

Molybdenum cofactor deficiency in a Malaysian child

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ABSTRACT

Molybdenum cofactor deficiency is a rare autosomal recessive disorder with devastating neurological manifestations, characterised by neonatal-onset encephalopathy mimicking hypoxic-ischaemic insult, intractable seizure, and feeding and respiratory difficulties. It is often fatal in the early life. We report an affected 8-year-old boy, who has presented with severe neurological manifestations since birth, but without clinically-significant seizure. Molybdenum cofactor deficiency must be included in the differential diagnosis of patients presenting with unexplained encephalopathy in the newborn period, and whose neuroimaging findings are consistent with hypoxic ischaemic encephalopathy. The classic laboratory hallmark of this disorder is low serum uric acid, positive urine sulphite dipstick test, and elevated urinary S-sulphocysteine, hypoxanthine and xanthine.

Keywords: molybdenum cofactor deficiency, S-sulphocysteine, uric acid, urine sulphite

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INTRODUCTION

Molybdenum cofactor deficiency (MoCD) is a rare, autosomal recessive inborn error of metabolism, caused by defects in the biosynthesis of molybdenum-complexed pterin cofactor. This results in a combined deficiency of three molybdenum-requiring enzymes: sulphite oxidase, xanthine dehydrogenase and aldehyde oxidase. Affected individuals typically display severe neurological dysfunction, resembling ischaemic encephalopathy in the newborn period or early infancy. The prognosis is generally poor, with few surviving beyond infancy.⁽¹⁻³⁾ We report an eight-year-old boy with severe neurological manifestations but had a prolonged survival.

CASE REPORT

An eight-year-old boy, born at term to a healthy non-consanguineous Malay couple following an uncomplicated pregnancy, with a birth weight of 3.4 kg, length of 50 cm and head circumference of 33 cm, is the

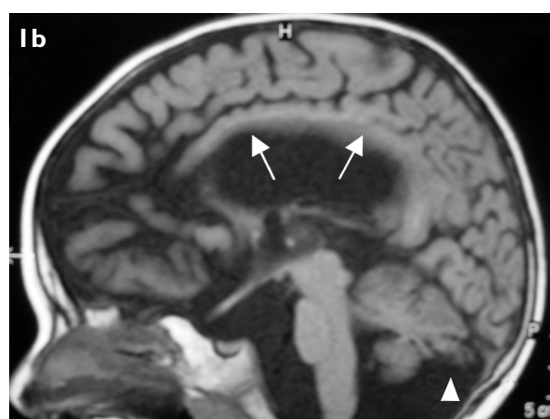
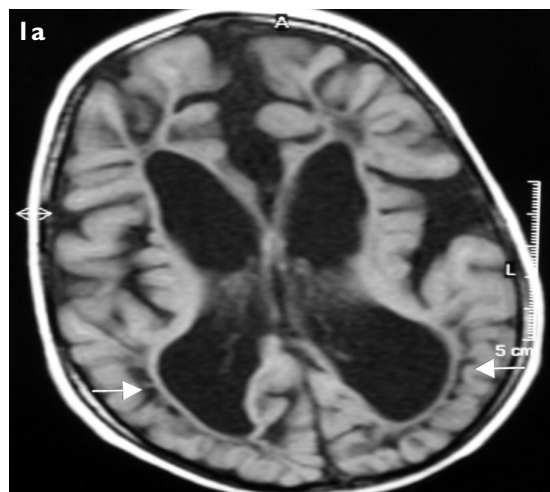


Fig. 1 (a) Axial T1-W image of the brain shows diffuse cerebral atrophy, lateral ventricles dilatation and multiple subcortical cystic cavities (arrows). (b) Mid-sagittal T1-W image shows a very thin corpus callosum (arrows) and hypoplastic cerebellum (arrowhead).

eighth of nine children. There were two unexplained early infantile deaths in the family. The infant was discharged home on the second day of life. He was readmitted on the third day for being inactive with poor sucking. He was treated for presumed neonatal meningitis though cerebrospinal fluid biochemistry and cultures were non-supportive. Incidentally, a coarctation of the aorta was detected, and was corrected later at five months of age. His developmental milestone was globally delayed. He had significant feeding difficulties due to poor sucking and swallowing incoordination, which led to multiple episodes of aspiration, and he finally ended up with Ryle's tube feeding.

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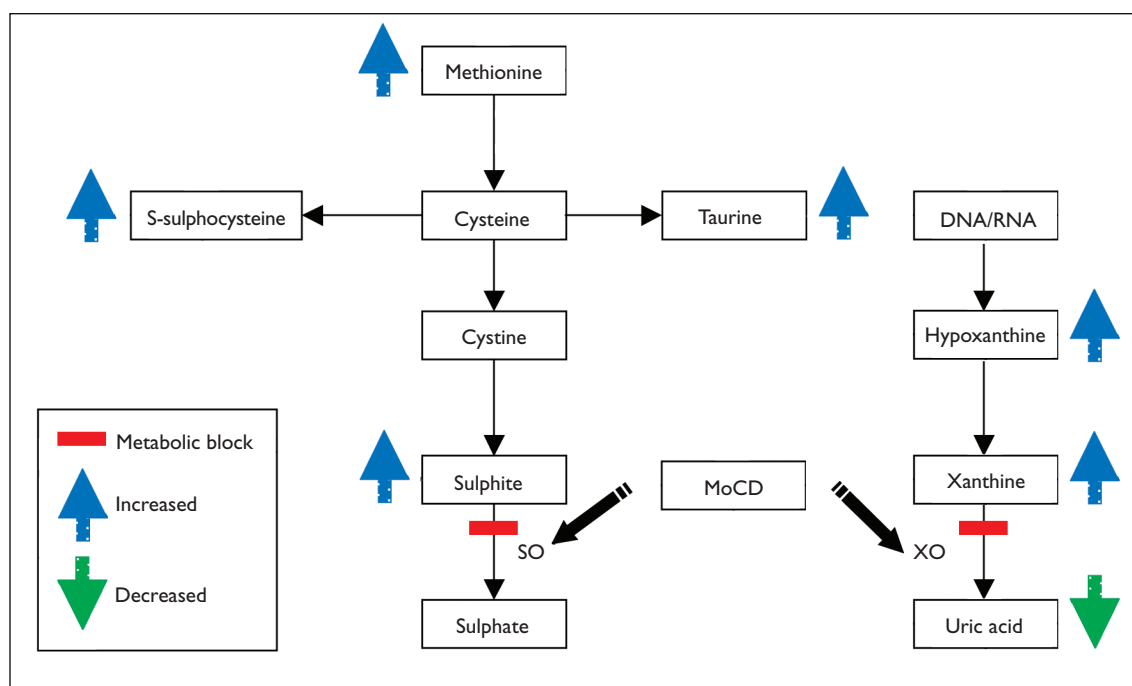
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Table I. Metabolic investigation results of the patient.

Metabolic test	Result	Normal values
Serum uric acid ($\mu\text{mol/L}$)	34	120–320
Urinary uric acid ($\mu\text{mol/mmol creatinine}$)	98.1	117 \pm 188
Urinary xanthine ($\mu\text{mol/mmol creatinine}$)	237.9	40.1 \pm 51.1
Urinary hypoxanthine ($\mu\text{mol/mmol creatinine}$)	530.0	49.3 \pm 48.5
Urinary sulphite	positive	Not detected
Urinary s-sulphocysteine ($\mu\text{mol/mmol creatinine}$)	118	< 43
Plasma methionine ($\mu\text{mol/L}$)	78.9	5–32
Plasma taurine ($\mu\text{mol/L}$)	177.1	11–93

**Fig. 2** Chart shows the metabolic pathways affected by molybdenum cofactor deficiency.

SO: sulphate oxidase; XO: xanthine oxidase; MoCD: molybdenum cofactor deficiency

When the molybdenum cofactor is deficient, the enzyme activities of SO and XO will be decreased or absent. Decreased SO activity will disturb the catabolism of the sulphur amino acids and result in the accumulation of sulphite, methionine and S-sulphocysteine in the patient's body fluids. Decreased XO activity will cause a reduction in the conversion of hypoxanthine and xanthine to form uric acid.

The patient was first presented to us at almost five years of age. He was unable to sit without support, was only able to vocalise non-specifically, and was not able to follow or grasp objects. He had poor visual contact although ophthalmological assessment revealed no structural abnormalities. His weight, length, and head circumference were all below the third percentile. He was not dysmorphic. The neurological examination revealed axial hypotonia but hypertonicity of the four limbs. Magnetic resonance imaging of his brain showed a diffuse atrophy with multiple cystic cavities in the cerebral hemispheres (Fig. 1). His electroencephalogram showed a diffuse slowing of background activity, but there was no associated epileptiform discharges.

All routine laboratory investigations were normal except for a persistently low serum uric acid. This

led us to perform a urinary sulphite strip test on a freshly-voided urine sample, which demonstrated a strongly-positive reaction. Specialised tests were subsequently performed, and revealed elevated urinary S-sulphocysteine and disturbed purine metabolism with elevated urinary xanthine and hypoxanthine but low uric acid (Table I). Thus, the diagnosis of MoCD was confirmed (Fig. 2). He was given a trial low protein diet, including a synthetic amino acid mixture without cystine and methionine, but no clinical benefit was observed. He was last seen at eight years of age.

DISCUSSION

MoCD was first described by Duran et al in 1978.⁽⁴⁾ Since then, more than 100 patients have been diagnosed worldwide.⁽²⁾ Affected infants normally come to clinical

attention soon after birth because of neurological symptoms such as intractable seizures, exaggerated startle reactions, alterations in muscle tone, progressive encephalopathy, and feeding and respiratory difficulties. Neuroradiological findings mimicking hypoxic-ischaemic changes usually develop as the disease progresses. Those who survive the early years are invariably severely handicapped and may develop non-neurological complications such as lens dislocation and urinary calculi.⁽¹⁻³⁾ Our patient presented with all the described neurological manifestations, except that there was no clinically significant seizure for a reason that is unknown to us.

Among the three molybdenum cofactor-dependent enzymes, sulphite oxidase deficiency possibly contributes most significantly to the brain injuries, through the accumulation of sulphite, a neurotoxic metabolite.⁽²⁾ Deficiency of xanthine oxidase causes lens dislocation and urinary calculi, but otherwise probably contributes little to the neuropathology. Deficiency of aldehyde oxidase has no known clinical consequence. Isolated sulphite oxidase deficiency can present with similar neurological phenotype as MoCD. The differentiation between MoCD and isolated sulphite oxidase deficiency can be made based on biochemical findings – low plasma uric acid, high urine xanthine and hypoxanthine are seen in MoCD, while normal plasma uric acid, urine xanthine and hypoxanthine levels are found in isolated sulphite oxidase deficiency.⁽⁵⁾

MoCD is possibly under-diagnosed. Although there is no effective treatment for the severely-affected patients, some measures such as a restriction on the intake of the precursor sulphur amino acids and appropriate anticonvulsant therapy may benefit patients with a milder clinical picture. In addition, diagnosis is important for genetic counselling and prenatal diagnosis

in subsequent pregnancies. Therefore, we suggest that these disorders should be considered in all children with unexplained neurological symptoms, with or without intractable seizures. The urine sulphite dipstick test is a useful and very simple screening tool for both disorders. Fresh urine must be used since sulphite is rapidly destroyed by oxidation at room temperature.⁽⁶⁾ However, one needs to be aware that although it is useful, there are many false positives and false negatives associated with the urinary dipstick test. Therefore, additional biochemical tests, including analyses of the urinary S-sulphocysteine and purine metabolites, are required to confirm the diagnosis. Biosynthesis of molybdenum cofactor in humans require the products of at least four genes: molybdenum cofactor synthesis (*MOCS*) 1 (gene map locus 6p21.3), *MOCS2* (5q11), *MOCS3* (20q13.13), and *GEPH* (14q23.3). To date, disease-causing mutations have been identified in *MOCS1*, *MOCS2* and *GEPH*.⁽⁷⁾

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