

Molybdenum Cofactor Deficiency: Report of Three Cases Presenting as Hypoxic-Ischemic Encephalopathy

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ABSTRACT

We report three infants with the diagnosis of molybdenum cofactor deficiency. The key findings leading to diagnosis were neonatal seizures unresponsive to treatment, craniofacial dysmorphic features, hyperexcitability, low blood uric acid levels, and neuroimaging findings. The parents were consanguineous in two of these patients. The diagnosis was established by the presence of low blood uric acid levels, positive urine sulfite reaction, quantitative aminoacid analysis, and high-voltage electrophoresis of the urine sample showing a typical increase of S-sulfo-L-cysteine. Skin fibroblast cultures confirmed the diagnosis. Magnetic resonance imaging findings were suggestive of encephalomalacia with cystic changes due to hypoxic-ischemic encephalopathy. We conclude that molybdenum cofactor deficiency must be included in the differential diagnosis of patients presenting with intractable seizures in the newborn period who have computed tomography and magnetic resonance imaging findings reminiscent of those of hypoxic-ischemic encephalopathy, and the urine sulfite dipstick test can be a part of the evaluation of these infants in neonatal intensive care units. (*J Child Neurol* 2001;16:264–270).

Molybdenum cofactor deficiency is a rare, autosomal-recessive fatal disease, leading to a combined deficiency of the enzymes sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase.^{1,2} Although clinical spectrum may show variations among patients, the main features are neonatal seizures unresponsive to antiepileptic drugs, axial hypotonia, peripheral hypertonicity, lens dislocation, abnormal facial features, feeding difficulties, urinary calculi, and mental retardation.³

Biochemically, there are decreased uric acid levels in serum and increased excretion of sulfite, thiosulphate, S-sul-

focysteine, taurine, xanthine, and hypoxanthine in urine (Figure 1).⁴ Diagnosis is based on a sulfite strip test and absent sulfite oxidase activity in skin or liver fibroblast culture.^{4,5} Prenatal diagnosis may be performed by assay of sulfite oxidase activity in cultured amniotic cells or chorionic villus biopsy.^{6,7} Molybdenum cofactor replacement seems to be ineffective because isolated molybdenum cofactor is unstable. Dietary methionine restriction, cysteine and sulfate supplementation, and low sulfur-containing amino acids can be used for treatment, but, besides having a positive biochemical response, they do not change the neurodevelopmental outcome and prognosis.⁸ Existence of at least two complementation groups, A and B, suggests genetic heterogeneity, and linkage of a *MoCoD* gene to a 8cM region on chromosome 6p21.3 is defined; this can be further used to perform prenatal diagnosis.⁹

CASE REPORTS

Case 1

The patient was a 3.5-month-old male infant who was born following an uncomplicated delivery by cesarean section with a birthweight of 3900 g. Parents were second-degree relatives. In the first hour of life, he developed tonic convulsions of the eyes and upper extremities. He had a computed tomographic (CT) scan showing encephalomalacia with cystic changes that were thought to be

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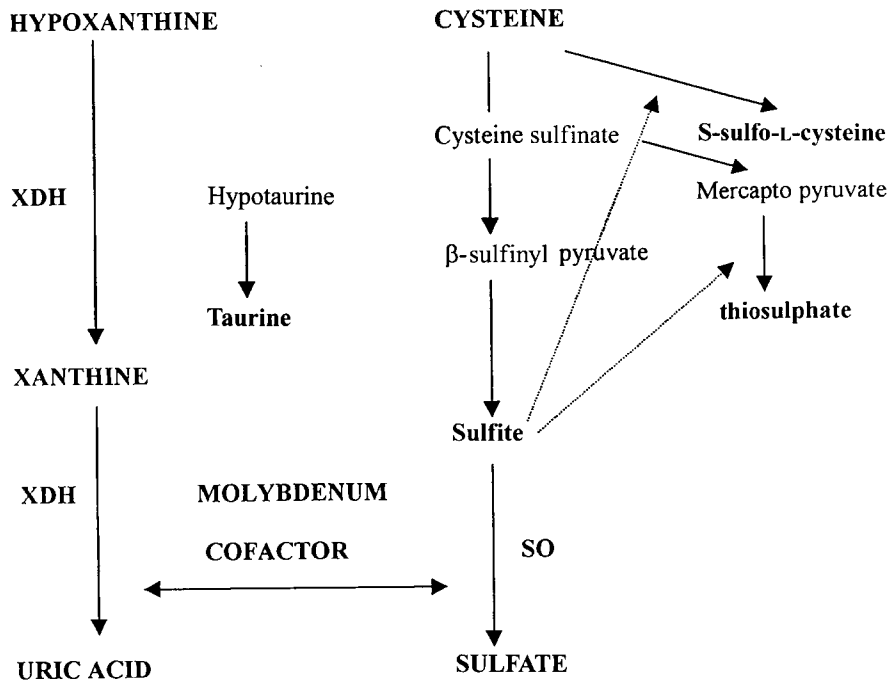


Figure 1. The role of the molybdenum cofactor in the hypoxanthine and cysteine biochemical pathway. XDH = xanthine dehydrogenase, SO = sulfite oxidase.

resulting from intrauterine asphyxia. He was given phenobarbital for his convulsions, but he did not respond well and continued to have especially right-sided tonic convulsions by the first month of age. His electroencephalogram (EEG) at that time showed right-hemisphere central epileptiform focus. He did not respond well to the medication and was referred to our hospital for his continuing convulsions. On his physical examination, the head circumference was 39 cm (10th–25th percentile), and he had a coarse facial appearance, opisthotonus, and hyperexcitability, but lens dislocation was not present (Figure 2). The first magnetic resonance image (MRI), obtained when he was 1 month old, revealed severe cystic changes in the cerebral hemispheres, especially in the subcortical regions (Figures 3, A–C). Some of the cystic areas had well-defined margins with the surrounding parenchyma. Increased T_1 signal



Figure 2. Coarse facial appearance and hypertonicity of the patient (case 1) at the age of 10 months.

intensity was noted in focal areas in the cortex bilaterally, with no specificity in the distribution. The lateral ventricles and the subarachnoid spaces were enlarged. Some extra-axial fluid collection was evident bilaterally (see Figure 3, B and C). The basal ganglia and thalami showed hyperintensity on T_1 -weighted images. Also noted was the increased T_1 signal intensity in the superior sagittal sinus, most likely resulting from slow flow. T_2 -weighted images showed signal void appearance, indicating the presence of flow and eliminating the possibility of thrombus. No abnormal appearance was present in the brain stem or cerebellum, taking the patient's age into consideration. The imaging findings were consistent with those of hypoxic-ischemic encephalopathy. He had blood uric acid levels of 0.29 mg/dL and 0.3 mg/dL (normal blood uric acid level: 2.4–5.7 mg/dL) repeatedly. The sulfite stick test was positive, and the urine thiosulfate level was elevated. Results of skin fibroblast culture confirmed the diagnosis of molybdenum cofactor deficiency. The second MRI was obtained when he was 10 months old (Figure 4). There was marked microcephaly with small cerebral hemispheres due to apparent parenchymal loss. The corpus callosum was markedly thin. The large cystic changes, some with well-defined margins, seemed resolved with the remaining small cystic foci in the subcortical region (see Figure 4, A and B). However, the remaining parenchyma was not normal but showed diffuse increased signal intensity on fluid-attenuated inversion-recovery and T_2 -weighted sequences, probably representing gliosis and de- and/or hypomyelination (see Figures 4, A–C). Myelination had not occurred in the supratentorial region. The gyri were small and atrophic with the appearance of ulegyria. The inferior frontal, anteroinferior temporal, and occipital regions were less affected. The lentiform nuclei were also hyperintense on T_2 -weighted images. The brain stem was spared. There was mild T_2 hyperintensity in the dentate nuclei and cerebellar white matter. The extra-axial fluid collection regressed, although it did not totally resolve (see Figure 4C). The appearance of the superior sagittal sinus had not changed.

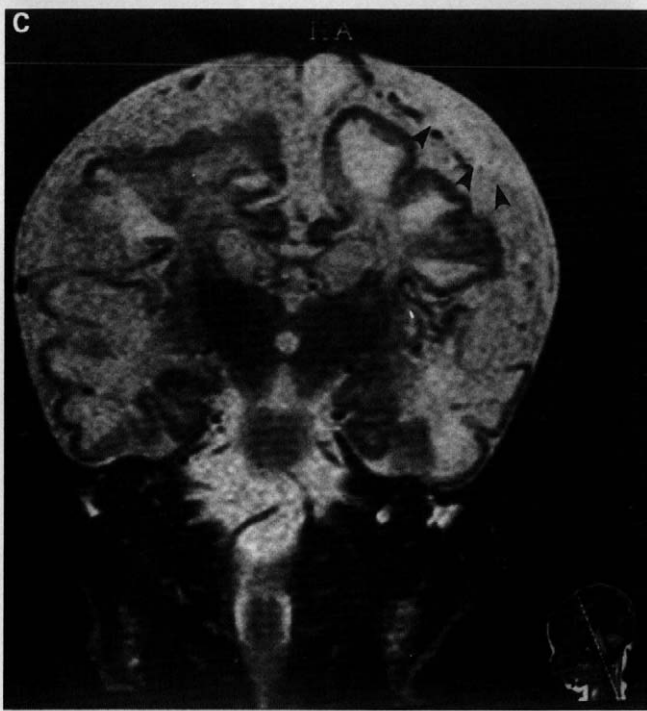
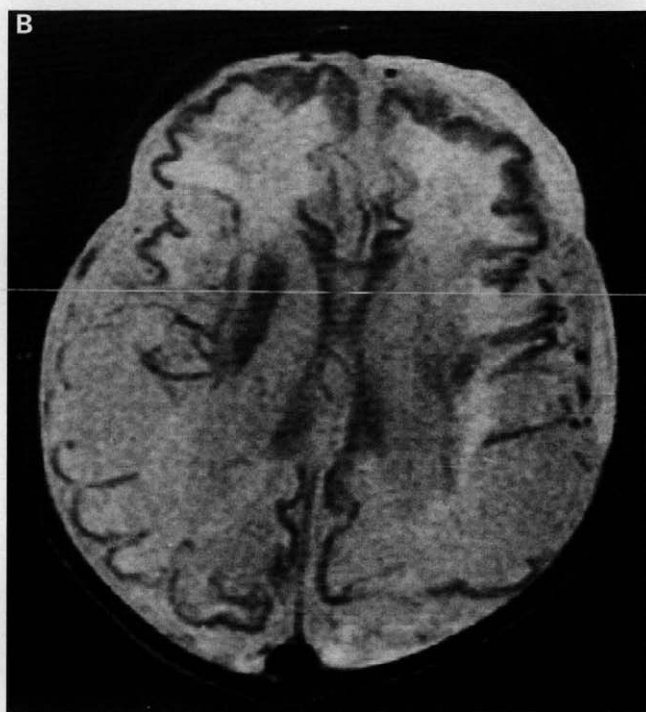
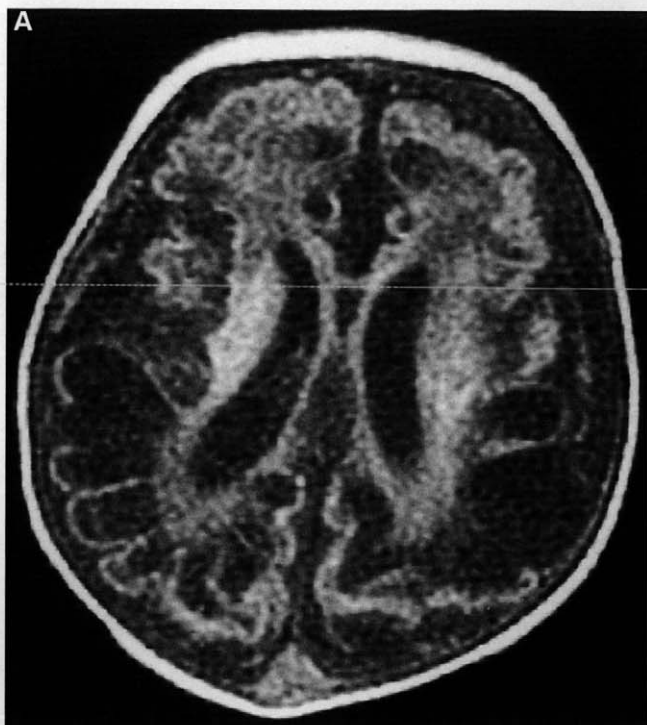


Figure 3. Case 1: the initial MRI at 1 month of age. T₁-weighted axial (A), T₂-weighted axial (B), and coronal (C) images showing large cystic areas, especially in the subcortical regions with extra-axial fluid collection (arrowheads).

Case 2

This was a second child of nonconsanguineous parents. The patient was born in our hospital, with a birthweight of 3470 g, following a 39-week gestation and an uncomplicated delivery. The first child of the family, a girl, was born with a birthweight of 4300 g in a local children's hospital and had cyanosis at birth. She had suffered from tremors and convulsions, which started on the first day of life. The CT examination had shown pathologic changes attributed to anoxia. She had a cranial CT examination obtained when she was 10 months old that showed marked ventricular dilation, more

severe on the left, associated with subcortical hypodense areas and atrophy. The cerebellar hemispheres were small, and there was mega cisterna magna. She died following a febrile illness at the age of 18 months.

The patient had convulsions on the second day of life, which were resistant to therapy. He had micrognathia and a coarse facial appearance; the physical examination was otherwise negative. Routine biochemical investigations of blood, urine and cerebrospinal fluid, serum lactate, pyruvate, ammonium, blood, and urine amino-acid levels were normal. Blood uric acid levels were 0.6 mg/dL and 0.1 mg/dL, repeatedly (normal blood uric acid: 2.4–5.7 mg/dL). Electroencephalography showed diffuse cerebral bioelectric abnormality and suspected paroxysmal activity. Cranial ultrasound demonstrated multiple cystic changes in the inter-hemispheric regions, third and lateral ventricular dilation, and loss of white- and gray-matter distinction. Cranial MRI, obtained when he was 3 months old, revealed marked hydrocephalic dilation of the third and lateral ventricles (Figure 5, A and C). The fourth ventricle was in continuation with the retrocerebellar cystic area, but the posterior fossa was not enlarged (Figure 5B). The cerebellar hemispheres and the vermis were small. The findings were consistent with the Dandy-Walker variant. Additionally, there was marked loss of cerebral parenchyma and small cystic foci in the subcortical regions (see Figure 5C). The cortical sulci were prominent despite the presence of hydrocephalus. The gyri were small with apparent atrophic changes, giving the appearance of ulegyria. The corpus callosum was thin. There was increased T₂ signal intensity in the periventricular white matter, more so than the signal intensity of immature myelin, which represented damaged white matter

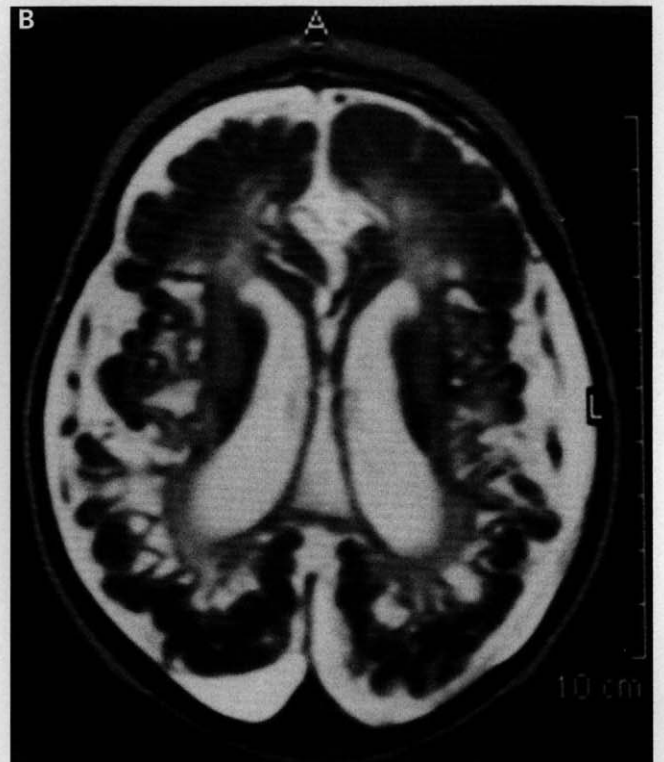


Figure 4. Case 1: follow-up MRI at 10 months of age. Corresponding fluid-attenuated inversion-recovery axial (A), T_2 -weighted axial (B), and coronal (C) images, through the same levels with Figure 1, demonstrating resolution of large cystic lesions with residual small subcortical cystic areas (arrows). The remaining parenchyma show diffuse increased signal intensity. The gyri in the most involved regions of the cerebral hemisphere are small. The extra-axial fluid collection is decreased, although it still exists.

or hemorrhage. The imaging findings suggested hypoxic-ischemic encephalopathy. The patient was given phenobarbital and diphenylhydantoin. The diagnosis of molybdenum cofactor deficiency was considered because of seizures unresponsive to therapy and low blood uric acid levels. The urine sulfite stick test was positive, and quantitative amino-acid analysis and high-voltage electrophoresis of the urine sample showed an increase of S-sulfo-L-cysteine. Hypoxanthine, xanthine, and thiosulfate were increased in the urine, and finally the diagnosis was confirmed by the deficient sulfite oxidase activity in skin fibroblast culture.

Case 3

The patient was transferred to our hospital in an emergency on her first day of life from an outside local medical center because of convulsions, a high-pitched cry, cyanosis, and a history of elder siblings who died in infancy with the same complaints. She was the fifth pregnancy of a 29-year-old mother following a 36-week gestation and had a birthweight of 2900 g. The parents were first cousins. The second and third pregnancies were term male infants who died on the second and third days of life, respectively, with convulsions, a high-pitched cry, and cyanosis. No further information was available to us. The fourth pregnancy resulted in an abortion.

The laboratory investigations were unremarkable except for low blood uric acid level, 0.1 mg/dL (normal blood uric acid level:

(see Figure 5C). There were foci of increased T_1 signal intensity in the basal ganglia and thalami (see Figure 5A). Minimal extra-axial fluid collection was present posteriorly on the left with no mass effect. Also noted on T_2 -weighted images were two foci of hypointensity at the wall of lateral ventricles with no corresponding signal change on T_1 -weighted images, which may represent calcification

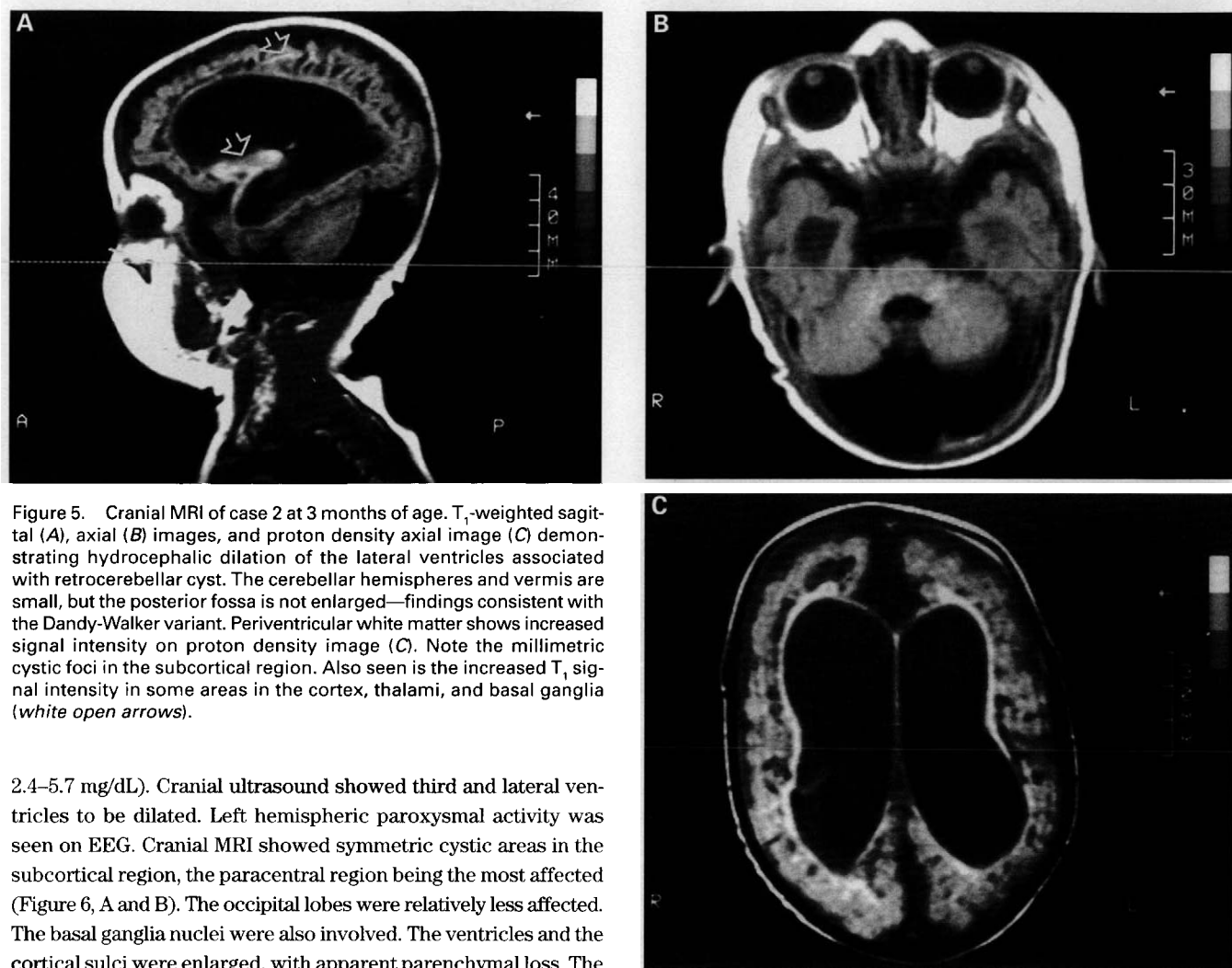


Figure 5. Cranial MRI of case 2 at 3 months of age. T_1 -weighted sagittal (A), axial (B) images, and proton density axial image (C) demonstrating hydrocephalic dilation of the lateral ventricles associated with retrocerebellar cyst. The cerebellar hemispheres and vermis are small, but the posterior fossa is not enlarged—findings consistent with the Dandy-Walker variant. Periventricular white matter shows increased signal intensity on proton density image (C). Note the millimetric cystic foci in the subcortical region. Also seen is the increased T_1 signal intensity in some areas in the cortex, thalami, and basal ganglia (white open arrows).

2.4–5.7 mg/dL). Cranial ultrasound showed third and lateral ventricles to be dilated. Left hemispheric paroxysmal activity was seen on EEG. Cranial MRI showed symmetric cystic areas in the subcortical region, the paracentral region being the most affected (Figure 6, A and B). The occipital lobes were relatively less affected. The basal ganglia nuclei were also involved. The ventricles and the cortical sulci were enlarged, with apparent parenchymal loss. The corpus callosum was markedly thin (Figure 6C). There was increased signal intensity on T_1 -weighted images in the thalami bilaterally (see Figure 6A), with mild hypointensity on T_2 -weighted images. The brain stem did not show any signal abnormality. The cerebellar hemispheres were small, and the cisterna magna was enlarged (see Figure 6C). The MRI findings were similar to those of hypoxic-ischemic insult. Also noted was the increased T_1 signal intensity in the superior sagittal sinus, which raised the suspicion of dural sinus thrombosis (see Figure 6C), but a central signal void was seen on T_2 -weighted images, indicating the presence of flow. Based on a positive urine sulfite stick test and high thiosulfate, S-sulfo-L-cysteine, and xanthine excretion in urine, the diagnosis of molybdenum cofactor deficiency was considered. Skin fibroblast culture showed deficient sulfite oxidase activity. The patient was followed under phenobarbital therapy, which was started on the day of admission. She had feeding difficulties, motor and mental retardation, and microcephaly. She died at the age of 3 months because of pneumonia.

DISCUSSION

Molybdenum-containing cofactor is essential for the function of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. The clinical phenotype appears to be similar

in isolated sulfite oxidase deficiency and molybdenum cofactor deficiency.^{10,11} Diagnosis of these rare metabolic diseases depends on the index of suspicion in the differential diagnosis of patients with neonatal seizures unresponsive to treatment, abnormal muscle tone, brain atrophy, myoclonic spasms, dislocated lenses, feeding difficulties, coarse facial features, and urinary xanthine stones. Diagnosis is suspected with low blood uric acid levels as in all our patients, which has been pointed out as the key to the diagnosis.¹² Further diagnosis was done by quantitative amino-acid analysis and high-voltage electrophoresis of the urine sample showing an increase of S-sulfo-L-cysteine, hypoxanthine, xanthine, and thiosulfate. As in the second case, we also confirmed the diagnosis with absent sulfite oxidase activity in skin fibroblast culture in our other two patients.

Although it is not confirmed by laboratory evaluation, we think that molybdenum cofactor deficiency could be the possible diagnosis in the sister of the second case, who had convulsions and encephalomalacia with cystic changes on CT scan, and in the siblings of case 3, who had neonatal convulsions, a high-pitched cry, a coarse facial appearance, and feeding difficulties.

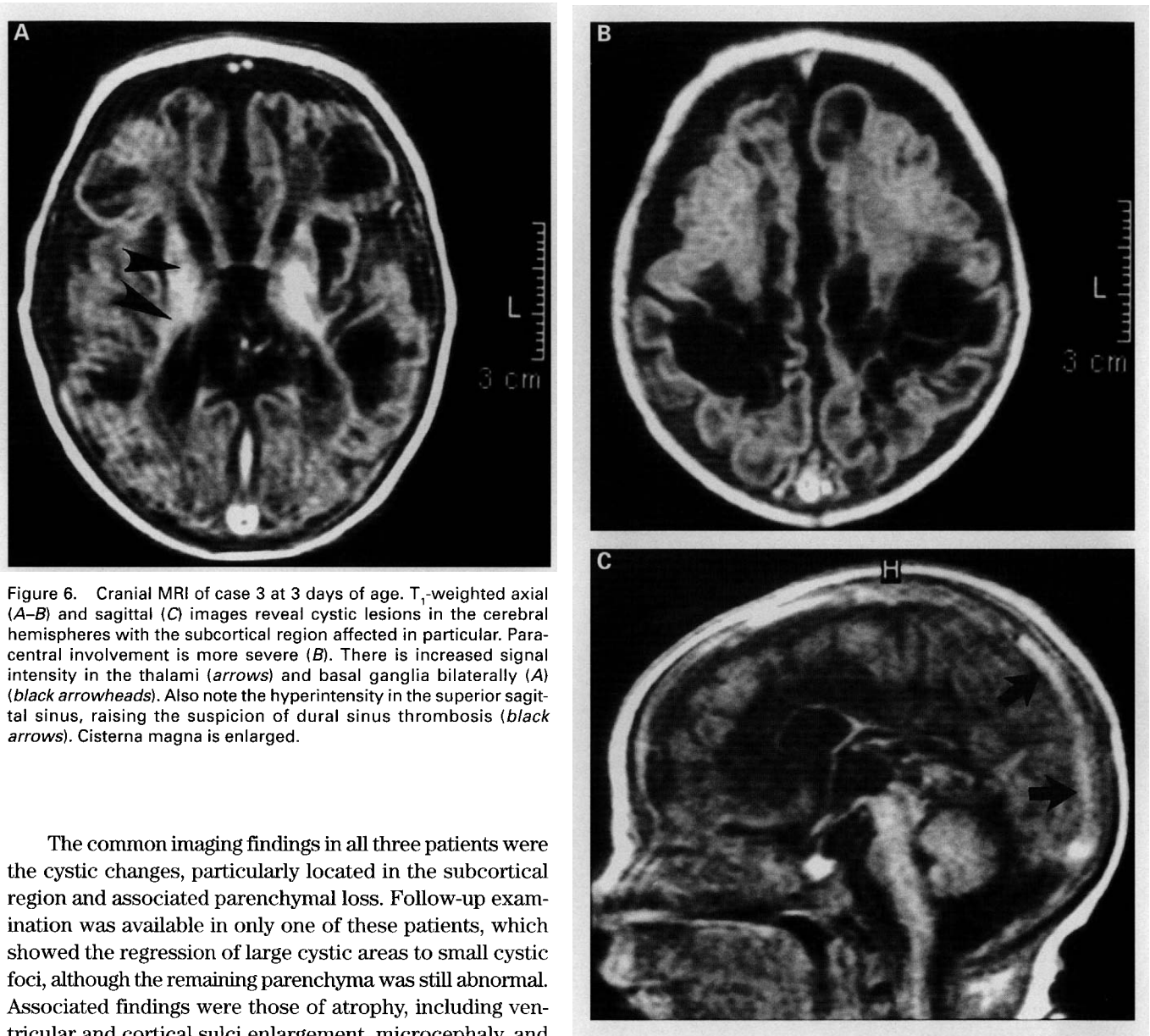


Figure 6. Cranial MRI of case 3 at 3 days of age. T₁-weighted axial (A–B) and sagittal (C) images reveal cystic lesions in the cerebral hemispheres with the subcortical region affected in particular. Paracentral involvement is more severe (B). There is increased signal intensity in the thalami (arrows) and basal ganglia bilaterally (A) (black arrowheads). Also note the hyperintensity in the superior sagittal sinus, raising the suspicion of dural sinus thrombosis (black arrows). Cisterna magna is enlarged.

The common imaging findings in all three patients were the cystic changes, particularly located in the subcortical region and associated parenchymal loss. Follow-up examination was available in only one of these patients, which showed the regression of large cystic areas to small cystic foci, although the remaining parenchyma was still abnormal. Associated findings were those of atrophy, including ventricular and cortical sulci enlargement, microcephaly, and extra-axial fluid collections. The corpus callosum was extremely thin in all patients, even when the fact that patients were imaged at a very early stage of infancy is taken into consideration. The caudate nuclei were atrophic, as mentioned in the report by Schuierer et al, and claimed to be suggestive of this entity.¹³ However, we did not necessarily notice a specific configuration in all of our patients; therefore, we do not feel strongly regarding the diagnostic value of this finding but rather consider it as an inherent part of global atrophy.

The subcortical cystic changes, parenchymal loss, and atrophy associated with increased T₁ signal intensity in the thalami and cortex were suggestive of hypoxic-ischemic injury.^{14,15} The pattern of involvement was similar to that seen in an asphyxiated term infant: both the superficial cortex and white matter (border zones), as affected in partial asphyxia, were susceptible to the injury in this entity. This similarity suggested a pathogenesis of energy depletion in the mechanism of brain damage. We had follow-up examination in

only one of the patients with no further damage but rather some maturation of the brain and regression in the cystic changes, suggestive of sequela of a previous brain insult rather than a progressive disease, unlike the case in the series of Schuierer et al.¹³

The imaging findings reflected the reported histopathologic changes.^{10,16} The cortical lamination at the gyral apices is found to be well preserved, whereas in the depths of the sulci, there is marked neuronal loss from and gliosis of the cortex, giving the appearance of ulegyria on imaging studies,¹⁰ as present in our patients. Small cavities in the white matter have been reported, especially in the insular region, sub- and juxtacortical regions, and gray matter.¹⁷ Histopathology of the involved white matter reveals a striking loss of white matter, axonal loss, gliosis around the numerous cysts, demyelination, and collections of macrophages in the centrum semiovale, suggestive of myelin destruction and

focal mineralization of the injured white matter.^{10,16} These histopathologic changes result in cystic appearances in the white matter, which indicates increased water content of the parenchyma and may be ascribed to the areas of gliosis, and myelin loss. Rupar et al reported the sparing of occipital subcortical white matter, which was also noticed in our patients.¹⁰

The presence of superior sagittal sinus thrombosis has been mentioned before,¹³ with the suspicion of possible vascular involvement raised, although not confirmed by others. We have also observed increased signal intensity on T₁-weighted images, possibly representing the similar finding in two of our patients. However, one may also attribute this appearance to slow flow in the dural sinuses, which may result from decreased blood circulation or be related to possible dehydration of the hospitalized infants with decreased oral intake rather than to the presence of thrombosis.

In one of the patients, there was associated malformation of the Dandy-Walker variant and in another mega cisterna magna, which is included in the spectrum of the same malformation (ie, cystic malformation of the posterior fossa). This association has been reported only in a case by Pintos-Morell et al, but the presence of cisterna magna has been noted before.^{18,19} Pintos-Morell et al suggested the possibility of a toxic accumulated metabolite leading to a precocious central nervous system injury.¹⁸

We conclude that the appearance of hypoxic-ischemic encephalopathy with diffuse encephalomalacia with cystic changes and involvement of basal ganglia and thalami with increased T₁ signal intensity and, particularly, the subcortical cystic changes on imaging studies of a newborn who presents with early intractable seizures may warn for a diagnosis of molybdenum cofactor deficiency. The association of cystic malformation of the posterior fossa, including mega cisterna magna or Dandy-Walker malformation, is not unusual in this entity. A urine sulfite dipstick test must be a routine part of evaluation of these patients in neonatal intensive care units.

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