* gene-related disorder as a distinct entity, based on clinical differences (early onset spastic tetraplegia with axial hypotonia) and loss-of-function mechanism of gene malfunction. This was however challenged by de Souza et al. (2021), when they reported five

Table 1 Molecular genetic test results

Gene	Variant coordinates	Protein	Zygosity	Inheritance	Variant classification
SOD1	NM_000454.4: c.335dup (Human Genome Build GRCh37/hg19)	p.Cys112Trpfs*11	Homozygous	Autosomal recessive	Pathogenic (PS4, PVS1, PM2, PP5)

cases from two consanguineous families from Brazil, proposing it to be a varied spectrum of the same disorder. The patients reported by de Souza et al. who had the same variant as our patient, also exhibited features of lower motor neuron disease like fasciculations and fibrillations. They proposed that these patients may represent a very early infantile-onset ALS. However, there is insufficient evidence to suggest the same and long-term studies are required.

Regarding parental carriers who are heterozygous for the variant c.335dupG (p.Cys112Trpfs*11) in the *SOD1* gene, it is not possible to comment about the future risk of them developing a neurodegenerative disease, but they are not expected to develop any symptoms of ALS due to the very nature of the variant (loss of function). However, a long-term clinical follow-up would be necessary to detect any neurological manifestations related to ALS or any other type of neurodegeneration.

The final word is yet awaited regarding the molecular mechanism of the disease as the pathophysiology continues to unfold. However, it is clear that monoallelic as well as biallelic variants in the *SOD1* gene should be studied carefully, keeping in mind the clinical features as well as the mechanism of gene dysfunction created by the variant before making a confirmed diagnosis.

Conflict of interests: None

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