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B A Appignani, E M Kaye and S M Wolpert

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CT and MR Appearance of the Brain in Two Children with Molybdenum Cofactor Deficiency

Barbara A. Appignani, Edward M. Kaye, and Samuel M. Wolpert

Summary: Imaging findings in two children with molybdenum cofactor deficiency included, in one, diffuse low attenuation on CT in cerebral white matter, caudate nuclei, and thalami soon after birth. MR in both patients later demonstrated progressive widening of the sulci, ventricles, and cisterna magna, and loss of brain volume. MR finally showed cessation of myelination at 31 months and 16 weeks of age.

Index terms: Children, diseases; Metabolic disorder

Molybdenum cofactor deficiency is a rare hereditary metabolic disorder producing neurologic deterioration and death in early childhood. It is one of the diagnosable causes of neonatal seizures. We report the computed tomography (CT) and magnetic resonance (MR) findings in two children who were diagnosed with this disorder and followed at our institution.

Case 1

A full-term girl was the second child of nonconsanguinous parents, born to a healthy 23-year-old mother at an outside institution. The newborn appeared healthy at birth, but when she was less than 24 hours old, tremulousness, seizures, and lactic acidosis developed. Pharmacologic control of seizures was of limited success.

Over the first few months of life, neurologic signs developed, including severe truncal hypotonia, poor head and motor control, limb contractures, and swallowing dysfunction. The head circumference, which was at the 90th percentile at birth, decreased progressively. At 7 months of age, the child's development was markedly delayed, being at the level of a 2 to 3 month old. Metabolic screening test results were normal, except for low serum uric acid. Normal muscle biopsy with oxidative enzyme studies excluded the diagnosis of a mitochondrial disorder. The diagnosis of molybdenum cofactor deficiency was made when results of repeated dipstick tests for urinary sulfite were positive.

The child now has been followed through her second birthday. She is severely neurologically impaired and has

no verbal expression. She has bilateral lens dislocation and no visual function. Her head circumference has dropped to the 10th percentile for age.

Brain CT performed soon after birth was reported to be normal. MR was performed at our facility (1.5-T magnet) at 7 months of age. The ventricles appeared moderately enlarged, and the extracerebral spaces and cisterna magna were wide. The cerebral white matter width appeared decreased, with the depths of some sulci approaching the lateral ventricular margins. A subsequent examination at 23 months of age showed marked brain volume loss, with further widening of the sulci, cisterns, and ventricles. The interhemispheric fissure, anterior cerebral, and pericerebellar subarachnoid spaces were extremely dilated. Myelination was patchy, with absence of the expected T2 hypointensity of the white matter in some regions of the cerebrum and in the cerebellar hemispheres (Figs 1A and B). Additionally, there were areas of signal abnormality on fast spin-echo long-repetition-time sequences (3500/34/1 and 3500/102/1 [repetition time/echo time/excitations]). These included 6- to 8-mm well-defined foci of increased signal in the posterior limbs of both internal capsules, extending into the corona radiata, and abnormal hyperintensity in the external capsules bilaterally, the corpus callosum, and the subcortical white matter tracts. Bilaterally, symmetric hyperintensity also was present in the occipital lobes involving the white matter up to the cortical margin, on the balanced and T2-weighted images. Eight months later, MR showed no further development of white matter myelination, and continued brain volume loss.

Case 2

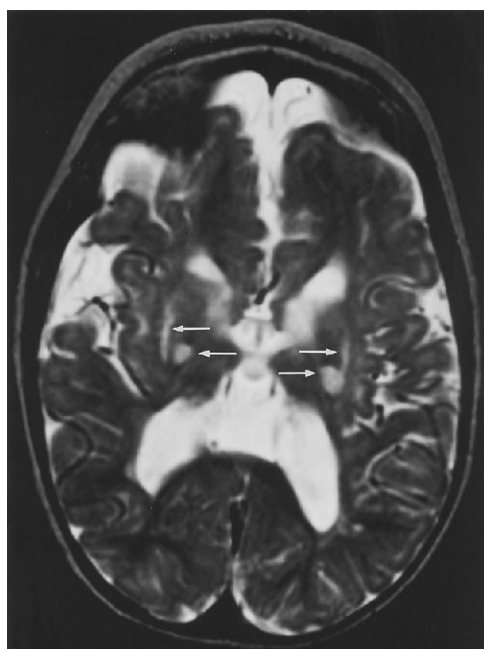
This was the first child of nonconsanguinous parents, born to a 20-year-old mother after induction of labor for a postterm gestation. At birth, this boy had poor tone and no spontaneous respiratory effort. On the first day of life, there was facial twitching and increased tone in the extremities. The next day, the child began to have continuous seizure activity with hypertonic decerebrate posturing.

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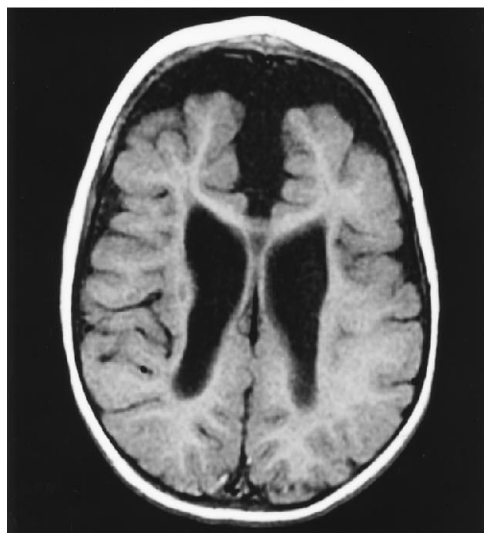
From the Departments of Neuroradiology (B.A., S.W.) and Pediatric Neurology (E.K.), Tufts New England Medical Center, Boston, Mass.

Address reprint requests to Barbara Appignani, MD, Department of Neuroradiology, Tufts New England Medical Center, 750 Washington St, Boston, MA 02111.

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A



B

Fig 1. Case 1. A, T2-weighted MR image demonstrates cerebral volume loss and signal hyperintensity of the internal and external capsules (arrows) at 23 months age.

B, A T1-weighted image from the same examination demonstrates cerebral volume loss, especially involving the white matter of the centrum semiovale.

There was no evidence of mitochondrial disorder on muscle biopsy. A dipstick urine sulfite test result was positive. The diagnosis of molybdenum cofactor deficiency was suspected on the basis of the biochemical studies, but a deficiency of sulfite oxidase could not be confirmed.

Noncontrast CT done on the third day of life demonstrated diffuse low attenuation in the cerebral white matter and in the caudate nuclei and thalami of a greater degree

than is typically seen in the newborn brain from immature myelination (Fig 2A). MR during the same 24-hour period showed a structurally normal newborn brain, with gray-white matter differentiation preserved. The white matter signal had the usual appearance of the newborn, so edema could not be excluded.

At 6 weeks of age, follow-up MR revealed dilatation of the ventricles, sulci, and cisternal spaces, indicating a loss of brain substance. There was decreased width of the periventricular cerebral white matter. The cerebral gyri appeared thinned. The cerebellar interfolial spaces had widened, and the vermis appeared markedly atrophied. Signal abnormalities were seen in the subcortical white matter in several locations, especially in the frontal and temporal lobes. These areas were hypointense on T1-weighted images, hyperintense on T2-weighted images, and without mass effect (Fig 2B).

MR at 16 weeks of life showed the myelination pattern to be unchanged from that of a newborn, with evidence of myelination seen only in the posterior limbs of the internal capsules and thalami (Fig 2C).

Discussion

Molybdenum cofactor is a constituent of three molybdoenzymes: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. The most physiologically significant result of molybdenum cofactor deficiency is the inactivation of sulfite oxidase. This enzyme oxidizes toxic sulfites, which are the metabolic products of sulfur-containing amino acids, to excretable sulfates (1). Increased sulfite levels are the suspected cause of central nervous system damage (1, 2, 3).

The clinical symptoms and biochemical abnormalities of molybdenum cofactor deficiency were linked by Duran and coworkers in 1978 (4). They described a child with a combination of xanthine oxidase (dehydrogenase) and sulfite oxidase deficiencies. Without molybdenum cofactor, xanthine and sulfite are not metabolized to uric acid and sulfite, respectively. Sulfite and xanthine are found in the urine. Knowing that the function of both enzymes depended on the presence of molybdenum cofactor, they concluded that a deficiency of this cofactor was responsible for their patient's illness.

The effects on the nervous system of isolated sulfite oxidase deficiency have been clinically and pathologically described (2, 4–6). Neonatal convulsions, mental retardation, spastic quadriplegia, and microcephaly are among the manifestations of sulfite oxidase deficiency. Ocular lens dislocation and impaired vision also occur. Xanthine oxidase deficiency alone is

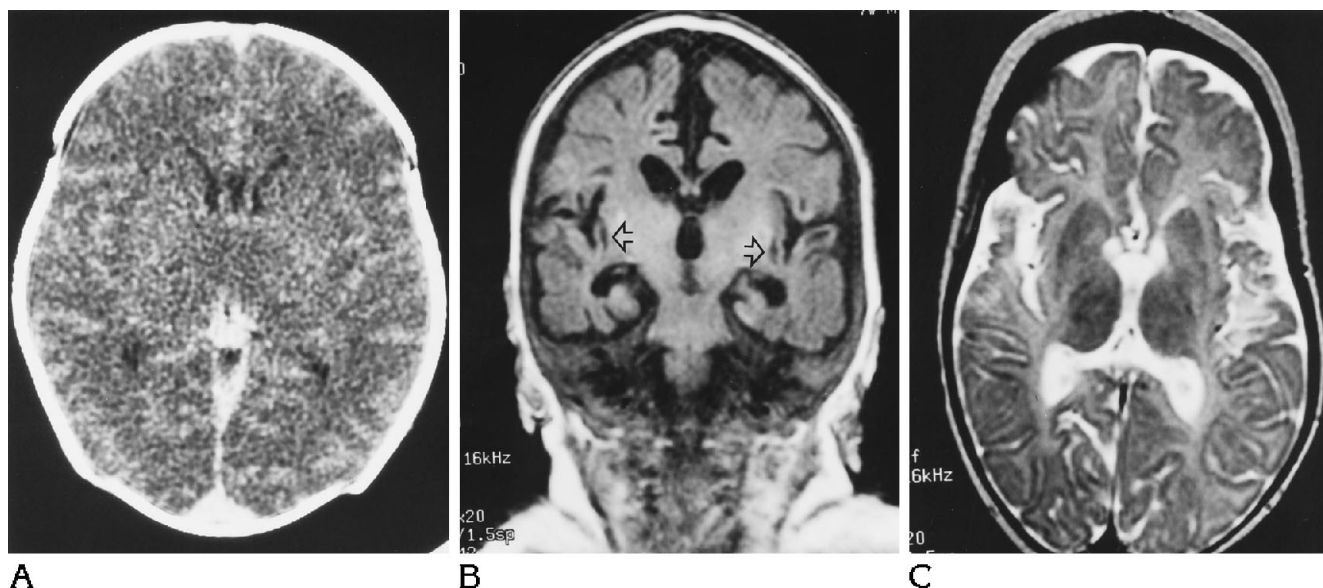


Fig 2. Case 2. A, Noncontrast CT of the newborn brain shows diffuse hypoattenuation of the cerebral white matter, caudate nuclei, and thalami.

B, T1-weighted coronal MR image shows severe volume loss and multifocal subcortical white matter hypointensities (arrows) at 6 weeks of age.

C, Hypomyelination is evident at 4 months of age on this T2-weighted image.

usually not symptomatic (1, 4). Severe diffuse brain atrophy is the dominant finding on gross pathologic examination of the central nervous system in sulfite oxidase deficiency. Microscopic inspection of the brain in patients with sulfite oxidase deficiency shows diffuse myelin loss, cortical and central neuronal loss, gliosis, and cystic changes in the brain substance, most notably in the basal ganglia (2, 3, 5). There also is loss of cerebellar neurons and absence of myelin with accompanying gliosis (5). The same pathologic appearance of the brain is described in patients with molybdenum cofactor deficiency (2, 3, 6, 7). This association led Roth et al to conclude that sulfite oxidase deficiency is the likely cause of neurologic deterioration in children with molybdenum cofactor deficiency (2).

As a child with molybdenum cofactor deficiency develops, the appearance of the pathologic changes in the brain unfolds on CT and MR. Just after birth, decreased CT attenuation of the cerebral white matter is observed (5, 6). Based on our observations and the reports of others, brain edema may be the first manifestation of the effect on white matter of this biochemical defect. A rapidly progressive diffuse pattern of brain atrophy then develops. Although we did not observe cerebral calcifications, Slot et al described thalamic calcifications

on the CT scan of a 3-month-old infant with molybdenum cofactor deficiency (6).

MR more clearly delineates the loss of brain tissue, distinguishing between the thinning of the white matter mantle and the gyral narrowing, which probably reflects cortical atrophy. There is arrested development of myelination and evidence of gliosis and cystic white matter changes.

Molybdenum cofactor deficiency has been found in siblings and in the children of consanguineous parents. The genetic defect responsible for this recessive trait is not known. Prenatal diagnosis of this disorder can be accomplished by assay for sulfite oxidase activity in amniotic cells. There is no effective therapy for children with molybdenum cofactor deficiency. Dietary restriction of sulfur-containing amino acids may decrease sulfite excretion, but it will not alter the ultimate progression of neurologic impairment (9).

Addendum

During preparation of this article's proofs, another description of the neuroimaging findings in children with molybdenum cofactor deficiency was published (10). The authors' findings agree with our own. White matter and basal

ganglionic destructive changes and massive cerebral volume loss is described.

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