KY Chan 陳國燕
CK Li 李志強
CK Lai 賴志剛
SF Ng 吳瑞芬
AYW Chan 陳恩和

Infantile isolated sulphite oxidase deficiency in a Chinese family: a rare neurodegenerative disorder

華人家庭中的嬰兒單一性亞硫酸鹽氧化酶缺乏症：一種罕見的神經變性紊亂

We report the clinical, biochemical, neuroradiological, and neurophysiological findings of a 4-year-old Chinese girl with infantile isolated sulphite oxidase deficiency. This is the first reported case in our locality. She presented at the age of 5 months with refractory seizures and developmental regression, and progressed rapidly to profound psychomotor retardation, spasticity, dystonia, microcephaly, and blindness. At the age of 3.5 years, she was admitted to the intensive care unit with septic shock. Ophthalmologic examination at this time revealed bilateral dislocation of the lens. Diagnosis of this very rare disorder was made on the basis of increased levels of urinary sulphite, thiosulphate, and sulphocysteine; normal urine xanthine and hypoxanthine; normal plasma uric acid; and low plasma cystine levels. The diagnosis was confirmed by the absence of sulphite oxidase activities in skin fibroblasts. Isolated sulphite oxidase deficiency is a rare inborn error of sulphur metabolism that is difficult to diagnose on clinical features and routine metabolic tests. The presence of ectopia lentis, seizures, and progressive neurological abnormalities should alert clinicians to the diagnosis.

我們報告了與一名患嬰兒單一性亞硫酸鹽氧化酶缺乏症的 4 歲華裔女童有關的臨床、生物化學、神經放射學及神經生理學的發現。這是本地首次報告的病例。病人在5個月大時出現難以控制的癲癇發作和發育衰退，很快發展到嚴重的神經運動延遲、痙攣、肌肉張力失常、頭小畸形和失明。病人3.5歲時因敗血性休克而入住深切治療病房。眼科檢查發現病人眼晶體雙邊脱位。這罕見的診斷基於下列尿檢和血檢結果：尿亞硫酸鹽、硫代硫酸鹽及硫胱氨酸水平增加；尿黃嘌呤和次黃嘌呤正常；血漿尿酸正常；血漿胱氨酸水平低。皮膚纖維原細胞測試證實病人嚴重缺乏亞硫酸鹽氧化酶。單一性亞硫酸鹽氧化酶缺乏是罕見的先天性硫新陳代謝病變，它難以根據臨床特徵和常規新陳代謝檢測確診。病人如出現晶體移位，癲癇發作及進行性的神經發展障礙等徵狀，臨床醫生應慎重考慮這病症的可能性。

Key words:
Cerebral palsy;
Lens subluxation;
Metabolism, inborn errors;
Seizures;
Sulfites

關鍵詞：
大腦麻痺；
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Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Kowloon, Hong Kong:
Department of Paediatrics and Adolescent Medicine
KY Chan, FRCP, FHKAM (Paediatrics)
CK Li, FRCP, FHKAM (Paediatrics)
SF Ng, MRCP, FHKAM (Paediatrics)
Department of Pathology
CK Lai, BSc, MSc
AYW Chan, MD, FRCPath

Correspondence to: Dr KY Chan

Introduction

Isolated sulphite oxidase deficiency (ISOD) is a rare autosomal recessive disorder in which the pathway of oxidative degradation of sulphur amino acids is impaired.[1] The conversion of sulphite to sulphate is affected, resulting in accumulation of toxic metabolites and a deficiency of sulphate (Fig).[2] This disorder is characterised by intractable seizures, progressive neurological dysfunction, failure to thrive, microcephaly, initial hypotonia then hypertonia, and often lens dislocation. The clinical features of ISOD are similar to the more common related variant, molybdenum cofactor deficiency. Molybdenum cofactor is essential for the function of sulphite oxidase and xanthine oxidase. The differentiation between ISOD and molybdenum cofactor deficiency is made on biochemical findings—low plasma uric acid, and high urine xanthine and hypoxanthine are found in molybdenum cofactor deficiency, while normal plasma uric acid, urine xanthine, and hypoxanthine levels are seen in ISOD.[3] About 16 cases of ISOD have been reported in the literature.[2-5] The disease is inherited as

an autosomal recessive trait, with heterozygotes displaying no symptoms. We report details of a 4-year-old female infant who presented with seizures at the age of 5 months and subsequently, evidence of neurological regression. This case report emphasises the importance of considering ISOD or molybdenum cofactor deficiency in infants with unexplained seizures and developmental delay or arrest.

Case report

The infant is the third child of consanguineous (first cousins) Chinese parents. Her two elder sisters have demonstrated normal development to date. However, two of her paternal uncles died at the age of 1 year and 3 years, respectively without a specific medical diagnosis. The child was born at-term by normal vaginal delivery in mainland China. The pregnancy and perinatal history were uneventful. The child developed normally until a febrile illness at 5 months, during which she had frequent attacks of generalised tonic-clonic convulsions, followed by opisthotonic posturing, generalised spasms with hypertonia, and subsequent regression in development. She was treated in mainland China and was given phenobarbitone for her seizures. Since then, she was noted to have recurrent convulsions, severe developmental delay, and feeding difficulty.

At the age of 3.5 years, shortly after coming to Hong Kong, she was admitted to the intensive care unit with septic shock. She was treated with fluid replacement therapy and antibiotics. All her growth parameters were noted to be significantly below the third percentile for her age. She was profoundly retarded, microcephalic, with spastic quadriparesis, and opisthotonic posturing. She showed no response to sound or visual stimuli. She was unable to feed orally and required nasogastric feeding. Although her convulsions were controlled with carbamazepine, she still had frequent painful spasms requiring chloral hydrate. The optic fundi were normal but bilateral superomedial dislocated lenses were evident. There were no clinical features of homocystinuria or Marfan's syndrome. Initial investigations including liver function tests, urea and electrolytes, ammonia, pyruvate, and lactate detected no abnormalities. Urine organic acids also showed a normal pattern and plasma uric acid levels were normal. There was increased urinary excretion of sulphite (positive Dipstick test), thiosulphate (490 μmol/mmolCr; normal level, <45 μmol/mmolCr), and sulphocysteine (869 μmol/L), and normal excretion of xanthine and hypoxanthine. Plasma sulphocysteine (39 μmol/L) was detected and the plasma cystine level (<1 μmol/L; normal range, 33-117 μmol/L) was very low. Isolated sulphite oxidase deficiency was suspected on the basis of an abnormal amino acid profile: detection of sulphocysteine in plasma and urine, together with a low concentration of plasma cystine, a normal urinary excretion of xanthine and hypoxanthine, plus normal plasma uric acid levels.

A skin fibroblast sample was cultured for the measurement of sulphite oxidase activity (Dr C Dorche, Laboratoire de Biochimie, Hôpital Debrousse, Lyon, France). No activity was detected in the patient's fibroblasts (control value=4.3 ukat Kg $prot^{-1}$), confirming the diagnosis of ISOD. Her electroencephalogram showed slow sharp waves in the right temporal and parietal regions. Auditory brainstem response was normal and visual evoked response was absent. Motor nerve conduction velocity studies were normal. Magnetic resonance imaging of the brain showed diffuse cerebral atrophy involving the cerebrum, brainstem and cerebellum; ventriculomegaly; and encephalomalacia over the paraventricular region and the basal ganglia.

The patient was given a low protein diet (1.27 g/kg/day) including synthetic amino acid mixture without cystine and methionine (Xmet, Cys Maxamaid, SHS International Ltd, Liverpool, UK). The child tolerated the diet well and became less agitated. Her general health and neurological status were stable. The special diet was recently discontinued during an episode of severe gastrointestinal infection. Family screening for urine sulphate, thiosulphate, xanthine, and hypoxanthine showed normal findings.

Discussion

Isolated sulphite oxidase deficiency is characterised by severe neurological dysfunction, intractable seizures, spasticity, choreoathetiod movements, lens dislocation, and accumulation and excretion of sulphite, thiosulphate and

Table. Reports in the literature of patients with isolated sulphite oxidase deficiency

Patients	1[4]	2[4]	3[4]	4[6]	5[6]	6[3]
Sex	Male	Male	Female	Female	Male	Male
Onset	NR†	NR	NR	Day 1	Day 3	11 months
Feeding difficulty	+‡	NR	NR	+	+	-§
Respiratory problems	+	+	NR	+	+	-
Abnormal muscle tone	+	+	+	+	+	+
Seizures	+/-	+	+/-	+	+	+
Dislocated lens	NR	NR	NR	+	-	-
Psychomotor retardation	+	NR	NR	+	+	+
Computed tomography/magnetic resonance imaging brain abnormality	NR	NR	NR	+	+	-
Age at death	32 months	9 days	-	4 years	19 months	-
Consanguinity	-	+	+	+	-	+

* These patients are siblings
† NR not reported
‡ + present
§ - absent

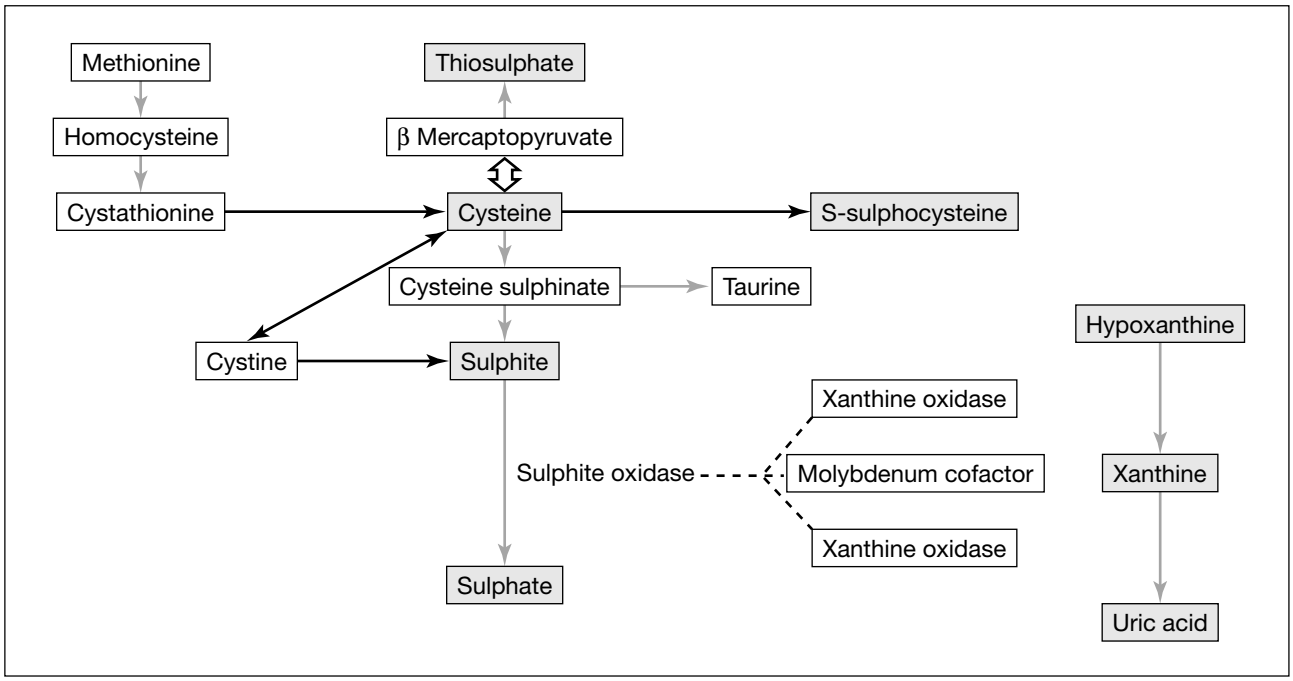

Fig. Metabolic pathway of sulphur amino acids to sulphite and sulphate

S-sulphocysteine.[6] Most cases presenting early in life will have serious disease resulting in severe handicap. However, milder forms of this disease have been reported.[7] Until recently, there was no known therapy to prevent the progression of neurological deterioration. However, Touati et al[8] have since reported significant clinical and biochemical improvement after specific dietary therapy in two patients with mild ISOD. No neurological deterioration and evidence of progress in psychomotor development were noted in these two cases. Therefore, early awareness and detection of this disorder in infants with neurodevelopmental disorder are important, as the disease may be successfully treated with dietary therapy.

Isolated sulphite oxidase deficiency is a rare disorder but it is probably also an underdiagnosed condition. The clinical features of this patient are compared with other reported cases in the Table. The clinical expression of ISOD is variable. The majority of early-onset cases presenting with intractable seizures, feeding and respiratory difficulties, die in early childhood. Late-onset cases are less common but usually run a milder course. Neuroradiological findings of cerebral and cerebellar atrophy, ventriculomegaly, and encephalomalacia usually develop as the disease progresses. Lens dislocation has been observed as early as 2 months. However, it is usually not present at birth, developing during the second or third year of life. Thus, delay in diagnosis commonly occurs. In this patient, appropriate investigations were performed only at the time when lens dislocation was diagnosed.

Long-term outcome therefore depends greatly on the clinical type of disease, early detection, and treatment. Urine sulphite screening by Dipstick testing appears to be a very simple and sensitive method for detecting excess sulphite accumulation in urine in ISOD or molybdenum cofactor deficiency. Fresh urine must be used since sulphite is rapidly destroyed by oxidation at room temperature. Negative urine sulphite Dipstick testing has been reported in some cases of ISOD.[3] The gene defect responsible

7/8[9]*	9[4]	10[7]	11/12[2]*	13/14[5]*	15[8]	16[8]	This case
Female/female Day 1/Day 2	Male Day 2	Male 9 months	Female/male 3 months/1 year	Male/male Newborn/Day 1	Male 15 months	Female 8 months	Female 5 months
+	+	-	+	+	-	-	+
NR	+	-	+	+	-	-	+
+	+	+	+	+	+	+	+
+	+	-	+	+	-	-	+
NR/-	+	-	-/+	NR/+	-	+	+
+	+	+	+	+	-	-	+
NR/+	+	-	+	+	+	+	+
8 months/-	32 months	-	2 years/4 years	10 months/-	-	-	-
+	-	+	-	-	-	+	+

for sulphite oxidase deficiency has been reported recently and in the future, this may allow accurate DNA-based diagnosis of this rare disorder and the possibility of prenatal screening.[4]

Conclusion

Isolated sulphite oxidase deficiency is a rare neurometabolic disorder which is difficult to diagnose by clinical presentation alone. The finding of lens subluxation in infants with seizures and diffuse brain dysfunction should alert clinicians to the diagnosis. Early diagnosis and intervention are important as a special diet (low in sulphur amino acids) is effective in preventing neurological and mental deterioration in some mild cases.

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1005A Melbourne Plaza, 33 Queen's Road, Central, Hong Kong
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香港銅鑼灣軒尼詩道555號東角中心1810室
Tel: 2891 3738 Fax: 2891 3803

1215 Argyle Centre Phase 1, 688 Nathan Road, Mongkok, Kowloon
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