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Case Report

Severe isolated sulfide oxidase deficiency with a novel mutation

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ABSTRACT

Background. Isolated sulfite oxidase deficiency (ISOD), caused by mutations in *SUOX* gene, is an autosomal recessive disease manifesting with early onset seizures, developmental delay, microcephaly, and spasticity. It mimics hypoxic-ischemic encephalopathy (HIE) in the neonatal period and is characterized by progressive severe neurological impairment due to accumulation of toxic metabolites.

Case. This report presents a late diagnosed male patient with ISOD manifesting with neonatal-onset seizures, developmental delay, microcephaly, and spastic quadriplegia. Brain magnetic resonance imaging of the patient showed bilateral subcortical multi-cystic encephalomalacia involving bilateral parieto-occipital regions. A novel homozygous c.590_595delAGCCTC in-frame deletion in *SUOX* gene was identified in the patient, while both parents were heterozygous for that mutation.

Conclusion. The mutation identified in our patient causes severe ISOD. Early diagnosis of ISOD is essential for accurate genetic counseling and achieving prenatal diagnosis. Screening for urinary sulfite in patients with neonatal or early infantile onset seizures, developmental delay, microcephaly and cystic encephalomalacia in neuroimaging mimicking HIE helps in early diagnosis.

Key words: sulfite oxidase, isolated sulfite oxidase deficiency, ISOD, SUOX, seizure.

Sulfite oxidase (SO) is a mitochondrial, molybdenum-cofactor dependent enzyme encoded by *SUOX* gene. It catalyzes the oxidation of toxic sulfite to non-toxic sulfate which is excreted into the urine. SO also participates in the electron transfer from sulfites by means of cytochrome-c in mitochondria. Isolated sulfite oxidase deficiency (ISOD; MIM #272300) is an autosomal recessive disorder characterized by severe neurological impairment caused by mutations in the *SUOX* gene.[1] Eighteen different mutations in *SUOX* gene have been described in about 50 patients to date.[1-4] Most of the patients reported had severe neurological findings, mainly related with sulfite toxicity, presenting in the neonatal period. The severity of the disease depends on the mutation and associated residual enzyme activity.[1,2] Herein, we present a patient with severe ISOD presenting with intractable neonatal-onset seizures, feeding difficulty, microcephaly, spastic quadriplegia and brain magnetic resonance imaging (MRI) findings compatible with hypoxic ischemic encephalopathy (HIE) due to a novel six-base-pair deletion mutation (c.590_595delAGCCTC) in the *SUOX* gene at the age of six.

Case Report

This study has been approved by the appropriate ethics committee and the informed consent was taken from the parents. The patient is the first born child with a birth weight of 3220 grams at term after prolonged labor by induced vaginal delivery to first-

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degree consanguineous parents. His prenatal history was unremarkable. We learned that he had generalized cyanosis resolved within minutes with oxygen of %40 at birth. He had been presented with agitation, excessive crying, poor suckling, myoclonic jerks in the arms and pedalling movements of the legs in the second day of life. Seizure control had been achieved with phenobarbital treatment in that time. Initial assessments for inborn errors of metabolism (IEM), thrombophilic conditions, and screening for intrauterine infections had been found to be normal. Brain MRI of the patient on the 3rd day of life showed hemorrhagic changes in the bilateral periventricular areas. Brain MRI at one month of age revealed features of hypoxic-ischemic brain injury and diffuse subcortical cystic encephalomalacia, especially in the parieto-occipital lobes, and corpus callosum hypoplasia. The patient was first diagnosed as HIE due to perinatal asphyxia. In the follow-up, the patient hasddeveloped intractable seizures, progressive microcephaly, axial hypotonia, severe spasticity, and recurrent respiratory infections.

At one year of age, the patient was admitted to our hospital with severe respiratory tract infection. He was taking levetiracetam, lamotrigine, phenobarbital and clonazepam for resistant epilepsy. First-degree consanguinity, prominent progressive microcephaly (43 cm; <3rd percentile), axial hypotonia, severe spastic quadriplegia, severe seizures starting in the neonatal period, inconclusive metabolic investigations including normal serum uric acid levels (3.4 mg/dl) and multicystic changes in brain MRI (Fig. 1) further raised the suspicion of ISOD. Elevated levels of sulfide [80 mg/L (normal <15)] and thiosulfate [980 micromol/gram creatinine (normal <400)] were detected in the urine. Mutation analysis of *SUOX* gene in the patient revealed a homozygous c.590_595delAGCCTC variation, while both parents were heterozygous for that mutation.

Discussion

The incidence of neonatal seizure in full-term newborns is approximately 1-3.5/1000 live births. Inborn errors of metabolism account for approximately 1-3% of neonatal seizure cases, while HIE is the most common cause of neonatal seizures accounting for about two-thirds of cases.[5,6] Among them, the inherited inability of conversion of sulfite to sulfate caused by SO deficiency has clinical presentation resembling those in neonatal HIE. SO deficiency may be caused by ISOD or defects in the biosynthesis of molybdenum cofactor which is an essential component of three molybdenum-requiring enzymes including SO.[1] ISOD and molybdenum cofactor deficiency (MoCoD) have similar clinical manifestations characterized by neonatal-onset severe and progressive neurologic deterioration and intractable seizures, progressive microcephaly and feeding difficulties. The main neuroimaging finding of ISOD and MoCoD is multicystic encephalomalacia, which resembles HIE. The progressive neurologic deterioration is mainly related with toxic sulfite accumulation in tissues, which mainly affects the central nervous system in both conditions.[7] Increased urinary sulfite excretion that can be detected by dipstick testing in a very fresh urine sample, is a practical approach in identifying patients with ISOD and MoCoD from HIE. Differential diagnosis of two conditions can be easily achieved by measuring plasma uric acid level, which is normal in ISOD. Other laboratory findings include increased thiosulfate in urine, increased S-sulfocysteine and taurine in plasma and urine; normal plasma methionine, lowered plasma cysteine and homocysteine in ISOD.[1-4] Our patient's amino acid analysis including homocysteine was found to be normal.

ISOD was suspected in our patient with findings of intractable seizures, microcephaly, axial hypotonia, spastic quadriplegia, bilateral subcortical multi-cystic encephalomalacia

on brain MRI, normal plasma uric acid level, elevated urine sulfite and thiosulfate levels. The identification of homozygous c.590_595delAGCCTC mutation in the patient, and heterozygosity of the mutation in the parents further confirmed the diagnosis of ISOD. The clinical spectrum of ISOD varies from an early-onset severe disease (classical ISOD) to a late-onset mild disease. Classical ISOD is characterized by neonatal-onset intractable seizures, feeding difficulties, rapidly progressive encephalopathy presenting as abnormal tonus followed by progressive microcephaly, profound intellectual disability, lens subluxation/dislocation and even death at an early age. ISOD was reported first in 1967 and the majority of approximately 50 patients reported to date presented with classical ISOD.[1-4] Our patient presented with intractable seizures, axial hypotonia and feeding difficulty in the neonatal period which is compatible with classical ISOD. Cerebral-cerebellar atrophy, ventricular distension, thin corpus callosum, abnormal intensities in globus pallidi, diffuse subcortical cystic encephalomalacia seen in our patient are compatible with previous imaging findings reported in ISOD patients (Fig. 1).

SUOX gene encodes SO enzyme, a 545 amino acid protein, localized to the mitochondrial intermembrane and catalyzes the oxidation of sulfur-containing amino acids.[1,3] The missense mutations in the transit peptide and cytochrome b5 heme-binding domain of the enzyme cause to milder presentations of ISOD; while all kinds of mutations of the other domains (missense, nonsense, or frameshift) are associated with

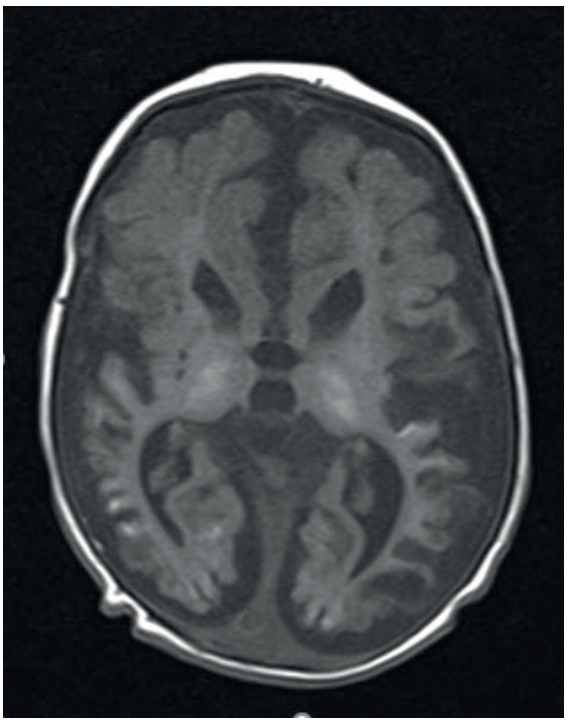

Fig. 1. Coronal T1-weighted axial magnetic resonance imaging showing bilateral subcortical multi-cystic encephalomalacia mainly in the parieto-occipital regions with bilateral hyperintensities in the corticomedullary junction and thalamus.

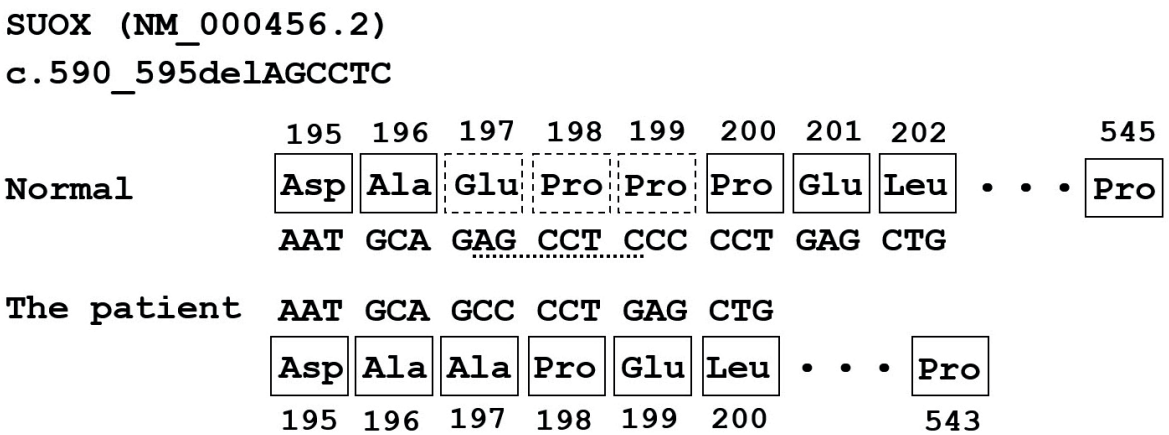

Fig. 2. *SUOX* gene encodes sulfide oxidase enzyme which is constructed by 545 amino acids. The mutation detected in our patient results in the substitution of glutamic acid with alanine at the 197 locus and the deletion of two proline amino acids.

severe clinical manifestations with onset within the first year of life.[1] The mutation identified in our patient is an in-frame deletion that does not disturb the reading frame of the sequence. However, any in-frame variant in *SUOX* gene has not been described before as a disease-causing mutation, the reported variant resulted in the substitution of glutamic acid with alanine at the 197 position and the deletion of two proline amino acids at the 198 and 199 positions (Fig. 2). The deletion described in our patient is between the hinge and molybdopterin-binding domains and close to the molybdopterin-binding domain. The c.599C>T (p.Pro200Leu) variant next to the amino acids changed in our patient has been described as likely pathogenic in a patient with delayed speech, language and global development, central hypotonia, synophry, low anterior hairline.[8] The SO enzyme has one conserved three consecutive proline (tripled PPP) sequence at the 198-200 amino acids. The c.590_595delAGCCTC mutation causes the missing of the tripled PPP sequence. The role of a single PPP motif is not known exactly, but human proteins richest in polyproline motifs are involved in DNA binding and transcription, actin cytoskeleton, RNA processing, splicing and metabolism, and signaling/ligand/receptor.[9] Mitochondrial valyl-tRNA synthetase has also one conserved tripled PPP sequence. The tripled PPP sequence of valyl-tRNA synthetase is critical for $tRNA^{Val}$ charging and editing activities and mutations within the proline triplet of valyl-tRNA synthetase reduce growth and viability of E. coli.[10] We could not perform SO enzyme analysis or functional studies on the c.590_595delAGCCTC mutation, but we suggest that the mutation described in our patient may disturb the binding of molybdenum to the enzyme and/or the missing of the tripled PPP sequence on SO may cause the loss of the enzyme activity.

The clinical and radiological similarity to HIE, the presence of a normal uric acid levels in ISOD, limited awareness of the condition, and misbelief of needing sophisticated tests to reach a presumptive diagnosis of IEM delay the diagnosis of ISOD by using routine screening tests. Early diagnosis is essential in treatable IEM to prevent permanent damage. No curative treatment exists for the underlying metabolic defect in ISOD, but early diagnosis of an untreatable inherited disease is also essential for accurate genetic counseling and achieving prenatal diagnosis.[1] Clinical and radiological findings, elevated urine sulfite and thiosulfate levels let the diagnosis at six year of age in our patient. Prenatal diagnosis was not done in the next pregnancy of the mother because of no precise diagnosis of the index patient at that time, fortunately the sibling was not affected. She is now four years old with normal growth and development, and was found heterozygous for the mutation.

We report here a late diagnosed patient with a novel mutation in *SUOX* gene causing classical ISOD. We suggest that the c.590_595delAGCCTC mutation described here may cause the loss of the SO enzyme activity by preventing the binding of molybdenum to the enzyme and/or the effects of the missed tripled PPP sequence on the enzyme. Further functional studies are needed to understand the effects of that mutation on the enzyme.

Early diagnosis of ISOD requires high index of clinical suspicion. To diagnose ISOD, sulfite levels in a very fresh urine sample should be checked carefully in every patient with neonatal or early infantile onset seizures, developmental delay, microcephaly and cystic encephalomalacia in neuroimaging mimicking HIE. Genetic counselling for future pregnancies is crucial to reduce the incidence of inherited diseases.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HİA, TS, İZE; data collection: ME, NY, EPÖ, BÇ; analysis and interpretation of results: HİA, BÇ,

TS, İZE; draft manuscript preparation: ME, NY, EPÖ, HİA. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare no competing interests.

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