

4. Deputy SR, Tilton AH: New-onset headache in an adolescent with MASS syndrome. *Semin Pediatr Neurol* 1999;6:177–181.
5. Diaz JH: Epidemiology and outcome of postural headache management in spontaneous intracranial hypotension. *Reg Anesth Pain Med* 2001; 26:582–587.
6. Fukutake T, Sakakibara R, Mori M, et al: Chronic intractable headache in a patient with Marfan's syndrome. *Headache* 1997;37:291–295.
7. Kroin JS, Nagalla SKS, Buvanendran A, et al: The mechanisms of intracranial pressure modulation by epidural blood patch and other injectates in a postdural puncture rat model. *Anesth Analg* 2002;95:423–429.
8. Davenport RJ, Chataway SJS, Warlow CP: Spontaneous intracranial hypotension from a CSF leak in a patient with Marfan's syndrome. *J Neurol Neurosurg Psychiatry* 1995;59:516–519.

Molybdenum Cofactor Deficiency Presenting With Severe Metabolic Acidosis and Intracranial Hemorrhage

ABSTRACT

Molybdenum cofactor deficiency leads to combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase enzyme activities. The major clinic symptom is intractable seizures seen soon after birth. No definite therapy is available. We report here a newborn with molybdenum cofactor deficiency–associated Dandy-Walker malformation who presented with severe lactic acidosis and intracranial hemorrhage. (*J Child Neurol* 2004; 19:155–157).

Molybdenum cofactor deficiency is an autosomal recessive metabolic disorder.¹ The molybdenum cofactor is essential for the function of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase enzymes.² Molybdenum cofactor deficiency can occur owing to mutation at either of the two separate steps in the formation of molybdenum cofactor. *MOCS1* encodes two enzymes for the synthesis of the precursor (complementation group A). The conversion of the precursor into the organic moiety of molybdenum cofactor is catalyzed by molybdopterin synthase (*MOCS2*). *MOCS2* is defective in patients with complementation group B deficiency. In addition, a third type of molybdenum cofactor deficiency, type C, is caused by mutation in the *gephyrin* gene. However, the phenotype is identical in all complementation groups.³

The most common clinical symptoms are neonatal intractable seizures and feeding difficulties. Biochemically, there are decreased uric acid levels in serum and increased excretion of sulfite, thiosulfate, *S*-sulfocysteine, taurine, xanthine, and hypoxanthine in urine.⁴ Brain computed tomography (CT) and magnetic resonance imaging (MRI) can show multicystic leukomalacia involving both the gray matter and the white matter while preserving the brainstem.^{5,6} A definite diagnosis of molybdenum cofactor deficiency is based on a sulfite dipstick test and absent sulfite oxidase activity in either skin or liver fibroblast culture.^{4,7}

Prenatal diagnosis of molybdenum cofactor deficiency is possible by demonstration of either sulfite oxidase deficiency in a chorionic villus sample or an increased *S*-sulfocysteine level in the amniotic fluid.^{8,9} The amniotic fluid uric acid level is not helpful in the prenatal diagnosis.⁸ Although there is no definite therapy, dietary methionine restriction, cysteine and sulfate supplementation, and low sulfur-containing amino acids can be used for treatment that does not change neurodevelopmental outcome and prognosis.¹⁰ If these patients survive beyond the neonatal period, they suffer

severe psychomotor retardation and intractable seizures caused by progressive cerebral degeneration.⁶

We report here a newborn with molybdenum cofactor deficiency associated with Dandy-Walker malformation who presented with severe lactic acidemia and intracranial hemorrhage.

Case Report

A female infant was born at term as the product of the third pregnancy of a 34-year-old mother. The patient was transferred to our hospital on her second day of life owing to feeding difficulty. The prenatal history was unremarkable. The parents of the patient were first cousins. She had one healthy brother and sister. Although her birthweight and length were in the normal ranges for gestational age, her head circumference was above the 90th percentile.

On physical examination, hypotension, tachypnea, grunting, cyanosis, a coarse face appearance, and hypotonia were identified. Newborn reflexes were absent. An ophthalmologic examination was normal. On laboratory examination, complete blood count, blood glucose, routine urinalysis, renal and liver function tests, serum proteins and lipids, coagulation tests, ammonium, pyruvate, and blood and urine amino acid analysis were within normal limits. Reducing substance and ketone were negative in the urine, as were serum ketones. She had severe metabolic acidosis and hypoxia (pH 6.8, HCO₃ 4.3 mmol/L, base excess –25 mEq/L, PO₂ 38 mm Hg, saturated PO₂ 57%, PCO₂ 95 mm Hg). Serum lactate levels were elevated (157 mg/dL, normal range < 14 mg/dL). Urine organic acid analysis revealed lactic acidosis. The serum uric acid level was very low (0.3 and 0.07 mg/dL). Cardiac enzyme levels were increased (creatinine phosphokinase–myocardial band 76.9 ng/mL, normal range 0–5 ng/mL; troponin-t 3 ng/mL, normal range 0–0.1 ng/mL). Chest radiography demonstrated cardiomegaly. An electrocardiogram (ECG) revealed ST segment elevation, and echocardiography demonstrated decreased myocardial contractility (ejection fraction of 30%). Renal ultrasonography was normal.

The patient was put on mechanical ventilation. On the fourth hour of her admission, a tonic-clonic seizure developed. Phenytoin was initiated, and then phenobarbital, pyridoxine, folic acid, and corticosteroid were added to control the seizure. Finally, the patient responded well to intravenous infusion therapy of midazolam. An EEG showed bioelectrical silence. On the ninth hour of hospitalization, peritoneal dialysis was initiated owing to refractory acidosis. The peritoneal dialysis resulted in normalization of acid-base balance within 2 days of initiation of treatment. Cranial ultrasonography on the fifth day of life demonstrated dilatation of the lateral ventricles and intraventricular hemorrhage. Cranial CT on the eighth day of life revealed Dandy-Walker variant, corpus callosum hypogenesis, hemorrhages in the lateral ventricles and parenchyma, and diffuse cystic cavities involving the temporal and parietal lobes bilaterally (Figure 1). Cranial MRI 3 weeks after cranial CT demonstrated hypoplasia of the cerebellum, Dandy-Walker malformation, corpus callosum hypogenesis, dilated lateral and third ventricles, and intraventricular and intraparenchymal subacute hemorrhages in the right temporal and bilateral parietal lobes. In addition, hyperintensities in the basal ganglia on T₂-weighted images and diffuse cystic changes in the cerebral white matter bilaterally without intrinsic signal abnormality of the brainstem were identified (Figure 2). At this time, intrauterine and postnatal asphyxia were thought to result in the constellation of findings of intracranial hemorrhages, cystic changes of the cerebral hemispheres, bioelectrical silence on EEG, lactic acidosis, and cardiac failure. The urine sulfite dipstick test was positive for sulfite reaction. Urine thiosulfate level was increased at 410 mmol/mol creatinine (normal range < 115 mmol/mol creatinine). An extremely low plasma uric acid level and a positive urinary sulfite dipstick test suggested the diagnosis of molybdenum cofactor deficiency. The diagnosis was confirmed by the finding of decreased sulfite oxidase activity in skin fibroblast culture.

The patient was discharged on her 35th day of life. Cranial CT was performed 2 months later, which demonstrated severe triventricular hydrocephalus, diffuse cystic changes throughout the cerebral hemispheres with severe parenchymal destruction, and cerebral atrophy. Unfortunately, the patient suffered severe feeding difficulties and motor and mental retardation and died of pneumonia at 4 months of age.

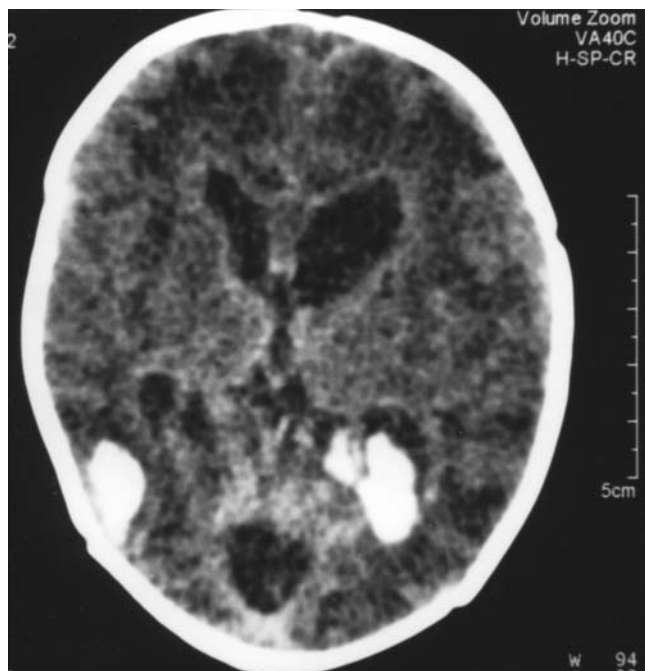


Figure 1. Unenhanced brain computed tomographic image demonstrating an acute intraparenchymal hemorrhage in the right temporal lobe and an intraventricular hemorrhage in the occipital horn of the left lateral ventricle. There is also extensive encephalomalacia throughout the cerebral hemispheres bilaterally.

Discussion

Molybdenum cofactor is necessary for the activity of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase enzymes.¹ When molybdenum cofactor is deficient, all three enzyme activities are decreased or absent. The clinical and laboratory findings were consistent with sulfite oxidase and xanthine dehydrogenase deficiency in our patient. However, an isolated enzyme deficiency can also occur in these patients. In the isolated sulfite oxidase deficiency, there are increased levels of sulfite, sulfocysteine, taurine, and thiosulfate in the urine, whereas the blood uric acid level remains normal.¹¹ In xanthine dehydrogenase deficiency, hematuria is the first renal sign, whereas renal stones, xanthine deposits in the muscle, xanthinuria, and hypouricemia are observed without accompanying symptoms.¹²

A history of perinatal hypoxia can result in the mistaken diagnosis of hypoxic-ischemic encephalopathy.⁶ In fact, there can be severe neurologic manifestations that resemble anoxic encephalopathy, leading to further misinterpretation.¹² In our patient, there were severe clinical and laboratory findings of hypoxia, including respiratory distress, severe acidosis, cardiac failure, seizure, bioelectrical silence, and intracranial hemorrhage. However, very low levels of serum uric acid level and intractable seizures were highly suggestive of molybdenum cofactor deficiency, which was confirmed by skin fibroblast culture.

Topcu et al. reported three infants with the diagnosis of molybdenum cofactor deficiency who presented with the incorrect initial diagnosis of hypoxic-ischemic encephalopathy.¹³ They proposed that molybdenum cofactor deficiency should be included in the theoretical differential diagnosis of patients presenting with intractable seizures in the newborn period who have CT and MRI findings akin to hypoxic-ischemic encephalopathy.

The encephalopathy symptoms are related to sulfite metabolites, especially *S*-sulfocysteine and thiosulfate.^{6,14} Sulfite might damage mitochondrial function, either directly via disruption of membrane integrity or indirectly by interfering with the tricarboxylic acid cycle.¹⁴ Uric acid is a potent antioxidant and a normal product of this cycle. However, if uric acid levels decrease in the blood, reactive oxyradicals can accumulate and contribute to neurologic injury (a characteristic of molybdenum cofactor deficiency)^{13,14}.

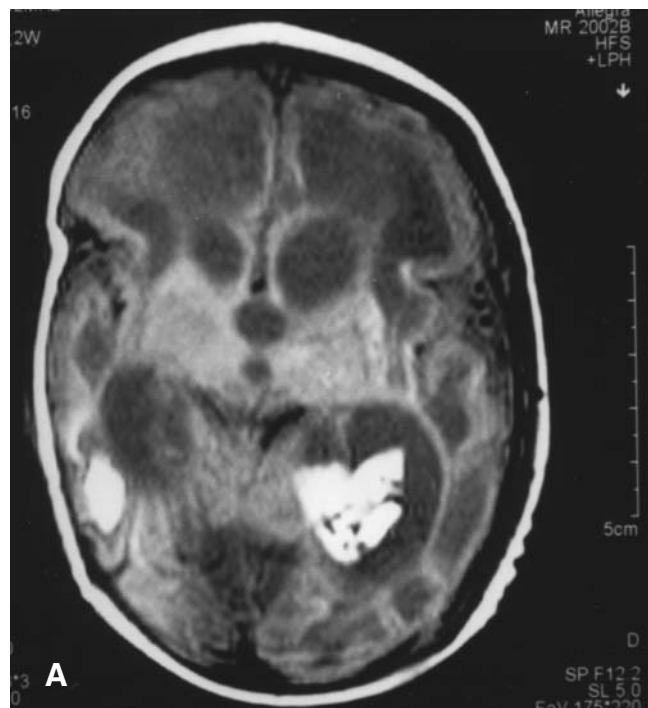


Figure 2. A, Axial T₁-weighted magnetic resonance image demonstrating subacute intraparenchymal hemorrhages in the right temporal lobe and an intraventricular hemorrhage within the occipital horn of the left lateral ventricle. Extensive cystic encephalomalacia is also noted throughout the cerebral hemispheres bilaterally. B, Sagittal T₁-weighted magnetic resonance image demonstrating cystic dilatation of the posterior fossa with vermian hypoplasia and hypoplasia of the corpus callosum.

The typical imaging findings in molybdenum cofactor deficiency are cystic changes, particularly located in the subcortical region, with associated parenchymal loss and atrophy.¹³ Other findings include dilated ventricles, severe volume loss of the basal ganglia (particularly the caudate nucleus), and atrophy of the corpus callosum, which can also occur in the setting of

hypoxic-ischemic encephalopathy.⁵ Our patient's CT and MRI findings were also similar to the findings observed in asphyxiated term infants with hypoxic-ischemic encephalopathy. However, to our knowledge, the findings of intraventricular hemorrhages, intraparenchymal hemorrhages, and diffuse cystic changes throughout the brain have not been reported previously in patients with molybdenum cofactor deficiency, although molybdenum cofactor deficiency associated with Dandy-Walker variant has been reported in a few patients.^{2,13,15}

Impaired platelet aggregation secondary to acidosis can be a factor in perinatal intracerebral hemorrhage.¹⁶ The degree of hypoxia and other factors, such as hypotension and hypercarbia, affecting cerebral blood flow are also important in the pathogenesis of cerebral damage in perinatal hypoxia.¹⁷ Also, Bakkeren et al reported excessive excretion of lactic acid in the urine of two premature newborns with severe respiratory distress and cerebral hemorrhages.¹⁸ That study suggested that an abnormal urinary organic acid excretion pattern was probably caused by severe tissue hypoxia.

Lactic acidosis is an uncommon feature of molybdenum cofactor deficiency. Kang et al reported infants with molybdenum cofactor deficiency who had elevated lactate levels in the blood and cerebrospinal fluid.¹⁹ In our patient, initially, the lactic acidosis was considered to be secondary to severe hypoxia. However, it is understood that the lactic acidosis was most likely due to molybdenum cofactor deficiency. Salvan et al found that the parieto-occipital area was characterized by accumulation of lactate in brain proton magnetic resonance spectroscopy in a 20-day-old infant with molybdenum cofactor deficiency.²⁰ The presence of a prominent lactic acid peak in proton magnetic resonance spectroscopy can be suggestive for the development of cavitations in cerebral hemispheres. However, severe seizures can also be the underlying factor leading to elevated lactate levels. Therefore, it is difficult to differentiate the primary reason of the lactic acidosis because our patient had intractable seizures.

In conclusion, hypoxic-ischemic encephalopathy is not necessarily the sole cause of diffuse intraparenchymal cystic changes that can be associated with intracranial hemorrhages because molybdenum cofactor deficiency is another potential etiology of these findings albeit less common. Therefore, molybdenum cofactor deficiency should be included in the differential diagnosis in a newborn who presents with early intractable seizures, hypouricemia, and diffuse intraparenchymal cystic changes that are associated with intracranial hemorrhages on imaging studies.

Ozlem Teksam, MD
Murat Yurdakok, MD
Turgay Coskun, MD
Department of Pediatrics
Division of Neonatology
Hacettepe University School of Medicine
Ihsan Dogramaci Children's Hospital
Ankara, Turkey

Received Aug 1, 2003. Received revised Jan 26, 2004. Accepted for publication Feb 10, 2004.

Address correspondence to Dr Ozlem Teksam, Department of Pediatrics, Division of Neonatology, Hacettepe University School of Medicine, Ihsan Dogramaci Children's Hospital, Sıhhiye/Ankara 06100, Turkey. Tel: +90 312 3051390; fax: +90 312 3105509; e-mail: oteksam@yahoo.com.

References

- Johnson JL, Wadman SK: Molybdenum cofactor deficiency, in Scriver CR, Beaudet AL, Sly WS, Valle D (eds): *The Metabolic Basis of Inherited Disease*. New York, McGraw-Hill, 1995, 2271–2281.
- Pintos-Morell G, Naranjo MA, Artigas M, et al: Molybdenum cofactor deficiency associated with Dandy-Walker malformation. *J Inherit Metab Dis* 1995;18:86–87.
- Shalata A, Mandel H, Dorche C, et al: Prenatal diagnosis and carrier detection for molybdenum cofactor deficiency type A in northern Israel using polymorphic DNA markers. *Prenat Diagn* 2000;20:7–11.
- van Gennip AH, Abeling NG, Stroemer AE, et al: The detection of molybdenum cofactor deficiency: Clinical symptomatology and urinary metabolite profile. *J Inherit Metab Dis* 1994;17:142–145.
- Schuijter G, Kurlmann G, Bick U, Stephani U: Molybdenum-cofactor deficiency: CT and MR findings. *Neuropediatrics* 1995;26:51–54.
- Kavukcu S, Soylu A, Sahin B, et al: Clinical quiz. Molybdenum cofactor deficiency. *Pediatr Nephrol* 2000;14:1145–1147.
- Endres W, Shin YS, Gunther R: Report on a new patient with combined deficiencies of sulphite oxidase and xanthine dehydrogenase due to molybdenum cofactor deficiency. *Eur J Pediatr* 1988;148:246–249.
- Gray RG, Green A, Basu SN, et al: Antenatal diagnosis of molybdenum cofactor deficiency. *Am J Obstet Gynecol* 1990;163:1203–1204.
- Johnson JL, Rajagopalan KV, Lanman JT, et al: Prenatal diagnosis of molybdenum cofactor deficiency by assay of sulphite oxidase activity in chorionic villus samples. *J Inherit Metab Dis* 1991;14:932–937.
- Boles RG, Ment LR, Meyn MS, et al: Short-term response to dietary therapy in molybdenum cofactor deficiency. *Ann Neurol* 1993;34:742–744.
- Coskun T, Yetuk M, Yurdakok M, Tekinalp G: Blood uric acid as a pointer to the diagnosis of molybdenum cofactor deficiency. *Acta Paediatr* 1998;87:714–715.
- Arnold GL, Greene CL, Stout JP, Goodman SI: Molybdenum cofactor deficiency. *J Pediatr* 1993;123:595–598.
- Topçu M, Coskun T, Haliloglu G, Saatci I: Molybdenum cofactor deficiency: Report of three cases presenting as hypoxic-ischemic encephalopathy. *J Child Neurol* 2001;16:264–270.
- Olney JW, Misra CH, de Gubareff T: Cysteine-S-sulphate: Brain damaging metabolite in sulfite oxidase deficiency. *J Neuropathol Exp Neurol* 1975;34:167–177.
- Arslanoglu S, Yalaz M, Goksen D, et al: Molybdenum cofactor deficiency associated with Dandy-Walker complex. *Brain Dev* 2001;23:815–818.
- Foley ME, McNicol GP: An in-vitro study of acidosis, platelet function, and perinatal cerebral intraventricular haemorrhage. *Lancet* 1977;1:1230–1232.
- Karch D: Hypoxia during the perinatal period and the formation of cerebral lesions. *Klin Wochenschr* 1982;60:1427–1434.
- Bakkeren JA, Sengers RC, Trijbels JM, Engels PH: Organic aciduria in hypoxic premature newborns simulating an inborn error of metabolism. *Eur J Pediatr* 1977;127:41–47.
- Kang PB, Hunter JV, Kaye EM: Lactic acid elevation in extramitochondrial childhood neurodegenerative diseases. *J Child Neurol* 2001;16:657–660.
- Salvan AM, Chabrol B, Lamoureux S, et al: In vivo brain proton MR spectroscopy in a case of molybdenum cofactor deficiency. *Pediatr Radiol* 1999;29:846–848.

Topiramate-Valproate-Induced Hyperammonemic Encephalopathy Syndrome: Case Report

ABSTRACT

A 15-year-old boy with inverted duplication of chromosome 15 was admitted for acute onset of irritability, increasing sleepiness, and worsening of seizures. He had been on valproate and other anti-convulsants. However, he was found to have hyperammonemia within 2 weeks after the addition of low-dose topiramate to valproate. He recovered within 7 days after discontinuation of valproate. Topiramate was tailed off. The reintroduction of valproate monotherapy caused hyperammonemia again without clinical features of encephalopathy. He also developed anticonvulsant hypersensitivity syndrome following the use of phenytoin. We propose the term topiramate-valproate-induced hyperammonemic encephalopathy