Cranial Ultrasonography in Maple Syrup Urine Disease

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Summary: We performed serial cranial ultrasonography in four newborns affected by maple syrup urine disease. Symmetric increase of echogenicity of periventricular white matter, basal ganglia (mainly pallidi), and thalami was detected in the acute stage. The degree of ultrasonography abnormalities paralleled the clinical course of the disease.

Index terms: Brain, ultrasound; Infants, diseases; Maple syrup urine disease

Maple syrup urine disease is a rare inborn error of branched-chain amino acid (leucine, valine, and isoleucine) metabolism. Accumulation in body fluids of toxic levels of branched-chain amino acids and their related compounds leads to severe neurologic deterioration and to the characteristic maple syrup urine odor. Dietary restriction of offending amino acids is the therapeutic approach (1). Brain computed tomography (CT) and magnetic resonance (MR) in maple syrup urine disease patients have shown diffuse involvement of the cerebral and cerebellar white matter as well as localized changes at the level of basal ganglia, thalami, and brain stem (2–7). We performed serial cranial ultrasonography in four newborns affected by maple syrup urine disease during the acute stage and in the follow-up.

Methods

We have serially examined by means of ultrasonography four newborns affected by maple syrup urine disease. Results were correlated with CT and MR findings. The main clinical and biochemical data of our patients at the onset of symptoms and at the follow-up are summarized in the Table. All patients had remission of symptoms and biochemical abnormalities within 3 weeks from the start of treatment. Ultrasonography was first performed in the acute stage at the time of diagnosis, then repeated at the follow-up, when patients were metabolically stable. In patient 2, ultrasonography also was done during an acute relapse at the age of 10 months. CT studies were performed in all patients at the time of the first ultrasonography. MR was performed once at follow-up in the first three patients, when they were in good metabolic condition. Ultrasonography was carried out with 5- and 7.5-MHz transducers. MR imaging was performed with a 1.5-T unit.

Results

In all patients, ultrasonography at the onset of symptoms and during an acute relapse (patient 2) was represented by symmetrically increased echogenicity involving the periventricular white matter, the basal ganglia (mainly the pallidi), and the thalami (Fig 1A–D). After normalization of clinical and biochemical abnormalities, serial controls documented regression of the previous ultrasonography findings (Fig 2A and B) with some little differences among the four patients (Table). CT showed symmetric low-density areas throughout the cerebral white matter, but also involving basal ganglia, thalami, internal and external capsules, brain stem, and deep cerebellar white matter (Fig 3A–D). MR, done only during follow-up in three patients, showed symmetric hyperintense areas in T2-weighted sequences with the same topographic distribution (Figs 4, 5, 6A and B). By this time, lesions were obviously less marked, because the disease was controlled by dietary treatment.

Discussion

Maple syrup urine disease is a rare inborn error of branched-chain amino acid metabolism caused by deficient decarboxylative breakdown

Received April 14, 1994; accepted after revision May 1, 1995.

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AJNR 17:311–315, Feb 1996 0195-6108/96/1702–0311

Correlation between clinical, biochemical, and ultrasonography studies in four patients with maple syrup urine disease

Patient	Age	Leucine, μmol/L†	Symptoms	Ultrasonography Abnormalities*		
				Periventricular white matter	Pallidi	Thalami
1	10 d	2874	Vomiting, hypotonia, seizures	++	++	++
	35 d	250	None	−	−	−
2	8 d	2500	Hypotonia, lethargy, vomiting	+++	+++	+++
	50 d	460	None	+	−	+
	10 mo	1200	Hypotonia, lethargy, vomiting	−	++	−
3	12 d	2754	Hypotonia, lethargy, vomiting	+++	+++	+++
	3 mo	61	None	−	+	−
4	16 d	4200	Coma	+++	+++	+++
	23 d	70	None	+	−	+

* − indicates no involvement; +, degree of involvement.

† Normal values, 49 to 216 μmol/L.

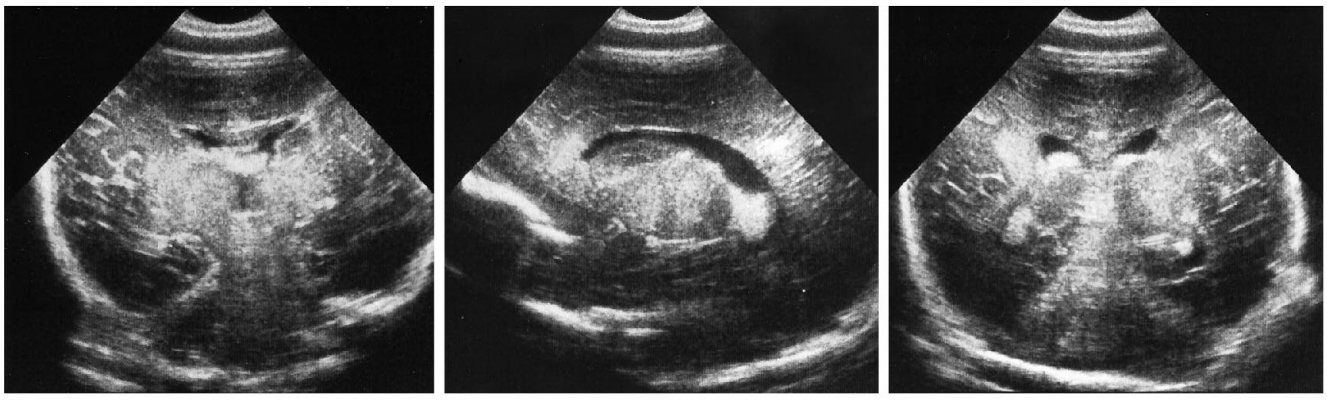
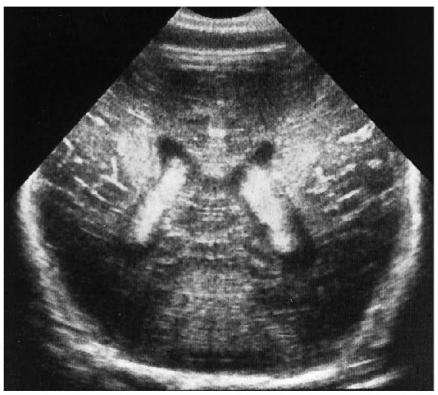


Fig 1. Ultrasonography examination. Coronal (*A*, *C*, *D*) and sagittal (*B*) scans show hyperechogenicity of periventricular white matter, thalami, and pallidi.



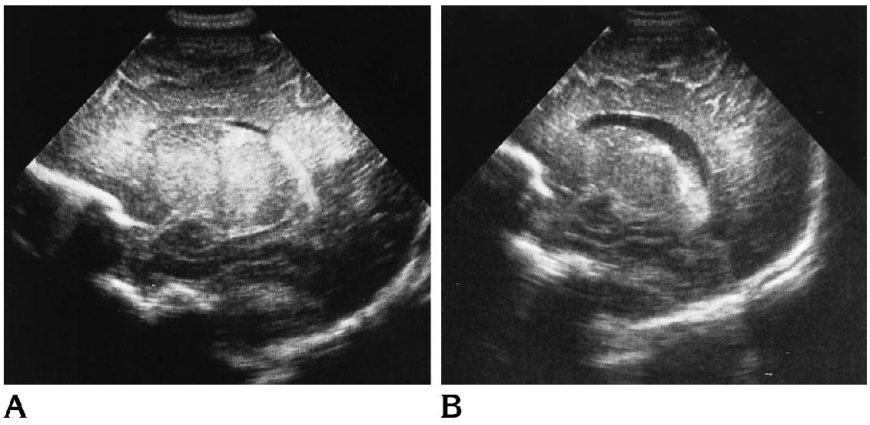
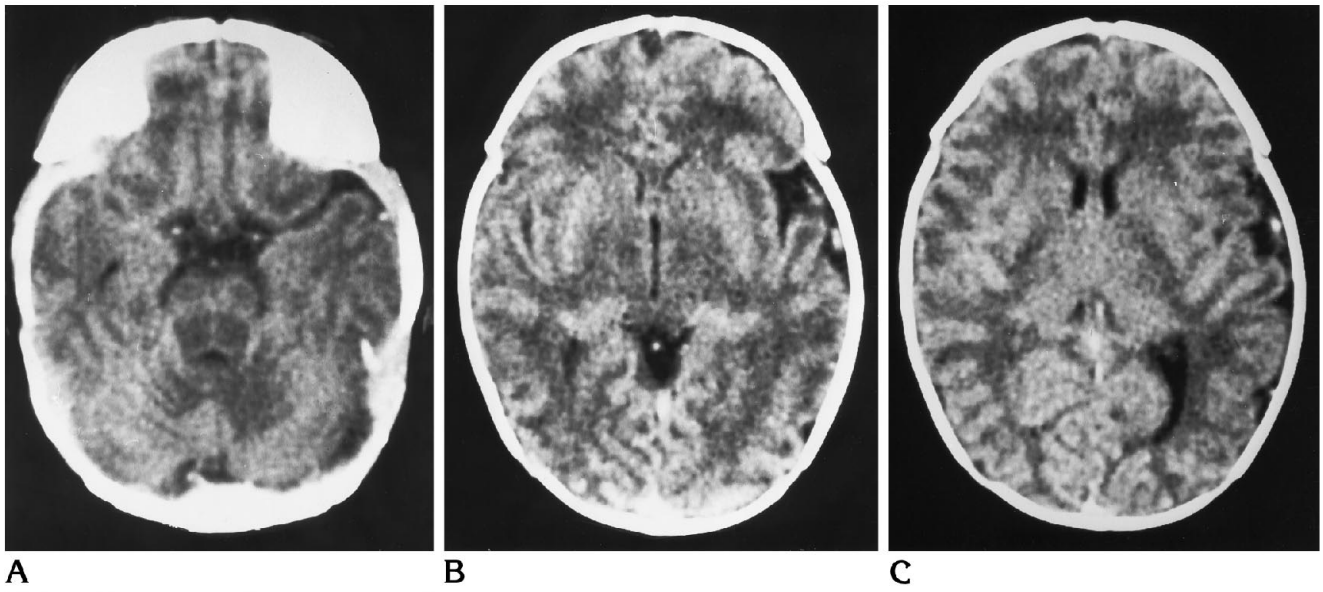


Fig 2. Ultrasonography examination. Comparison of two sagittal scans before (*A*) and 4 weeks after (*B*) institution of therapy shows hyperechogenity of periventricular white matter, thalamus, and pallidus (*A*) and regression of ultrasonography abnormalities (*B*).



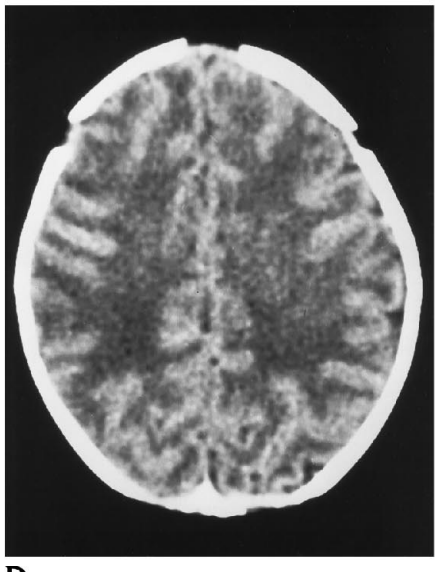
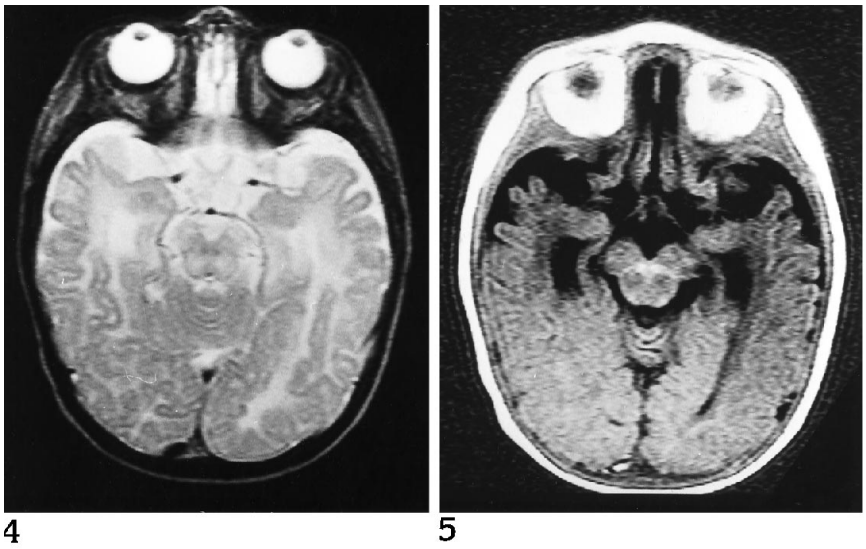


Fig 3. CT examination (axial scans) shows diffuse symmetric, low-density areas involving deep cerebellar white matter and brain stem (*A*), thalami (*B*), pallidi (*C*), and cerebral white matter (*D*).



Figs 4 and 5. MR shows slightly hyperintense signal in the T2-weighted sequence (Fig 4) and hypointense signal in the I.R. sequence (Fig 5) involving brain stem, periventricular white matter, and pallidi. Severe cortical atrophy also is evident.

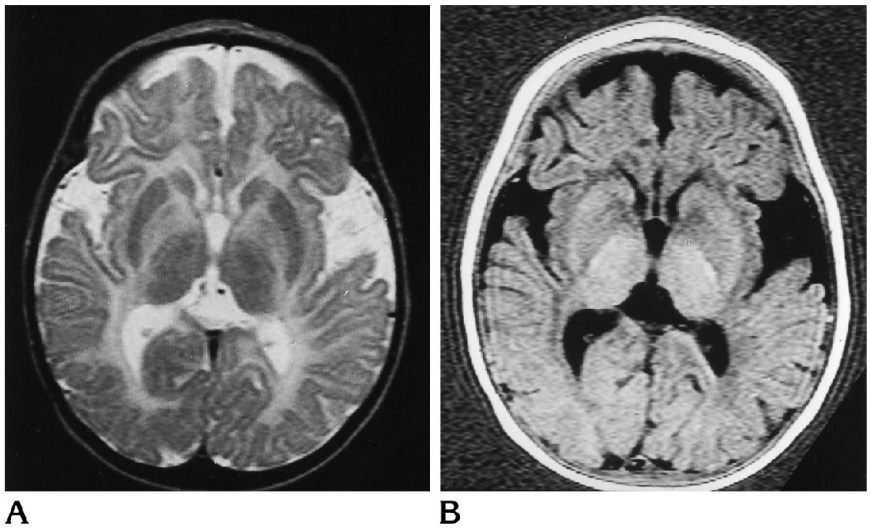


Fig 6. MR shows slightly hyperintense signal in the T2-weighted sequence (*A*) and hypointense signal in the inversion recovery sequence (*B*) involving brain stem, periventricular white matter, and pallidi. Severe cortical atrophy also is evident.

of α-ketoacids deriving from leucine, valine, and isoleucine. In the classic form, patients present acutely in the first days of life with poor feeding, vomiting, seizures, lethargy, and coma. Maple syrup urine odor is characteristic. Some variants have been described and classified as intermittent, mild, and thyamine responsive (1). Therapy is based on dietary restriction of branched-chain amino acids, which produces clinical and biochemical improvement. Although the long-term prognosis still remains severe, the earlier the therapy is instituted the more favorable the course.

Neuropathologic changes in maple syrup urine disease are represented by deficient myelination with spongy degeneration of the white matter and basal ganglia. There is an increased brain water content, and the number of oligodendrocytes and astrocytes in the white matter is reduced (1). Although the diagnosis of maple syrup urine disease is mainly based on clinical and biochemical data, some studies can be found in the literature dealing with CT and MR findings and their correlation with clinical evolution and subsequent neuropathologic changes (2–7). Most of the authors report brain CT symmetric hypodensity involving diffusely the cerebral white matter, the internal and external capsules, the brain stem, and the deep cerebellar white matter, but also the basal ganglia (mainly the pallidi) and the thalami (3–7). The low-density areas on CT seem to be consistent with

increased water content (2, 4, 6), but also with delayed or altered myelination (3, 6). These neuropathologic changes also account for high-signal areas on MR examination in T2-weighted sequences (3, 4, 6, 7). CT and MR findings in our patients fit with those reported by other authors.

Ultrasonography in our four patients showed symmetric increase in echogenicity of periventricular white matter, basal ganglia regions (mainly involving the pallidi), and thalami. The extent and degree of ultrasonography changes appeared to parallel the clinical stage. Similar but not identical ultrasonography findings involving thalami, basal ganglia, and white matter can be observed in congenital infections, asphyxia, hyperbilirubinemia, congenital heart diseases, and diabetic fetopathy (7, 8). Differential diagnosis is based, besides on clinical signs, on progression of lesions during follow-up. A limited number of pathologic changes, obviously, can be detected by means of ultrasonography when compared with the other imaging techniques. In particular, brain stem and cerebellar echostructure are assessed with great difficulty. Despite these limitis, we believe echography can provide a useful, innocuous, and manageable means of diagnosing and monitoring patients with maple syrup urine disease, at least in the first months of life, as long as the anterior fontanel remains patent.

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