Isolated Sulfite Oxidase Deficiency: Response to Dietary Treatment in a Patient with Severe Neonatal Presentation

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Monica Boyer[1], Mary Sowa[1], Raymond Wang[1,2], Jose Abdenur[1,2]

Abstract

Isolated sulfite oxidase deficiency (ISOD) is a devastating, neurometabolic disorder caused by mutations in the *SUOX* gene necessary for the final step in the sulfur-containing amino acid catabolic pathway. Patients classically present in the neonatal period with neurologic manifestations. Biochemical findings include elevated sulfocysteine, low cystine and undetectable homocysteine with normal uric acid levels. Other associated biochemical markers include elevated plasma alpha-aminoadipic semialdehyde and piperideine-6-carboxylic acid. We report a patient with classic neonatal onset ISOD (refractory seizures, hypertonicity, brain abnormalities, pathogenic *SUOX* mutations). Her clinical course was marked by extreme irritability, prompting the use of a low methionine and cystine diet to decrease toxic metabolites thought to be contributing to her symptoms. Biochemical markers and extreme irritability improved with dietary treatment (methionine=30mg/kg/day). She died of sepsis in early infancy, precluding long term follow-up. This case reviews the potential benefits and limitations of diet therapy in this rare disorder.

Keywords

ISOD, SUOX, sulfocysteine, hypoxic ischemic encephalopathy, methionine restriction.

Isolated sulfite oxidase deficiency (ISOD) is a rare, autosomal recessive, neurometabolic disorder caused by mutations in the *SUOX* gene that encodes sulfite oxidase [1]. The sulfite oxidase enzyme catalyzes the conversion of toxic sulfite (SO_3^{2-}) to nontoxic sulfate (SO_4^{2-}) in the final step of sulfur-containing amino acid catabolism [1]. Patients typically present with neonatal intractable seizures, encephalopathy, abnormal muscle tone (axial hypotonia, peripheral hypertonia) and diffuse brain abnormalities (multicystic leukoencephalopathy resembling hypoxic ischemic changes) [1]. Lens dislocation is a common later finding [1]. Characteristic biochemical findings include elevated urinary sulfocysteine, thiosulfate, low plasma cystine and undetectable plasma total homocysteine with normal plasma uric acid levels [1]. The natural history of ISOD is characterized by severe neurologic impairment and early death [2].

ISOD was first reported by Irreverre et al in 1967 [3]. The patient presented with a classic phenotype (neonatal onset neurologic abnormalities, limb hyperextension, tremors, poor feeding, opisthotonic posture, bilateral ectopia lentis at 1 year) and a history of 3 siblings who died in the neonatal period with an undiagnosed neurologic disease [3]. Since then, ISOD remains rare and infrequently reported in the medical literature. This might be due to underdiagnosis, since the neuropathology and clinical presentation mimics severe perinatal asphyxia and might be mistaken for hypoxic ischemic encephalopathy (HIE) [4]. Despite the discovery of the genetic defect, improved biochemical diagnosis and better understanding of the pathophysiology, there is currently no curative treatment. Shih et al. (1977) first proposed a dietary treatment aimed at limiting the sulfur containing amino acids to decrease the accumulation of toxic sulfite [5]. While most authors report no long term benefit with dietary treatment for patients with a classic phenotype [1,2,6], patients with a milder disease may benefit [1,7,8]. We report a new case of severe neonatal ISOD, describing its clinical course, MRI

[1] Division of Metabolic Disorders, CHOC Children's Hospital, Orange, CA, USA
[2] Department of Pediatrics, University of California-Irvine, Orange, CA, USA

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Corresponding Author:
Jose E. Abdenur, Division of Metabolic Disorders, CHOC Children's Hospital, Orange, CA, USA.
Email: jabdenur@choc.org

findings, striking biochemical abnormalities and highlight the importance of including ISOD in the differential diagnosis of HIE. Additionally, we report on the patient's clinical and biochemical response to dietary treatment.

Case Report

A term female infant was born by spontaneous vaginal delivery to Hispanic primigravida parents without known consanguinity. She was small for gestational age (birth weight 2.5 kg [3.5 percentile], head circumference 32.4 cm [9.5 percentile]). Apgar scores were not recalled, but there were no reported labor and delivery complications. She presented on day of life 8 with a one-day history of poor feeding and irritability. Neurology examination was grossly abnormal and included marked hypertonicity, opisthotonic posturing and status epilepticus. Initial lab results were concerning for metabolic acidosis (venous blood pH 7.26, reference range [RR] 7.30-7.40), lactic acidosis (8.6 mmol/L, RR 0.7-2.1 mmol/L) and ketosis (beta hydroxybutyrate 5.93 mg/dL, RR 0.21-2.81 mg/dL).

Brain magnetic resonance imaging (MRI) demonstrated diffusely abnormal signal in the periventricular white matter of both cerebral hemispheres, increased signal on the FLAIR sequences and the diffusion-weighted sequence in both temporal and parietal cortex and thinning of the corpus callosum (Figure 1, A & B). Due to the acute onset of symptoms and MRI findings implying HIE, non-accidental trauma was included in the initial differential diagnosis. An ophthalmology exam was obtained and revealed bilateral intraretinal hemorrhages (later determined to be birth related). A skeletal survey was also obtained and was negative.

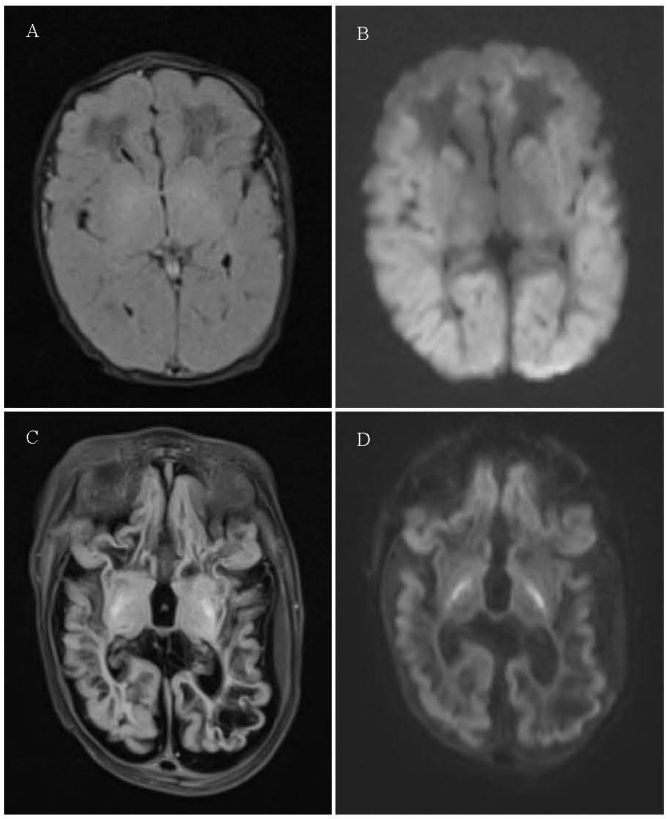

Figure 1. MRI scans. A-B: Axial cuts of the MRI of the brain obtained on DOL 8. A = T2 flair, B = diffusion-weighted sequence. Images show diffusely abnormal signal in the periventricular white matter of both cerebral hemispheres. There is also increased signal in the temporal and parietal cortex. C-D: Corresponding images of a repeat MRI of the brain at 6 weeks of life with severe global volume loss, cystic encephalomalacia and bilateral moderate subdural effusions.

Metabolic test results were significant for markedly elevated urinary sulfocysteine, undetectable plasma homocysteine, low or undetectable plasma cystine, normal uric acid, normal urinary xanthine and hypoxanthine and elevated plasma alpha-aminoadipic semialdehyde (AASA) and piperideine-6-carboxylic acid (P6C; Table 1).

Molecular sequencing was performed at Duke University Molecular Diagnostics Laboratory and a homozygous single nucleotide duplication in exon 2 (c.192dupG) was detected. This mutation has not been previously reported, but the sequence change was predicted to be pathogenic since it led to a frameshifting insertion that resulted in a premature termination codon. Parental testing could not be performed, but they were presumed to be heterozygous carriers for the same duplication.

She had multiple seizures, characterized by tremors and stiffening. EEGs confirmed these clinical findings and also revealed occasional subclinical seizures. Her seizures were difficult to control as phenobarbital, topiramate, and pyridoxine were required for partial seizure suppression. A repeat ophthalmology exam at 3 weeks of age was improved and did not demonstrate ectopia lentis.

She was initially NPO on admission and when enteral feedings were established she was fed breastmilk. At 2 ½ weeks of age, feedings were stopped due to intolerance and concern for necrotizing enterocolitis (bilious residuals, abdominal distention), requiring a prolonged NPO period for bowel rest and total parenteral nutrition (TPN) support. Her hospital course was marked by extreme irritability during this period, that required frequent morphine administration. At 6 weeks of life, enteral feedings were restarted with an elemental, hypoallergic formula (Neocate®). Once she reached goal feedings, she was transitioned to a low methionine and cystine diet in an attempt to improve biochemical markers and quality of life. Neocate® infant formula was utilized as a source of intact protein to meet a target methionine intake of 30 mg/kg/day (extrapolated from published protocols for treatment of Homocystinuria[9]). Additional methionine and cystine free medical food (Xmet Xcys Analog®, Nutricia, USA) and a protein free powder (Pro-Phree®, Abbott Nutrition) were incorporated into her formula to meet total protein (3 g/kg/day) and energy requirements. Quantitative amino acids were obtained to monitor methionine levels and methionine intake was adjusted accordingly.

A repeat MRI of the brain was completed at 6 weeks of life (prior to diet initiation) and demonstrated severe global volume loss, cystic encephalomalacia, and bilateral moderate subdural

Table 1. Urine and plasma biochemical markers at the time of diagnosis and during follow up.

	Initial - DOL 9		**Prior to diet - DOL 53**		**With diet - DOL 64**	
Nutrition Source	Breast Milk		Neocate ®		Metabolic Formula	
Methionine mg/kg/day	27		48		30	
(U) sulfocysteine	**643 H**	(<200)	**1518 H**	(<200)	**825 H**	(<200)
(U) xanthine	16,8	(0-59)	ND	ND	ND	ND
(U) hypoxanthine	8,3	(0-31)	ND	ND	ND	ND
(P) homocysteine	**<1.5 L**	(4-15)	**<1.5 L**	(4-15)	**<1.5 L**	(4-15)
(P) cystine	**4 L**	(17-98)	**0 L**	(16-84)	**2 L**	(16-84)
(P) methionine	17	(10-60)	11	(9-42)	14	(9-42)
(P) uric acid	4,4	(2–7)	2,9	(2–7)	ND	ND
(P) AASA	**0.5 H**	(< 0.4)	0,3	(< 0.3)	0,2	(< 0.3)
(P) P6C	**1.6 H**	(< 0.8)	**0.9 H**	(< 0.5)	0,5	(< 0.5)

DOL, day of life; P, plasma; U, urine; BOLD=abnormal values.

effusions (Figure 1, C & D). With dietary treatment, her extreme irritability markedly improved, correlating with an improvement in the biochemical parameters (Table 1). However, she remained severely developmentally delayed, with no developmental gains. She was discharged from the NICU at 2 months of age, but she was re-hospitalized with pneumonia and feeding intolerance at 3 months of age (requiring metabolic formula discontinuation and TPN support). The protein content in her TPN was lowered to approximate her methionine intake from her metabolic treatment plan and she was discharged home with TPN and trophic feeds. At 4 months of age she presented to the emergency department in septic shock (pH 6.6) and her parents elected to allow for natural death and she died of gram negative sepsis.

Discussion

ISOD is a devastating, neurometabolic disorder with a poor prognosis. Neurologic development is typically arrested at the level of brain stem function with no acquired developmental achievements [2]. Our patient's constellation of symptoms were representative of the classic phenotype and included progressive microcephaly, spasticity, severe developmental delay, cystic MRI changes and premature death [4,6,10]. Patients with longer survival often develop ectopia lentis. As in most inborn errors, there is a wide clinical heterogeneity and milder phenotypes have been described [2,6]. Late onset cases often lack the more characteristic features like neonatal onset seizures. Atypical presentations have included metabolic stroke [8] and a movement disorder with ectopia lentis and regression [11].

The pathophysiology underlying the neurological manifestations of this disorder is not known [4,6]. There are several proposed mechanisms by which elevated sulfite leads to neurotoxicity and clinical symptoms [2]. In vitro studies implicate sulfite accumulation in oxidative stress, disturbances of brain mitochondrial energy homeostasis and mitochondrial permeability transition pore opening resulting in neuronal damage characteristic of ISOD [12,13]. Lens dislocation is speculated to occur as a result of reduced levels of cystine (weakening the zonule of the lens) or secondary to elevated sulfites (causing disruption of cysteine disulphide bonds) [4]. The characteristic biochemical findings of low plasma cystine and homocysteine occur when alternative pathways for cysteine degradation result in accumulated sulfite conjugating with the above metabolites to form sulfocysteine [14].

Sulfite oxidase deficiency can be due to an isolated defect in the sulfite oxidase enzyme (ISOD) or secondary to defects in the cofactor (molybdenum cofactor)[1,15,16]. Since the molybdenum cofactor is also essential for xanthine oxidase and aldehyde oxidase, ISOD can be differentiated from Molybdenum cofactor deficiency by the presence of normal uric acid, xanthine and hypoxanthine levels [1,4,6].

Our case presentation highlights the importance of homocysteine and uric acid as readily available laboratory tests for the screening of ISOD or Molybdenum cofactor deficiency in patients with severe neonatal seizures or suspected HIE [6,14,16]. The presence of low or absent plasma homocysteine and normal uric acid should prompt further biochemical testing for ISOD (urine sulfocysteine levels) [6].

Another interesting biochemical finding that was seen in our patient and has been previously reported in the literature in patients with ISOD and Molybdenum Cofactor Deficiency was elevated AASA and P6C [17,18]. These markers are classically associated with pyridoxine dependent epilepsy (PDE) and are usually included in the initial investigation of severe neonatal seizures [17,18]. The initial finding of elevated AASA and P6C could have led to unnecessary investigations to rule out PDE, but since we had a strong suspicion for ISOD based on clinical presentation and an undetectable homocysteine level, we were not misled. In vitro studies have shown that AASA and PC6 accumulate in ISOD due to inhibition of alpha-aminoadipic semialdehyde dehydrogenase by elevated sulfites [17]. The accumulated P6C reacts with pyridoxal phosphate (PLP),

resulting in PLP deficiency [17,19]. The latter can be corrected with pyridoxine (vitamin B6) treatment and it has been theorized that treatment with pyridoxine may benefit patients with ISOD [17,18,19]. Pyridoxine was used in the antiepileptic treatment plan for our patient, but due to the simultaneous use of other medications, it is difficult to know if it played any role in improving the patient's seizure control.

Increased irritability and hyperekplexia have been previously reported in patients with ISOD [10,6,7,4] and were seen in our patient. These symptoms were first noted while receiving TPN (protein=3-3.5g/kg/day). It is possible that the amount of methionine received through the TPN (~115mg/kg/day) contributed to the patient's irritability, by increasing the burden of toxic metabolites. In comparison, methionine intake from the elemental formula (Neocate ®) used briefly after TPN was discontinued, was 48mg/kg/day.

Dietary interventions aimed at reducing the intake of methionine and cystine have been previously attempted, but reportedly did not change the natural history or demonstrate clear benefit in patients presenting with severe neonatal onset ISOD [4]. In two patients, however, a low methionine and cystine diet was associated with improved agitation [6,20]. Therefore, dietary interventions were implemented in our patient to lower potentially toxic metabolites that were thought to be contributing to her persistent irritability. Our experience demonstrated improvement in important quality of life indicators (decreased irritability, crying and restlessness). Prior to metabolic diet initiation, our patient required morphine 1-2 times per day to control her marked irritability. After dietary interventions, there was considerable subjective improvement in the patient's capacity to handle stimulation, allowing improved nursing care and parental bonding and she was discharged home without the need for morphine.

Objective biochemical results were obtained over the course of treatment and are summarized in Table 1. Pre-treatment urine sulfocysteine levels were 1518 and decreased with dietary treatment by 36% to 825. Of note, this value was similar to the one obtained while the patient was receiving breast milk, with a similar methionine intake. Because our patient died of an unrelated complication, it is unclear if our positive response to dietary interventions would have been sustained. However, given the low risk for harm and notable biochemical and subjective clinical improvement with dietary interventions, a low methionine and cystine diet should be considered in all patients with ISOD.

Conclusions

This case demonstrates the importance of homocysteine as a readily available laboratory-screening tool for ISOD and increases the awareness of elevated plasma AASA and P6C as additional biochemical markers associated with ISOD. We also highlight the potential benefits of a low methionine and cystine diet to ameliorate symptoms and improve quality of life in this rare disease.

References

1. Claerhout H, Witters P, Régal L, et al. Isolated sulfite oxidase deficiency. *J Inherit Metab Dis*. 2018;41(1):101-108. doi:10.1007/s10545-017-0089-4
2. Bosley TM, Alorainy IA, Oystreck DT, et al. Neurologic Injury in Isolated Sulfite Oxidase Deficiency. *Can J Neurol Sci*. 2014;41(1):42-48. doi:10.1017/S0317167100016243
3. Mudd SH, Irreverre F, Laster L. Sulfite oxidase deficiency in man: demonstration of the enzymatic defect. *Science*. 1967;156(3782):1599-1602. doi:10.1126/science.156.3782.1599
4. Hobson EE, Thomas S, Crofton PM, Murray AD, Dean JCS, Lloyd D. Isolated sulphite oxidase deficiency mimics the features of hypoxic ischaemic encephalopathy. *Eur J Pediatr*. 2005;164(11):655-659. doi:10.1007/s00431-005-1729-5
5. Shih VE, Abroms IF, Johnson JL, et al. Sulfite oxidase deficiency. Biochemical and clinical investigations of a hereditary metabolic disorder in sulfur metabolism. *N Engl J Med*. 1977;297(19):1022-1028. doi:10.1056/NEJM197711102971902
6. Tan W-H, Eichler FS, Hoda S, et al. Isolated sulfite oxidase deficiency: a case report with a novel mutation and review of the literature. *Pediatrics*. 2005;116(3):757-766. doi:10.1542/peds.2004-1897
7. Touati G, Rusthoven E, Depondt E, et al. Dietary therapy in two patients with a mild form of sulphite oxidase deficiency. Evidence for clinical and biological improvement. *J Inherit Metab Dis*. 2000;23(1):45-53. doi:10.1023/A:1005646813492
8. Del Rizzo M, Burlina AP, Sass JO, et al. Metabolic stroke in a late-onset form of isolated sulfite oxidase deficiency. *Mol Genet Metab*. 2013;108(4):263-266. doi:10.1016/j.ymgme.2013.01.011
9. Acosta PB. *Nutrition management of patients with inherited metabolic disorders*. Sudbury, Mass.: Jones and Bartlett Publishers; 2010.
10. Holder JL Jr, Agadi S, Reese W, Rehder C, Quach MM. Infantile spasms and hyperekplexia associated with isolated sulfite oxidase deficiency. *JAMA Neurol*. 2014;71(6):782-784. doi:10.1001/jamaneurol.2013.5083
11. Rocha S, Ferreira AC, Dias AI, Vieira JP, Sequeira S. Sulfite oxidase deficiency—an unusual late and mild presentation. *Brain Dev*. 2014;36(2):176-179. doi:10.1016/j.braindev.2013.01.013
12. Grings M, Moura AP, Amaral AU, et al. Sulfite disrupts brain mitochondrial energy homeostasis and induces mitochondrial permeability transition pore opening via thiol group modification. *Biochim Biophys Acta*. 2014;1842(9):1413-1422. doi:10.1016/j.bbadis.2014.04.022
13. Grings M, Moura AP, Parmeggiani B, et al. Disturbance of brain energy and redox homeostasis provoked by sulfite and thiosulfate: potential pathomechanisms involved in

the neuropathology of sulfite oxidase deficiency. *Gene*. 2013;531(2):191-198. doi:10.1016/j.gene.2013.09.018

14. Bindu PS, Christopher R, Mahadevan A, Bharath RD. Clinical and imaging observations in isolated sulfite oxidase deficiency. *J Child Neurol*. 2011;26(8):1036-1040. doi:10.1177/0883073811401399
15. Relinque B, Bardallo L, Granero M, Jiménez PJ, Luna S. Isolated sulfite oxidase deficiency. *J Neonatal Perinatal Med*. 2015;8(1):53-55. doi:10.3233/NPM-15814029
16. Sass JO, Gunduz A, Araujo Rodrigues Funayama C, et al. Functional deficiencies of sulfite oxidase: differential diagnoses in neonates presenting with intractable seizures and cystic encephalomalacia. *Brain Dev*. 2010;32(7):544-549. doi:10.1016/j.braindev.2009.09.005
17. Mills PB, Footitt EJ, Ceyhan S, et al. Urinary AASA excretion is elevated in patients with molybdenum cofactor deficiency and isolated sulphite oxidase deficiency. *J Inherit Metab Dis*. 2012;35(6):1031-1036. doi:10.1007/s10545-012-9466-1
18. Struys EA, Nota B, Bakkali A, al Shahwan S, Salomons GS, Tabarki B. Pyridoxine-dependent epilepsy with elevated urinary α-amino adipic semialdehyde in molybdenum cofactor deficiency. *Pediatrics*. 2012;130(6):e1716-e1719. doi:10.1542/peds.2012-1094
19. Stockler S, Plecko B, Gospe SM Jr, et al. Pyridoxine dependent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. *Mol Genet Metab*. 2011;104(1-2):48-60. doi:10.1016/j.ymgme.2011.05.014
20. Lee HF, Mak BSC, Chi CS, Tsai CR, Chen CH, Shu SG. A novel mutation in neonatal isolated sulphite oxidase deficiency. *Neuropediatrics*. 2002;33(4):174-179. doi:10.1055/s-2002-34491