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Case report

Sulfite oxidase deficiency – An unusual late and mild presentation

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Abstract

Introduction: Sulfite oxidase deficiency (SOD) is an autosomal recessive inherited disease usually presenting in the neonatal period with severe neurological symptoms including seizures, often refractory to anticonvulsant therapy, and a rapidly progressive encephalopathy resembling neonatal hypoxic ischemia, with premature death. Most patients develop dislocated ocular lenses. Later or milder presentations of SOD are being reported with increasing frequency. These presentations include neurological regression with loss of previously acquired milestones or movement disorders. *Case report:* We report a four years old girl presenting with intermittent ataxia and uncoordinated limb movements. A similar episode of ataxia had occurred previously, one year before, with complete neurologic recovery and normal developmental milestones. Bilateral lens dislocation had been recently diagnosed. Cranial MRI demonstrated bilateral globus pallidus enhancement. Low homocysteine was found in plasma and Sulfitest^{R} was positive. Further investigations led to confirmation of isolated sulfite oxidase deficiency with no enzyme activity detected on skin fibroblasts culture. *Discussion:* This case illustrates the clinical variability of SOD and it is not only atypical but also seems to be the mildest form described so far. The association of ectopia lentis with a movement disorder, even without psychomotor regression, should prompt us to look for this diagnosis.

Keywords: Sulfite oxidase; Homocysteine; Ectopia lentis; Globus pallidus; Ataxia

1. Introduction

Sulfite oxidase is an enzyme in the terminal pathway of sulfur aminoacid degradation. Isolated sulfite oxidase deficiency (SOD) or deficiency of molybdenum, its cofactor (MoCoD), are autosomal recessive inherited diseases, usually with neonatal onset presenting with seizures often refractory to anticonvulsant therapy, axial hypotonia and limb hypertonicity and a rapidly progressive encephalopathy leading to a state resembling that of neonatal hypoxic ischemia. Most patients develop microcephaly, feeding difficulties and dislocated ocular lenses. A few patients present with a milder late onset form of the disease with dystonia and developmental regression [1–3].

Biochemical features of the isolated form include increased urinary excretion of sulfite, thiosulfate, taurine and S-sulfocysteine and low plasma cystine and homocysteine. Urinary excretion of xanthine and hypoxanthine is normal, and so is uric acid, unlike the combined deficiency of sulfite and xanthine oxidase seen in MoCoD (Fig. 1) [1–3].

The pathogenesis of neurotoxicity is not completely understood but could comprise the accumulation of glutamate, an excitotoxic neurotransmitter, due to the

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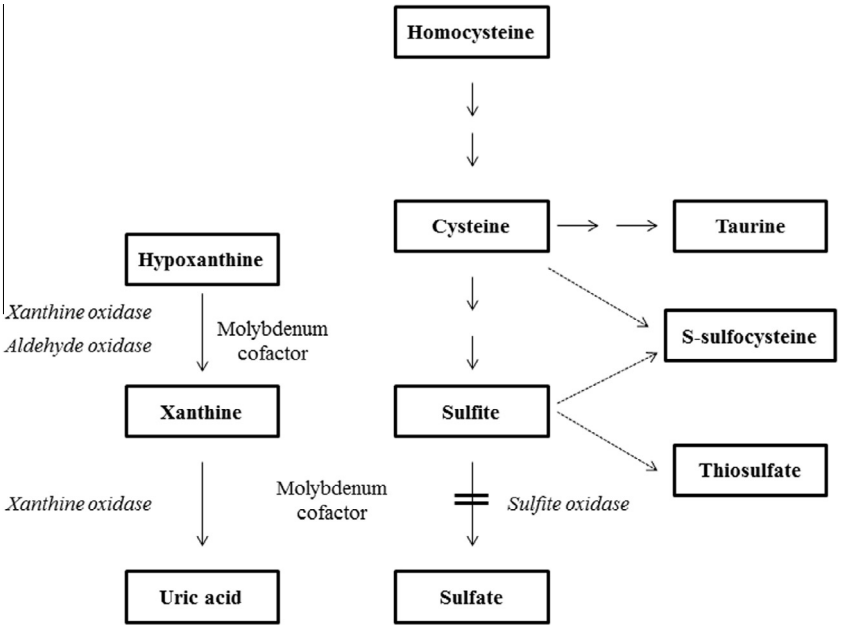

Fig. 1. Metabolic pathway of cysteine and xanthine metabolism.

combined inhibition of glutamate dehydrogenase (GDH) and possibly alfa-ketoglutarate dehydrogenase by sulfites [4].

We report the mildest presentation form described so far, with normal psychomotor development and recurrent episodes of ataxia.

2. Case report

This four-year-old girl was the second born, after a full term pregnancy and a normal delivery. Her birth weight was 3350 g, and the Apgar score was 9 and 10, at one and five minutes, respectively. The neonatal course was uneventful. The family history was unremarkable and there was no consanguinity.

Growth, including head circumference, and psychomotor development were normal, except for a mild delay of walking at 18 months. At 12 months of age, she presented with acute hypotonia, lasting a few hours. Neurological examination was normal and toxic screening was negative. At three years, after a common flu, she had a 24 h period of ataxia of which she recovered completely. Basic metabolic and a second toxic screening were negative.

At the age of four, three months after being diagnosed with bilateral lens subluxation, she was hospitalized because of persistent vomiting and moderate dehydration. On the second day in hospital, she suddenly presented with axial and limb ataxia and erratic eye and limb movements. Over the next few days, residual generalized hypotonia, trunk and gait ataxia were observed as well as two episodes of agitated behaviour, worsening of gait ataxia and choreic movements of lower limbs. She subsequently remained well except for slight truncal ataxia that subsided gradually. No further episodes were observed over the next thirteen months.

Her head circumference is on the 50th percentile and a formal psychomotor evaluation performed later on showed just some difficulties on gross motor skills.

CT-scan was normal and lumbar puncture showed normal pressure, no lymphocytes and no biochemical abnormalities. EEG was normal. The blood cell count, glucose, electrolytes, calcium, phosphate, pH, gases, ammonia and lactate were within normal ranges but plasma total homocysteine was extremely low (0,6 mol/L, normal values >4 mol/L), and uric acid was in the lower limit of reference values.

The diagnosis of SOD/MoCoD was suspected considering the context of dislocated lenses, a movement disorder and a very low homocysteine.

Urinary Sulfitest^{R} was performed and was positive. Plasma aminoacids revealed high levels of sulfocysteine (14 mol/L, RV: 0–0,1) and very low cysteine (5 mol/L, RV: 18–122). Urinary excretion of sulfocysteine was also markedly increased (141 mol/mmol creat, RV: 0–0,1), and taurine excretion was also high (280 mol/mmol creat, RV: 17–230). Urinary xanthine and hypoxanthine levels were normal. These findings were consistent with the diagnosis of isolated sulfite oxidase deficiency.

Sulfite oxidase activity in fibroblast culture was undetectable. Molecular analysis of SUOX gene in fibroblasts revealed homozygosity for a previously undescribed mutation on exon 2-c.182T > C-responsible for the replacement of a leucine by a proline at codon 61 (p.Leu61Pro).

Cranial MRI showed bilateral hyperintense signal of globus pallidi, together with a thin corpus callosum and an unusual dilatation of cerebral arteries (Fig. 2).

The patient was treated with a low protein diet and thiamine supplementation.

3. Discussion

Since its first description in 1967, several cases of SOD have been reported, mostly with neonatal onset showing tone abnormalities and refractory seizures mimicking hypoxic-ischemic encephalopathy, with a fatal course within few years [1–4]. Rare milder and later presentations have been described [5–7], characterized by a prominent movement disorder, usually with seizures and psychomotor regression or delay.

The quantification of plasma total homocysteine has been previously proposed as a simple screening test for this disorder (as the dipstick sulphite test may show false negative results) because it was almost undetectable in cases of isolated SOD and MoCoD [1,8–10]. Sulfites react readily with free thiol groups and conjugate with cystine forming sulfocysteine. An analogous reaction occurs with homocysteine, thus depleting plasma total homocysteine (Fig. 1). It was the clue, in this case, together with ectopia lentis, to search for this diagnosis.

The enzyme assay in cultured fibroblasts surprisingly showed undetectable activity but, as postulated before, this assay may be probably not sensitive to detect a residual activity in such mild forms [7].

Apart from the thin corpus callosum and abnormal intensities of globus pallidi, no other gray or white

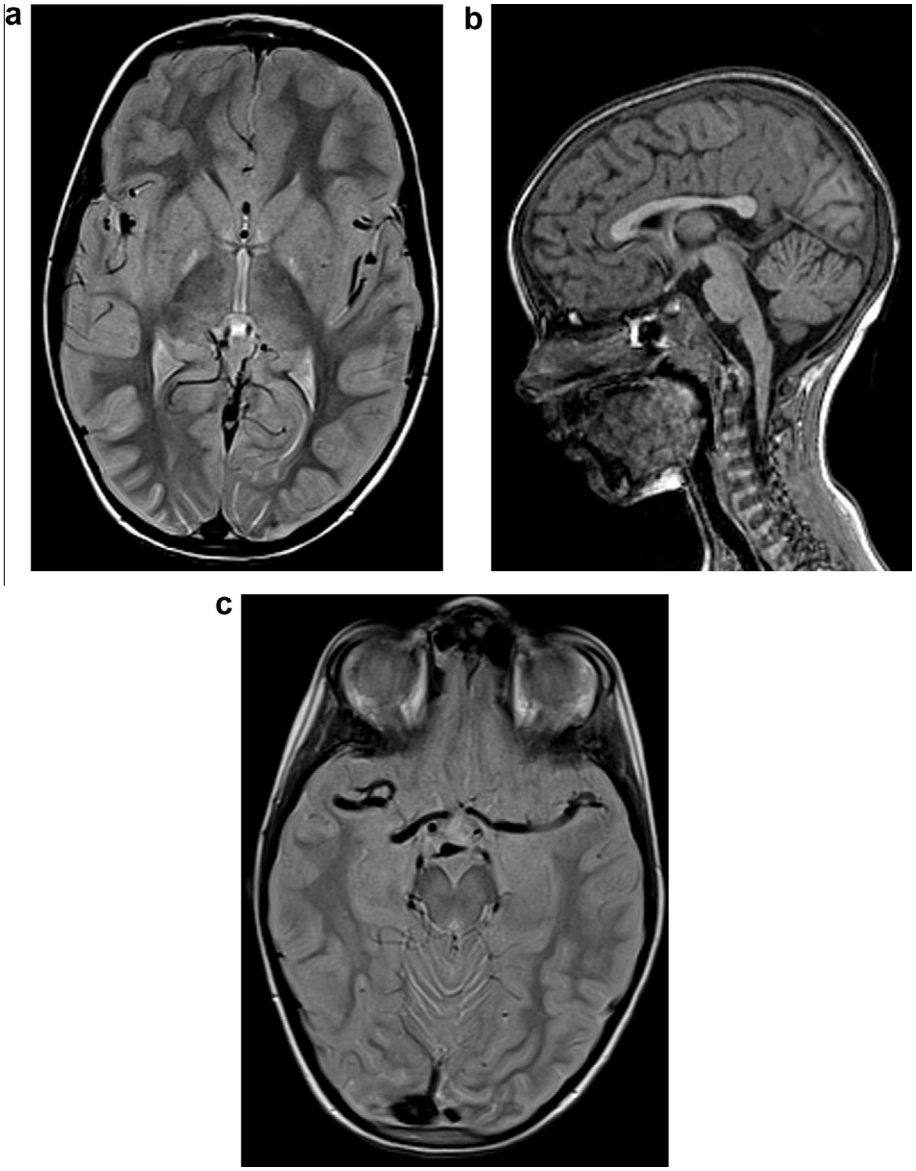

Fig. 2. (a) Axial PD-weighted image shows bilateral hyperintense signal of globus pallidi. (b) Sagittal T1-weighted image, showing a thin corpus callosum. (c) Axial PD-weighted image shows a mild and homogeneous ectasia of both distal internal carotid arteries and middle cerebral arteries.

matter MRI changes typical of the early onset disease, such as cystic lesions, cortical atrophy or cerebellar hypoplasia, were found [6,10,11].

There is previous evidence of a positive clinical and biochemical effect of a low protein diet from natural foods supplemented with a formula without methionine, cysteine and taurine in mild forms of isolated SOD [7]. We do not know if the improvement seen in our patient was related to the low protein diet or to a spontaneous recovery as in the previous episodes.

This case illustrates the phenotypic variability of SOD and also seems to be the mildest clinical form described so far.

The association of *ectopia lentis* with a movement disorder, even without psychomotor regression or epilepsy, should therefore prompt us to look for this diagnosis.

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