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Sulphite Oxidase Deficiency - A Report of Two Siblings

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ABSTRACT

Isolated sulphite oxidase deficiency is a rare metabolic disorder characterised by neurological abnormalities, lens subluxation and seizures. Inheritance is autosomal recessive. We report two siblings with onset of clinical symptoms at 6 months of age, progressing to severe mental retardation, spasticity and seizures which were difficult to control. One of the siblings had lens subluxation. Diagnosis is made upon the increased levels of urinary sulphite, and high plasma S-sulphocysteine and thiosulphate levels. No treatment is known to be of help. Prenatal diagnosis is possible from the analysis of uncultured chorionic villus material for sulphite oxidase.

Keywords: sulphite oxidase deficiency, diagnosis, treatment, features, review

INTRODUCTION

Isolated sulphite oxidase deficiency is a rare metabolic disorder which has been described in only about seven patients[1-3]. It is genetically linked and inheritance is autosomal recessive[2,4]. Sulphite oxidase deficiency can occur as an isolated enzyme defect or as part of a general deficiency of the group of enzymes that share the common molybdenum-pterin cofactor. The enzyme is found in many tissues with the highest levels found in the lungs, kidneys, liver and heart. No detectable activity in blood or skeletal muscle has been found. Sulphite is an important intermediary compound in the metabolic pathway from sulphur amino acids to inorganic sulphate, the enzyme responsible being sulphite oxidase (Fig 1). The enzyme is located in the intermembrane space of the mitochondrion. Oxidation of sulphite occurs at the molybdenum centre with reduction of the metal from Mo(VI) to Mo(IV). The electrons generated in the reaction are transferred to cytochrome c and thence to the electron transport chain[7,8]. The molybdenum is complexed to a substituted pterin nucleus to form the molybdenum cofactor. The molybdenum cofactor is an essential component for the function of at least three enzymes: sulphite oxidase, xanthine oxidase and aldehyde oxidase. In sulphite oxidase deficiency, sulphate production is decreased. The excessive amount of sulphite is converted to thiosulphate via the action of β-mercaptopyruvate sulphur-transferase and to S-sulphocysteine by a yet unknown pathway[2].

We describe two siblings who presented in infancy with neurologic abnormalities. The older child died at the age of two years without a diagnosis of the metabolic disorder. The younger child was diagnosed to have sulphite oxidase deficiency which retrospectively gave a diagnosis to the older sibling who had died.

CASE REPORTS

Case 1

SCY was the first child born to a pair of non-consanguineous Chinese parents. She was delivered at term by assisted forceps delivery. She had good Apgar scores at birth. Her birth weight was 3010 gms. The perinatal events were uneventful. She was noticed to be hypotonic at the age of 3 months with poor head control. However, she developed normally and was able to roll over, sit and crawl.

At 6 months old, she developed myoclonic jerks with flexion of the arms and neck towards the midline, with lip smacking. Her eyes appeared unfocussed during these episodes. Multiple EEGs done were reported as normal. CT scan of the head showed cerebellar and temporal lobe atrophy. She was started on anti-convulsants, sodium valproate and carbamazepine, for the seizures. Her milestones regressed and development was retarded.

At 18 months old, she developed opisthotonic posturing, generalised spasms with hypertonia. She developed swallowing difficulties and had to be fed via nasogastric tube.

By 2 years old, the child was profoundly retarded, microcephalic with spastic quadriparesis and opisthotonic posturing. Her fundi were normal and she did not have subluxation of lenses. An EMG done at the time showed severe, diffuse polyneuropathy probably of a demyelinating nature.

Her clinical course was characterised by multiple intercurrent infections, predominantly from aspiration, and seizures which were difficult to control. She succumbed to pneumonia at the age of 2 years. A post-mortem examination was not performed.

Case 2

STR was the third child born to the same parents. He was born at term with a birth weight of 2,990 gms. Again, the perinatal history was uneventful. He

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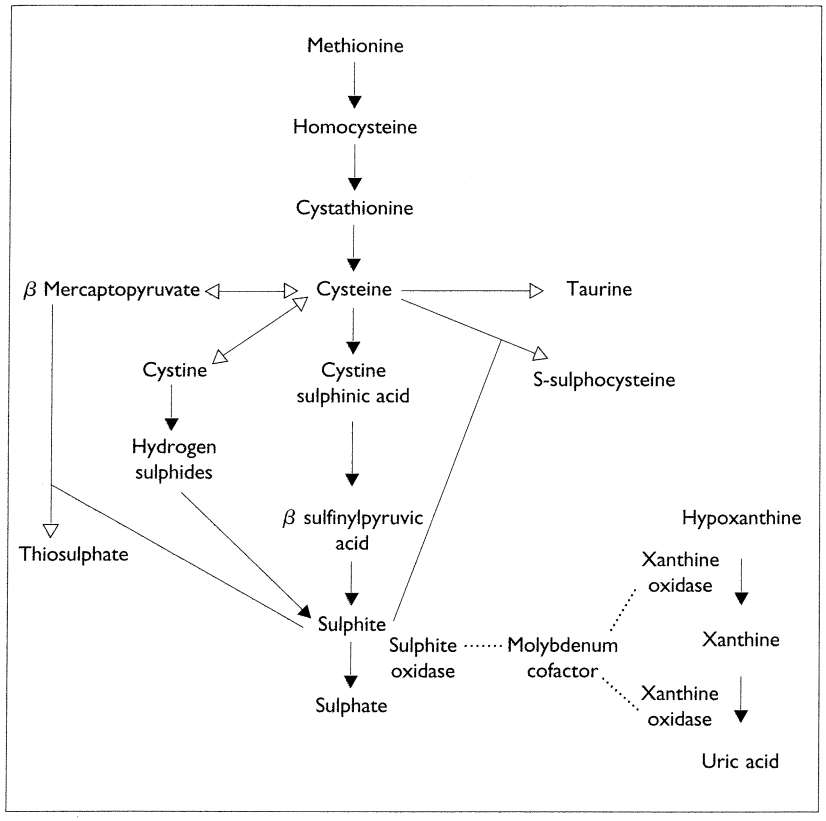

Fig 1 - Metabolic pathway of sulphur amino acids to sulphite and sulphate

developed normally till the age of one year. Like his sister, he developed myoclonic jerks associated with uncontrollable thrashing of the limbs at the age of six months. An EEG done was reported as normal. A CT scan of the head showed hypoplasia of the cerebellar vermis and enlargement of the cisterna magnum. He subsequently developed opisthotonic posturing with regression of milestones. An EMG done was reported as normal.

He was referred to an ophthalmologist for screening at the age of 1 $^1/_2$ years and was found to have bilateral subluxation of the lenses. There were no clinical features of homocystinuria or Marfan's syndrome. A urine metabolic screen was done and the urine aminogram was positive for sulphites. The family flew to Australia and had tests done in the Victoria Clinical Genetic Services of the Royal Children's Hospital in Melbourne, which showed increased urinary excretion of sulphite and high levels of S-sulpho-L-cysteine in the plasma which confirmed a diagnosis of sulphite oxidase deficiency. His plasma uric acid and 24-hour urine uric acid levels were normal.

His clinical course was also characterised by multiple intercurrent infections from aspiration and seizures, which were difficult to control. He was treated with sodium valproate and was on nitrazepam and chloral hydrate for the distressing opisthotonic posturing and spasms.

Besides having profound mental retardation, hypertonia with opisthotonic posturing and bilateral lens subluxation, he was also noted to have some dysmorphic features such as large, pliable ears, plagiocephaly, skin laxity and deep skin creases. He was unable to feed orally and required nasogastric feeding. The opisthotonic posturing and spasms resolved over time.

He finally succumbed to pneumonia at the age of four years.

DISCUSSION

The main clinical features of patients with sulphite oxidase deficiency are: neurologic dysfunction, proceeding to profound mental retardation; spasticity; progressive choreoathetoid movements and seizures, and the development of dislocated lenses. These features are similar to those of molybdenum cofactor deficiency, as this disease is characterised by symptoms and metabolic sequelae of both sulphite oxidase deficiency and xanthine oxidase deficiency. No clinical symptoms due to aldehyde oxidase deficiency have been identified. The onset of neurologic abnormalities can vary from the neonatal period[1,3] to early childhood, usually within the age of two years[2]. Thus early development may be normal until onset of neurologic symptoms leading to deterioration of milestones and profound mental retardation. Both of the patients described here presented with the classical features of sulphite oxidase deficiency.

As mentioned earlier , sulphite oxidase deficiency is a rare metabolic disorder, with only seven cases being reported so far in the literature. A summary of the main clinical features of these cases will be reviewed here.

Mudd et al[4] described a male child with neurological abnormalities at birth. He was found to have ectopic lenses at one year of age and died at aged 32 months.

Shih et al[2] described a male child who developed myoclonic jerks at aged 17 months. This evolved into generalised seizures with a right hemiparesis at aged 2 years. There was marked regression of milestones and speech. He was noted to have bilateral subluxation of lenses at 4 years of age. Shih also described a male child with acute encephalitic symptoms at 8 months old and choreoathetoid movements related to him via personal communication by Carton D from Belgium. This child had unilateral subluxation of lens.

Brown et al[3] described two cases of sulphite oxidase deficiency. The first was a girl born full-term to parents of consanguineous marriage. She developed seizures 2 hours after birth. An EEG done showed multifocal abnormalities. Neurological abnormalities included opisthotonic posturing and hypertonia. She was microcephalic with profound mental retardation. Spasticity, kyphoscoliosis and contractures were also present. The ophthalmologic abnormalities consisted of divergent strabismus, optic atrophy at 21 months and bilateral supranasal subluxation of lenses at 3 years old. She died of aspiration pneumonia at 4 years of age. The second case was a boy, born full-term of a non-consanguineous marriage. He developed jitteriness and poor suck associated with seizures on the third day of life. He later developed myoclonic jerks progressing to spasticity and microcephaly by 6

Table I - Biochemical results differentiating isolated sulphite oxidase deficiency from molybdenum cofactor deficiency

	Isolated sulphite oxidase deficiency	Molybdenum cofactor deficiency	Xanthine oxidase deficiency
Urine sulphite	↑	↑	N
thiosulphate	↑	↑	N
S-sulphocysteine	↑	↑	N
taurine	↑	↑	N
sulphate	↓	↓	N
xanthine	↓	↑	↑
hypoxanthine	N	↑	↑
uric acid	N	↓	↓
Plasma S-sulphocysteine	↑	↑	N
cystine	↓	↓	N
uric acid	N	↓	↓

months of age. He died at 19 months old. No lens subluxation was detected at the time of death.

J M van der Klei-van Moorsel et al[5] described a male child born of a consanguineous marriage who developed seizures and choreiform movements at 11 months. He also had hypotonia with delayed milestones. At the time of reporting, no ocular abnormalities had been detected.

The seventh case was reported by Vianey-Liaud et al[6]. This was a boy who was the fifth child of consanguineous Algerian parents. He developed respiratory distress at birth and had severe neurological symptoms consisting of hypotonia and abnormal movements. He also had dysmorphic features, macrocephaly, jaundice and hepatomegaly. The child died at 9 days old. No ophthalmic examination was done.

In all the cases reported, the biochemical results supported the diagnosis of sulphite oxidase deficiency.

The neuroradiologic findings of cerebellar and cerebral atrophy in our patients correlated well with the neuroradiologic findings reported by Brown et al[3]. They reported two patients whose CT studies showed gross cerebral and cerebellar atrophy, cystic changes and areas of calcifications. These changes may not be present at birth but will develop as the illness progresses. The atrophy is most severe in the parietal areas and less marked in the frontal regions[9].

The neuropathologic features of sulphite oxidase deficiency are distinctive, but generally non-specific as they are seen in patients with molybdenum co-factor deficiency as well[3,10,11]. The major histologic changes are loss of neurons and demyelination, cystic changes, glial proliferation in the white matter, proliferation of astrocytes and areas of calcification[2,3].

The mechanism of brain damage in sulphite oxidase deficiency remains unknown. There are three possible mechanisms postulated:

1. Sulphite toxicity
   Sulphites have been used as food additives. Toxicologic investigations have demonstrated gastric haemorrhage, growth retardation and kidney damage in laboratory animals given high doses of these compounds[12].
2. S-sulphocysteine toxicity
   Olney et al have shown that injecting S-sulphocysteine into rat brain induces neuronal degeneration and swelling of dendritic processes[13].
3. Cysteine and inorganic sulphate deficiency
   Depletion of tissue cysteine as a result of increased production of S-sulphocysteine and thiosulphate may have an adverse effect on the developing central nervous system in young infants[14]. Inorganic sulphate is the precursor of the organic sulphate ester in myelin and deficiency of sulphate in sulphite oxidase deficiency could be a contributing factor in the development of the neuropathologic changes seen. However, Percy et al studied the quality and concentration of sulphatides in the brain and kidney of the patient described by Mudd et al, and found them normal[15].

Presence of sulphite in the urine is not diagnostic of sulphite oxidase deficiency, as it is also present in molybdenum cofactor deficiency and xanthine dehydrogenase deficiency. It is useful as a quick screening test. Urinary sulphite is easily detected with a strip test (Merkoquant 10013 Sulfit Test or Machery - Nagel Quantofix SO_3^{2-}), but fresh urine must be used since sulphite is rapidly destroyed by oxidation at room temperature[16]. To identify the enzyme defect once urinary sulphite is detected, other tests are done.

Table I tabulates the biochemical results of isolated sulphite oxidase deficiency as differentiated from both molybdenum cofactor deficiency and xanthine oxidase deficiency. In sulphite oxidase deficiency, there will be high levels of plasma S-sulphocysteine with normal uric acid levels. Urinary sulphites, thiosulphate and S-sulphocysteine levels are raised with low urinary xanthine and normal hypoxanthine levels. In xanthine oxidase deficiency, there will be markedly elevated

levels of urinary xanthine and moderate levels of hypoxanthine. Uric acid levels are low in urine and plasma. Molybdenum cofactor deficiency is differentiated from both sulphite oxidase deficiency and xanthine oxidase deficiency by the presence of high levels of urinary thiosulphate, sulphites and S-sulphocysteine as well as xanthine and hypoxanthine but with low plasma and urine uric acid levels.

Treatment of sulphite oxidase deficiency should attempt to eliminate the overflow of sulphite. Attempts in administering D-penicillamine and 2-mercaptoethane sulphonic acid[17,18] failed to improve the profile of sulphur-containing metabolites in the urine. The poor results could be explained by the poor sulphonation of these compounds in *in vitro* assays. Cysteamine is readily sulphonated and is presently being used to treat children with nephropathic cystinosis[19] and may be of interest in the treatment of sulphite oxidase deficiency[20]. Shih et al attempted to lower sulphite and its metabolites in plasma by giving a low sulphur amino acid diet with supplementation of certain essential amino acids. They achieved good reduction in the biochemical abnormalities by dietary restriction but no substantial clinical improvement was seen[2]. This would imply that the brain damage in sulphite oxidase deficiency is probably irreversible. Whether dietary restriction early before the onset of clinical deterioration will prevent the development of symptoms is not known.

Prenatal diagnosis is possible with analysis of sulphite oxidase from uncultured chorionic villi or cultured amniotic fluid cells[21].

In summary, sulphite oxidase deficiency is a rare disorder which results in a severely retarded child. As yet, no treatment is known. However, prenatal diagnosis is possible and should be offered to parents who have had an affected child.

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REFERENCES

1. Irrevere F, Mudd SH, Heizer WD, Laster I. Sulphite oxidase deficiency: Study of a patient with mental retardation, dislocated ocular lenses, and abnormal urinary excretion of S-sulpho-L-cysteine, sulphite and thiosulphate. Biochem Med 1967: 187-217.
2. Shih VE, Abrouns IF, Johnson JL, Carney M, Mandell R, Robb RM, et al. Sulphite oxidase deficiency. Biochemical and clinical investigations of a hereditary metabolic disorder in sulphur metabolism. N Engl J Med 1977; 297:1022-8.
3. Brown GK, Scholem RD, Croll HB, Wraith JE, McGill JJ. Sulphite oxidase deficiency: Clinical, neuroradiologic, and biochemical features in two new patients. Neurology 1989; 39: 252-7.
4. Rosenberg LE, Seriver CR. Disorders of amino acid metabolism. In: Bondy PK, Rosenberg LE, eds. Metabolic Control and Disease 8th edition. USA:WB Saunders Co. 1980:671-2.
5. Van der Klei-van Moorsel JM, Smit LME, Brockstedt M, Jakobs C, Dorche C, Duran M. Infantile isolated sulphite oxidase deficiency: Report of a case with negative sulphite test and normal sulphate excretion. Eur J Pediatr 1991; 150:196-7.
6. Vianey-Liaud C, Desjacques P, Gaulme J, Dorche C, Vanlieferinghen P, Dechelotte P, et al. A new case of isolated sulphite oxidase deficiency with rapid fatal outcome. J Inher Metab Dis 1988; 11:425-6.
7. Wattiax-de Coninck S, Wattianx R. Subcellular distribution of sulphite cytochrome c reductase in rat liver tissue. Eur J Biochem 1971; 19:552-6.
8. Johnson JL, Rajagopalan KV. Tryptic cleavage of rat liver sulphite oxidase. Isolation and characterization of molybdenum and heme domains. J Biol Chem 1977; 252:2017.
9. Rosenblum WI. Neuropathologic changes in a case of sulphite oxidase deficiency. Neurology (Minneap) 1968; 18:1187-96.
10. Desjacques P, Mousson B, Vianey-Liaud C, Boulin R, Bory C, Ballassat P, et al. Combined deficiency of xanthine oxidase and sulphite oxidase: diagnosis of a new case followed by an antenatal diagnosis. J Inherited Metab Dis 1985; 8(suppl 2): 117-8.
11. Munnich A, Sandubray JM, Charpentier C, Ogier H, Conde FX, Frezal J, et al. Multiple molybdoenzyme deficiencies due to an inborn error of molybdenum cofactor metabolism: two additional cases in a new family. J Inherited Metab Dis 1983; 6 (suppl 2):95-6.
12. Til HP, Feron VJ, de Groot AP. The toxicity of sulphite I. Longterm feeding and multigeneration studies in rats. Food Cosmet Toxicol 1972; 10:291-310.
13. Olney JW, Misra CH, de Gubareff T. Cysteine-S-sulphate: Brain damaging metabolite in sulphite oxidase deficiency. J Neuropathol Exp Neurol 1975; 34:167-77.
14. Sturman JA, Ganll G, Raiha NCR. Absence of cystathionase in human fetal liver: is cystine essential? Science 1970; 169:74-6.
15. Percy AK, Mudd SH, Irrevere F, Laster L. Sulphite oxidase deficiency: sulphate esters in tissues and urine. Biochem Med 1968; 2:198-208.
16. Wadman SK, Cats BP, DeBree PK. Sulphite oxidase deficiency and the detection of urinary sulphite. Eur J Pediatr 1983; 141:6.
17. Endres W, Shin YS, Gunther R, Ibel H, Duran M, Wadman SK. Report on a new patient with dehydrogenase due to molybdenum cofactor deficiency. Eur J Pediatr 1988; 148: 246-9.
18. Tardy P, Parry P, Charpentier C, Bonnefont JP, Sandubray FM, Kamoun P. Attempt at therapy in sulphite oxidase deficiency. J Inherited Metab Dis 1989; 12 (suppl 2):95-6.
19. Sarolin LA, Clark KF, Thoene JG, Gahl WA, Scheinder JA. A comparison of the effectiveness of cysteamine and phosphocysteamine in elevating plasma cysteamine concentration and decreasing leukocyte free-cystine in nephropathic cystinosis. Paediatr Res 1988; 23:616-20.
20. Kamoun P, Tardy P. Therapeutic attempts in sulphite oxidase deficiency. Eur J Paediatr 1990; 149:594-6.
21. Gray RGF, Green A, Basu SN, Constantine G, Londie RG, Dorche C, et al. Antenatal diagnosis of molybdenum cofactor deficiency. Am J Obstet Gynecol 1990; 163:1203-4.