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AJNR Am J Neuroradiol 1987, 8 (1) 71-75
http://www.ajnr.org/content/8/1/71

MR of Leigh's Disease (Subacute Necrotizing Encephalomyelopathy)

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MR images of three patients with Leigh's disease (subacute necrotizing encephalomyelopathy) were compared with CT findings. In all patients typical lesions in the basal ganglia were identified with both MR and CT. In two patients MR permitted identification of additional lesions not detected with CT. In one patient progression of MR abnormalities over a 4-month period correlated well with clinical deterioration in neurologic status. T2-weighted images with a repetition time (TR) greater than 1950 msec and an echo time (TE) greater than or equal to 60 msec or inversion-recovery images with a 50-msec TE, 1213-msec inversion time, and 3000-msec TR were advantageous in identifying multiple necrotic lesions in the brainstem, deep gray matter, periventricular white matter, and cerebral cortex. In this series MR was more sensitive in detecting and localizing multifocal necrotic lesions of Leigh's disease than CT was, and thus may be a useful diagnostic tool for patients with the appropriate clinical and laboratory abnormalities.

Leigh's disease (subacute necrotizing encephalomyelopathy) is a rare neurodegenerative disease that usually affects infants and children, but occasionally has an adult onset. The precise metabolic defect in this fatal genetic disease is unknown [1–10], but it may be an abnormality of a mitochondrial enzyme system related to cytochrome-*c* oxidase and/or pyruvate dehydrogenase [1, 2]. Additional enzymatic defects identified include the presence of an inhibitor of thiamine pyrophosphate-adenosine triphosphate phosphoryl transferase [3, 10] and deficiency of liver pyruvate carboxylase [5]. This disease manifests itself in multiple neurologic deficits including hypotonia, ataxia, bulbar paresis, nystagmus, abnormal ocular movement, visual disturbances, and regressive psychomotor development [1–10]. Pathologic findings characteristically include symmetric areas of gray-matter necrosis of the putamen, thalamus, hypothalamus, dentate nuclei, cerebellum, and optic chiasm [6–8].

Materials and Methods

Three children (two boys and one girl) ranging in age from 2 months to 4½ years with a clinical, laboratory, and CT diagnosis of Leigh's disease were studied. The clinical and biochemical data on these children are charted in Table 1. Other diseases including nutritional deficiencies, infections, intoxications, and other metabolic diseases (for example, Wilson's disease) were excluded by a battery of studies, including plasma amino acid and organic acid assays, drug screening, heavy metal screening, endocrinologic assays (thyroid, prolactin), EEG, complete blood counts, electromyography, SMA-18, CSF cultures, and nerve conduction velocity evaluations.

All patients underwent CT and MR scanning. CT was performed with contrast enhancement (two cases) or without enhancement (one case); the interval between CT and MR examinations was 1–8 months. MR was performed with a 0.5 T superconductive magnet (Philips Corp.). T1- and T2-weighted sequences were evaluated. The multislice T1-weighted sequence was either a spin-echo series with a repetition time (TR) of less than or equal to 700 msec and echo time (TE) of 30 msec (two patients) or an inversion-recovery pulse sequence with TE

Received March 3, 1986; accepted after revision June 30, 1986.

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AJNR 8:71–75, January/February 1987
0195-6108/87/0801-0071

TABLE 1: **Clinical and Laboratory Abnormalities in Leigh's Disease**

	Case 1	Case 2	Case 3
Age at onset, gender	15 mo, female	21 mo, male	3 wk, male
Age at diagnosis	3.5 yr	4.75 yr	2 mo
Family history	No	Yes	No
Signs & symptoms	Vomiting, height & weight <5%, ataxia, sixth nerve palsy, ptosis, slurred speech, labored respirations, difficulty swallowing	Developmental delay, then regression to total care, apnea, vomiting	Hypotonia, poor respiratory drive (ventilator-dependent), vegetative state
Laboratory values[a]	↑ plasma alanine; urinary lactic acid 0.256; pyruvic acid 1.4 mg/dl; lactic acid 5.8 mmol/L; arterial blood gas: pH 7.43; CO_2 14; serum CO_2 9.3; skin fibroblasts: cytochrome *c* oxidase deficiency	↑ CSF pyruvate & lactate; ↑ plasma alanine; ↑ urinary alanine, OH-butyric acid, and lactic acid; serum lactate 33.1 mg/dl	Serum CO_2 18 (anion gap 16); initial normal CSF, ↑ CSF lactate on repeat; lactic acid 4.9 mmol/L

Note.—mo = month; wk = week; yr = year; CSF = cerebrospinal fluid.
[a] Normal laboratory values are urinary lactic acid, <0.1; pyruvic acid, 0.3–0.9 mg/dl; lactic acid, <2.2 mmol/L; serum lactate, 4.5–19.8 mg/dl.

50 msec, TR 3000 msec, and inversion time (TI) 1213 msec (one patient). The T2-weighted sequence was a multislice study with a TR greater than or equal to 1950 msec and a TE greater than or equal to 60 msec. A comparison was then completed between CT and MR abnormalities on the basis of intensity/attenuation and location of parenchymal lesions.

Results

Characteristic lesions on CT included focal, symmetric, nonenhancing, low-attenuation lesions in the putamen (three cases); focal, bilaterally symmetric, nonenhancing low-attenuation lesions in the periventricular white matter (two cases); focal, bilaterally symmetric, nonenhancing areas of cortical loss (one case); generalized low attenuation of the midbrain (one case); focal, bilaterally symmetric, nonenhancing punctate periaqueductal lesions (one case); and generalized volume loss (one case). The two patients who had contrast-enhanced CT demonstrated no areas of focal enhancement. Two patients (cases 1 and 3) reportedly had normal CT scans at the onset of symptoms.

Characteristic lesions on MR are contrasted with CT findings in Figures 1–3. MR abnormalities with a T2-weighted sequence included focal areas of increased signal in the striate nuclei (three cases), caudate nucleus (two cases), centrum semiovale (three cases), cerebral cortex (two cases), midbrain (three cases), and pons (two cases). Lesions identified on a T1-weighted spin-echo sequence were hypointense, but fewer lesions were identified with a T1- than with a T2-weighted sequence. Inversion-recovery images in the youngest and most severely affected child revealed striking hypointense focal lesions that progressed over a 4-month period (Fig. 3).

An anatomic comparison between CT findings and lesions identified by MR is charted in Table 2. No patients had visible lesions involving the cerebellar hemispheres, dentate nuclei, or medulla. Two patients had generalized volume loss for age both on MR and CT. In two patients (cases 1 and 2) MR demonstrated more lesions than CT and permitted a more precise anatomic localization of the abnormalities in the brainstem and deep central gray matter. On the T2-weighted sequence, the predilection of Leigh's disease for gray-matter nuclei, particularly in the brainstem, was striking (Fig. 1), with focal lesions seen by MR in the central nuclei anterior to the fourth ventricle, in the colliculi, and in the periaqueductal gray matter.

Discussion

The diagnosis of Leigh's disease is definitively made only postmortem; thus, this diagnosis may be difficult to confirm during life [11]. Clinical and metabolic abnormalities are helpful, but age of presentation, progression of disease, and specific metabolic abnormalities encountered are variable. CT has a confirmatory role when bilateral, symmetric, low-attenuation regions are identified in the basal ganglia [11–13]; however, CT is insensitive for detection of the multifocal necrotic lesions typical of this disease.

MR is more sensitive than CT in identifying nonenhancing lesions of multiple sclerosis, early infarction, and white-matter disease [14–16]; thus, it is logical that MR would be superior for detecting the focal necrotic lesions of Leigh's disease. In this series, MR and CT equally demonstrated symmetric, bilateral basal ganglia lesions. With MR, however, additional lesions were identified that were not visible on CT. The increased sensitivity of MR is multifactorial. MR is not limited by the beam-hardening artifacts of CT for imaging the posterior fossa [17]. MR is sensitive to slight changes in water content, and thus necrotic lesions are rendered visible. With T2-weighting, nuclei and tracts in the brainstem and deep gray matter that are not defined by CT may be identified; thus, a more accurate localization of lesions is achieved.

Neither CT nor MR is specific for Leigh's disease. With MR, other widespread parenchymal insults caused by multiple sclerosis, toxins, or anoxia might result in a similar appearance; however, the striking involvement of brainstem nuclei in Leigh's disease is helpful in excluding these diseases. Wilson's disease may result in MR abnormalities similar to those of Leigh's disease [18, 19], but it can be excluded by laboratory testing. On CT, carbon monoxide poisoning, other

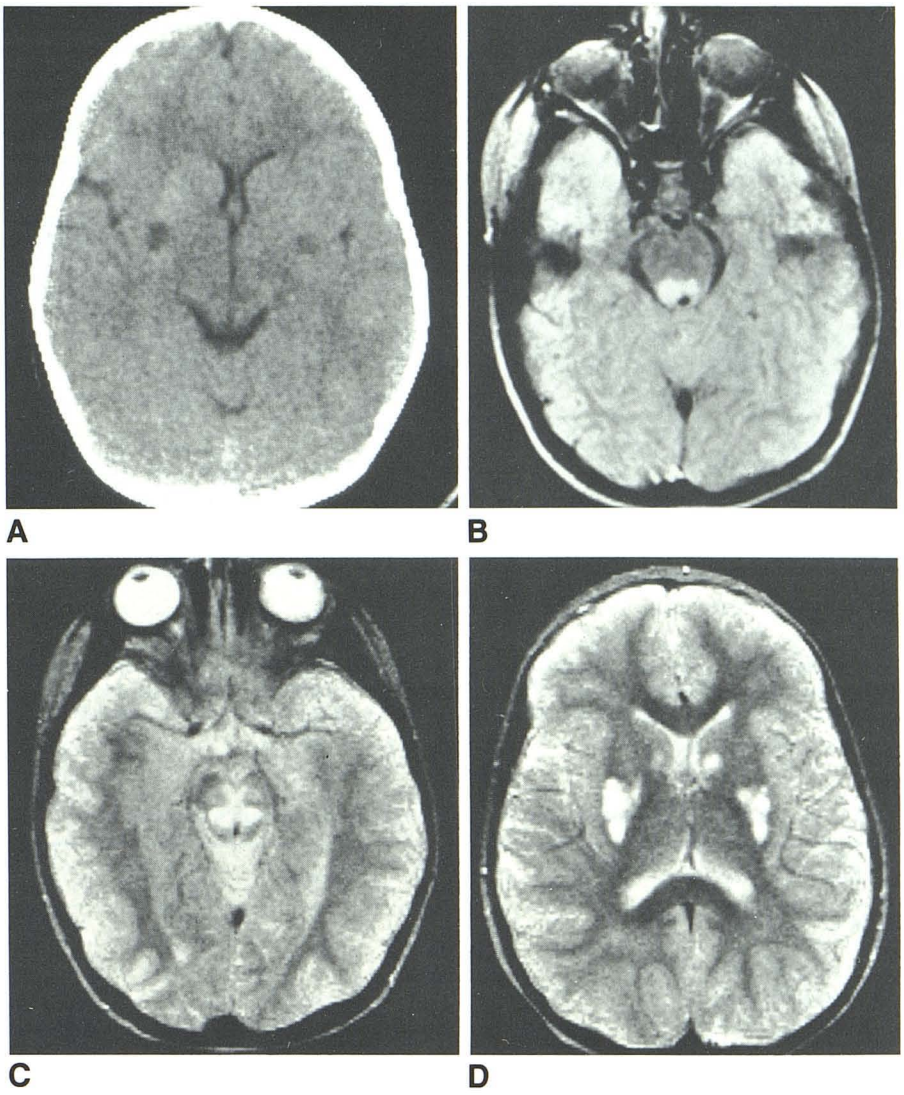

Fig. 1.—Case 1, 3½-year-old girl.
A, Unenhanced CT scan. Characteristic focal bilateral, symmetric lucencies in basal ganglia and questionable focal lucency in periaqueductal region.
B, T2-weighted studies (TE 50, TR 2000) revealed striking hyperintense lesions in central nuclei anterior to fourth ventricle.
C, Higher level. Multiple hyperintense lesions in midbrain (TE 100, TR 2000).
D, Higher level. Characteristic focal lesions of globus pallidus, putamen, and caudate.

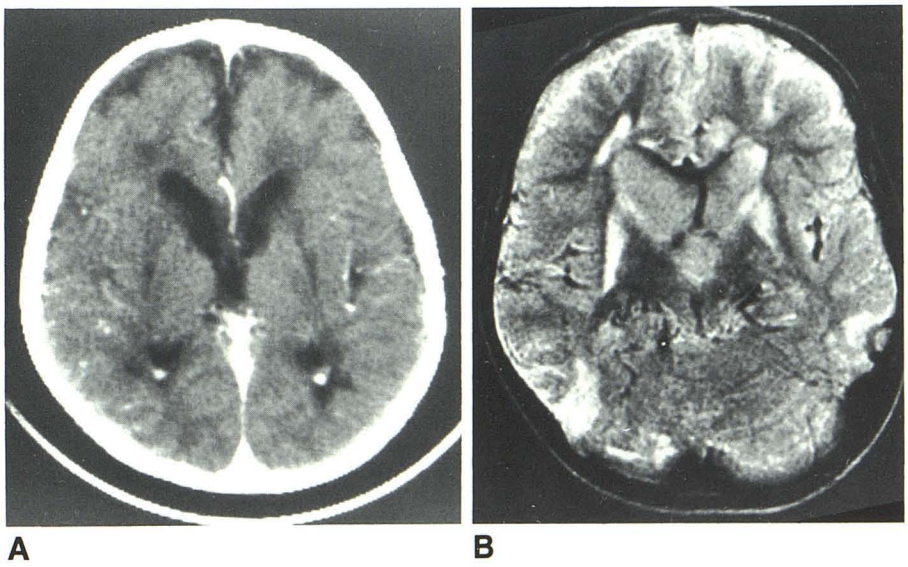

Fig. 2.—Case 2, 5-year-old boy.
A, Contrast-enhanced CT showed focal nonenhancing lesion of putamen and periventricular white matter with generalized volume loss for age.
B, T2-weighted image (TE 100, TR 1950). Focal symmetric areas of hyperintensity were noted in basal ganglia, caudate head, periventricular white matter, and cortex.

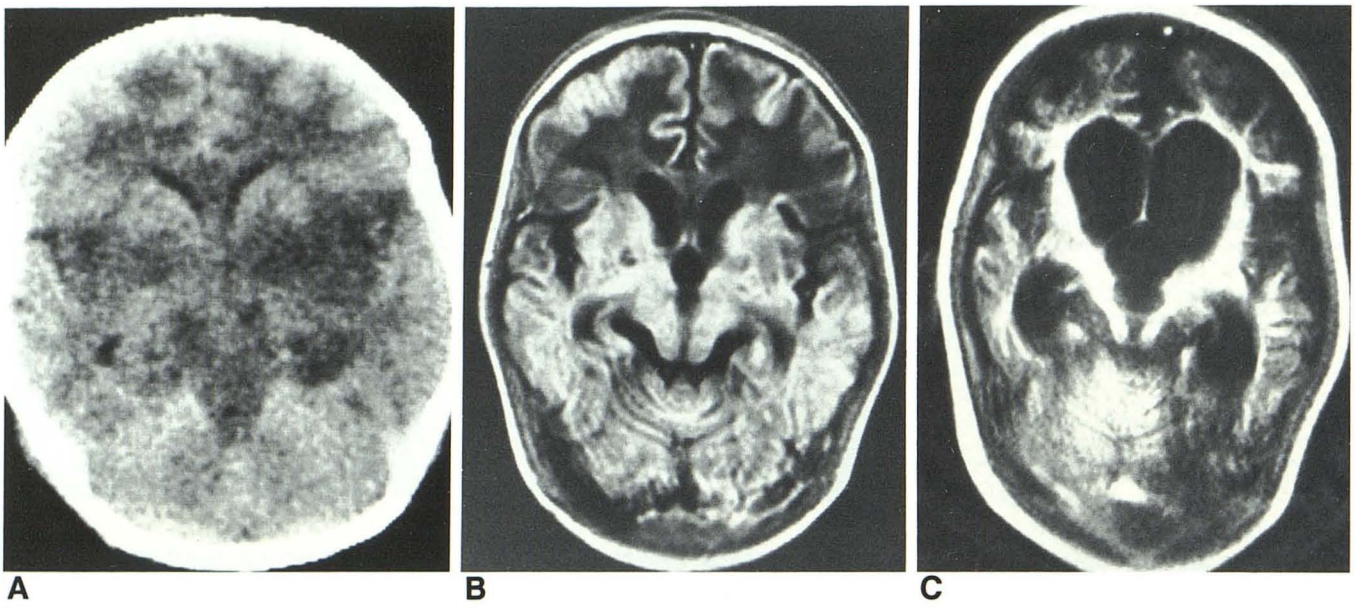

Fig. 3.—Case 3, 2-month-old girl.
***A*, Unenhanced CT scan at presentation. Severely abnormal midbrain, basal ganglia, thalamus, and periventricular white matter.**
***B*, Inversion recovery (TE 50, TI 1213, TR 3000). Abnormalities of frontal white matter and basal ganglia are striking.**
***C*, Follow-up inversion-recovery sequence (TE 50, TI 1213, TR 3000) 4 months later. Marked progression with severe generalized volume loss.**

TABLE 2: **MR and CT Correlation for Lesion Identification in Leigh's Disease**

Case No.: Study	Striate Nuclei	Caudate Nucleus	Thalamus	Centrum Semiovale	Cerebral Cortex	Corpus Callosum	Midbrain	Pons
Case 1:								
CT	+	−	−	+	−	−	+	−
T1-weighted MR	+	I	+	+	−	−	+	I
T2-weighted MR	+	+	+	+	−	−	+	+
Case 2:								
CT	+	+	−	+	−	−	−	−
T1-weighted MR	+	I	−	+	−	−	−	−
T2-weighted MR	+	+	−	+	+	−	+	I
Case 3:								
CT	+	−	+	+	+	+	+	+
T1-weighted MR	+	−	+	+	+	+	−	+
T2-weighted MR	+	−	+	+	+	−	+	+

Note.—I = Indeterminate.

anoxic insults, acute childhood hemiplegia, and encephalitis may mimic Leigh's disease [12, 20].

The variable severity of lesions encountered by MR in our series suggests a broad spectrum of presenting abnormalities and progression of lesions in this disease. With MR, lesion progression was documented over a 4-month period in one child. This suggests that MR might be a more useful indicator of the severity of disease and of its rate of progression than CT is. In addition, increased sensitivity of MR may potentially permit an earlier diagnosis for prognosis and grading of disease severity. In our series, although all three patients had characteristic CT findings at the time of the MR study, two of the three patients had normal CT scans by report at the onset of symptoms. Whether MR, at the time of the normal CT scan, would have contributed to an earlier diagnosis of this disease is worthy of speculation.

In summary, in our series MR and CT demonstrated equally the bilateral, symmetric basal ganglia lesions encountered in Leigh's disease. MR permitted identification of additional lesions in characteristic locations not found by CT. Potentially, an increased sensitivity of MR in identifying lesions will permit an earlier diagnosis of this disorder, a more accurate estimate of its severity, and a more sensitive means of evaluating its progression.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of Francine L. Hollowell and photographer Joe Jackson.

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