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MR Findings in Patients with Subacute Necrotizing Encephalomyelopathy (Leigh Syndrome): Correlation with Biochemical Defect

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MR studies were correlated with biochemical results in nine children who presented with lactic acidosis and/or abnormal MR findings in the basal ganglia. Neurologic development was delayed in all nine children. Seven of these patients were diagnosed as having subacute necrotizing encephalomyelopathy (SNE, or Leigh syndrome) on the basis of history, clinical findings, and biochemical studies; of the remaining two, one had congenital lactic acidosis and the other had familial bilateral striatal necrosis with no known biochemical correlate. Although the clinical presentation of these patients was similar, we found distinctive MR abnormalities in characteristic locations in the seven patients with SNE, with or without detectable specific mitochondrial enzyme deficiency in cultured skin fibroblast assays. In our case studies of SNE patients with detectable enzyme deficiency states, defects in pyruvate dehydrogenase complex and cytochrome c oxidase have been found. The MR finding of note in SNE is the remarkably symmetrical involvement, most frequently of the putamen. In our study, lesions were also commonly found in the globus pallidus and the caudate nucleus, but never in the absence of putaminal abnormalities. Other areas of involvement included the paraventricular white matter, corpus callosum, substantia nigra, decussation of superior cerebellar peduncles, periaqueductal region, and brainstem.

In patients who present with lactic acidosis and whose MR findings show symmetrical abnormalities in the brain, but with sparing of the putamen, the diagnosis of SNE is in doubt.

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Subacute necrotizing encephalomyelopathy (SNE, or Leigh syndrome) is a familial neurodegenerative disease conforming to an autosomal recessive mode of transmission, commonly manifested in infancy or childhood. The onset is usually insidious, and the course is intermittently progressive for several years. However, adult onset cases have been described, and the course can be acute [1, 2].

Clinical presentations may vary; however, most children are normal at birth. Common findings at the time of presentation include psychomotor regression and brainstem and cerebellar dysfunction resulting in ataxia, dystonia, and nystagmus. Limb weakness and optic nerve pallor are often noted [2, 3, 4]. Laboratory findings include metabolic acidosis with elevated lactate and pyruvate concentrations in the blood and CSF, suggesting that a disorder of pyruvate metabolism may be the primary biochemical defect. Specific mitochondrial enzyme deficiencies associated with SNE have been reported, including pyruvate carboxylase deficiency, pyruvate dehydrogenase complex defects, and cytochrome c oxidase deficiency [2, 5-7].

Pathologically, symmetrical focal necrotic lesions can be seen in the subcortical white matter, basal ganglia, thalamus, midbrain, medulla, and posterior column of the spinal cord. The mamillary bodies are rarely involved, which is a differential point in the diagnosis of Wernicke encephalopathy, in which the mamillary bodies are often involved [8, 9]. Microscopically, there is vascular proliferation, demyelination, and neuronal necrosis [10, 11].

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We describe here the characteristic MR findings in conjunction with the clinical and biochemical findings in the antemortem diagnosis of SNE.

Subjects and Methods

The MR images of nine patients who presented with progressive neurological involvement were reviewed. Patients' ages ranged from 6 months to 4 years old; eight had lactic acidosis and one had normal blood and CSF lactate values. Images were obtained on a 1.5-T

superconductive magnet. Axial T2-weighted images were obtained with a multislice spin-echo pulse sequence, 3500–3700/80–120 (TR/TE), and 5-mm-thick sections. Image acquisition was done on a 512 × 512 matrix. All patients had axial images, and one patient also had coronal views. MR findings were correlated with the clinical history and laboratory findings. Skin biopsies were performed on all patients after obtaining informed consent from the parents. The cultured fibroblasts were assayed for a battery of oxidative enzymes: pyruvate dehydrogenase complex, pyruvate carboxylase, NADH cytochrome *b₅* reductase, succinate cytochrome *c* reductase, NADH dehydrogenase, succinate dehydrogenase, and cytochrome *c* oxidase, as previously reported [2, 6, 7].

TABLE 1: Clinical, Laboratory, and MR Findings in Patients with Subacute Necrotizing Encephalomyelopathy

| Patient No. | Age at Onset | Clinical Findings | Laboratory Findings | MR Findings (T2-Weighted Images) |
|-------------|--------------|--|--|--|
| 1 | 6 months | Delayed neurologic development; feeding difficulties; hypotonia; hyporeflexia; dystonic posturing; bilateral Babinski signs; bilateral optic nerve pallor; nystagmus | Increased serum lactate and pyruvate; increased CSF lactate and pyruvate; cytochrome <i>c</i> oxidase deficiency (skin fibroblast assay) | Symmetrically increased SI in putamen, globus pallidus, subthalamic nuclei, substantia nigra, cerebral peduncles, decussation of superior cerebellar peduncles, brachium of inferior colliculi, periaqueductal region, olivary nucleus, and inferior medulla |
| 2 | 16 months | Delayed neurologic development; hypertonia; hyperreflexia; spasticity; dystonia; gait disturbance; bilateral Babinski signs; bilateral optic nerve pallor | Increased serum lactate and pyruvate; increased CSF lactate and pyruvate; pyruvate dehydrogenase deficiency (skin fibroblast assay) | Symmetrically increased SI in putamen, periaqueductal region, substantia nigra, olivary nucleus, and inferior medulla |
| 3 | 15 months | Delayed neurologic development; ataxia; dystonia (L > R); spasticity; hyperreflexia; bilateral Babinski signs; bilateral optic nerve pallor (patient died with fulminant metabolic acidosis; no autopsy) | Increased serum lactate and pyruvate; increased CSF lactate and pyruvate; normal enzymes | Symmetrically increased SI in putamen, globus pallidus, caudate, and periaqueductal region |
| 4 | 4 years | Delayed neurologic development; dysarthria; spasticity; hypertonia; dystonia (R > L); right hemiparesis; hyperreflexia; right Babinski signs; bilateral optic nerve pallor | Increased serum lactate and pyruvate; increased CSF lactate; normal enzymes | Symmetrically increased SI in putamen; cortical and subcortical involvement of frontal, parietal, and occipital regions |
| 5 | 20 months | Delayed neurologic development; hypotonia; hyperreflexia; right hemiparesis | Increased serum lactate; increased CSF lactate; normal enzymes | Symmetrically increased SI in putamen and paraventricular white matter |
| 6 | 3 years | Delayed neurologic development; mild hypotonia; hyporeflexia; optic atrophy and nystagmus; neurosensory hearing loss; Babinski equivocal | Increased serum lactate; increased CSF lactate; cytochrome <i>c</i> oxidase deficiency (skin fibroblasts) | Symmetrically increased SI in putamen and substantia nigra |
| 7 | 1 year | Delayed neurologic development; hypotonia; ataxic; hyperreflexia; bilateral Babinski signs | Increased serum lactate; increased CSF lactate; cytochrome <i>c</i> oxidase deficiency (skin fibroblasts) | Symmetrically increased SI in putamen, medial geniculate body, restiform bodies, brachium of inferior colliculi, and inferior medulla |

Note.—SI = signal intensity, L = left, R = right.

Results

Seven of our nine patients had a clinical picture compatible with the diagnosis of SNE (Table 1). CT scanning in four of these patients showed bilateral, hypodense, nonenhancing lesions in the basal ganglia. On the heavily T2-weighted MR images, all seven of the SNE patients had high-signal lesions, symmetrically involving the putamen. There also were lesions involving the globus pallidus (two patients), the caudate (one patient), the substantia nigra (three patients), the paraventricular white matter (two patients), the cortical gray matter (one patient), subthalamic nuclei (one patient), periaqueductal region (three patients), and the medulla (three patients) (Table 2).

Correlations made with enzyme activity assays revealed that of the seven patients with clinical diagnosis of SNE and characteristic MR findings, four had specific mitochondrial enzyme deficiencies. Patient 2 had pyruvate dehydrogenase deficiency; patients 1, 6, and 7 had cytochrome *c* oxidase deficiency; patients 3, 4, and 5 had normal enzyme activity in cultured fibroblasts. MR of patient 1 showed symmetrical foci of increased signal involving the medulla, substantia nigra, cerebral peduncles, decussation of superior cerebellar peduncles, brachium of inferior colliculi, subthalamic nuclei, periaqueductal region, putamen, and globus pallidus (Table 1 and Fig. 1). Patient 2 had symmetrical foci of increased signal in the substantia nigra, periaqueductal region, olives, and putamen (Table 1 and Fig. 2). Patient 3 showed symmetrical hyperintense foci in the periaqueductal region, putamen, globus pallidus, and caudate (Table 1). Patients 4 and 5 showed lesions on MR involving the paraventricular white matter and cerebral cortex, in addition to the lesions in the putamen; MR findings in patient 6 showed symmetrical lesions in the putamen and substantia nigra. Patient 7 showed lesions in the putamen, medial geniculate body, restiform bodies, brachium of inferior colliculi, and medulla. One of the nine patients presenting with lactic acidosis and developmental delay did not have clinical features of SNE. A review of this patient's MR studies showed areas of high signal involving the temporal

lobes, paraventricular white matter, and centrum semiovale; there was no involvement of the putamen (patient 8 in Table 3). He has congenital lactic acidosis of undetermined origin.

Discussion

The diagnosis of SNE can be confusing because of its variety of clinical manifestations and laboratory abnormalities. Most often, a definite diagnosis is made only at necropsy. Involvement of the basal ganglia has been described previously on CT [10, 12, 13], which shows symmetrical, hypodense, nonenhancing lesions with predominant involvement of the putamen. In 1981, Chi et al. [4] reported autopsy and CT findings of a 28-month-old child with Leigh syndrome. The CT scan of this patient showed symmetrical lesions of low attenuation involving the basal ganglia and white matter. At autopsy, this patient showed typical histologic changes of Leigh syndrome with symmetrical involvement of the putamen. In addition, there was involvement of the periaqueductal region, which was not seen on CT.

With the increasing availability of MR for the examination of children with progressive degenerative diseases of the CNS, more cases of this disease are being recognized. Recently, there have been three reports of the MR findings in this disease [2, 14, 15]. These articles documented the higher sensitivity of MR in detecting lesions overall as compared with CT, and also noted a high frequency of involvement of the basal ganglia, in particular, the putamen. In patients who present with lactic acidosis without Leigh syndrome, MR findings often are abnormal. Focal hyperintense signal lesions can be seen predominantly in the deep white matter, paraventricular in distribution, perhaps related to watershed zones.

There have been several reports of the pathologic findings in SNE. The original case was described by Leigh in 1951 [9]. The case he presented showed symmetrical lesions involving the thalamus, midbrain, pons, medulla (inferior olives), and posterior column of the spinal cord. In 1971, Monpetit et al. [8] reviewed the pathologic findings of 50 cases of this disease. They found the basal ganglia to be involved in more than 65% of cases and the brainstem to be involved in 98%. Pathologically, the lesions consisted of areas of vascular proliferation and demyelination, which ultimately progressed to necrosis and cavitation [8-11].

Now with the discovery of the enzyme deficiencies in some of these patients and the advent of MR imaging, the diagnosis of SNE can be made more accurately, which permits early identification of these patients. SNE is a syndrome that embraces a wide spectrum of clinical severity associated with pyruvate carboxylase, pyruvate dehydrogenase, and cytochrome *c* oxidase deficiencies. It is expected that deficiencies of other enzymes involved in cerebral oxidative metabolism will be found soon. Some of these mitochondrial enzymes may be tissue specific. Normal enzyme activity in cultured skin fibroblasts, therefore, may not necessarily reflect brain mitochondrial enzyme activity [11].

TABLE 2: Distribution of Lesions in Seven Patients with Subacute Necrotizing Encephalomyelopathy

| Location of Lesions | No. of Cases |
|--|--------------|
| Putamen | 7 |
| Globus pallidus | 2 |
| Caudate | 1 |
| Substantia nigra | 3 |
| Periaqueductal region | 3 |
| Inferior medulla | 3 |
| Paraventricular white matter | 2 |
| Cortical gray matter | 1 |
| Decussation of superior cerebellar peduncles | 1 |
| Olivary nucleus | 2 |
| Medial geniculate body | 1 |
| Splenium | 1 |
| Brachium of inferior colliculi | 2 |
| Restiform bodies | 1 |
| Subthalamic nuclei | 1 |

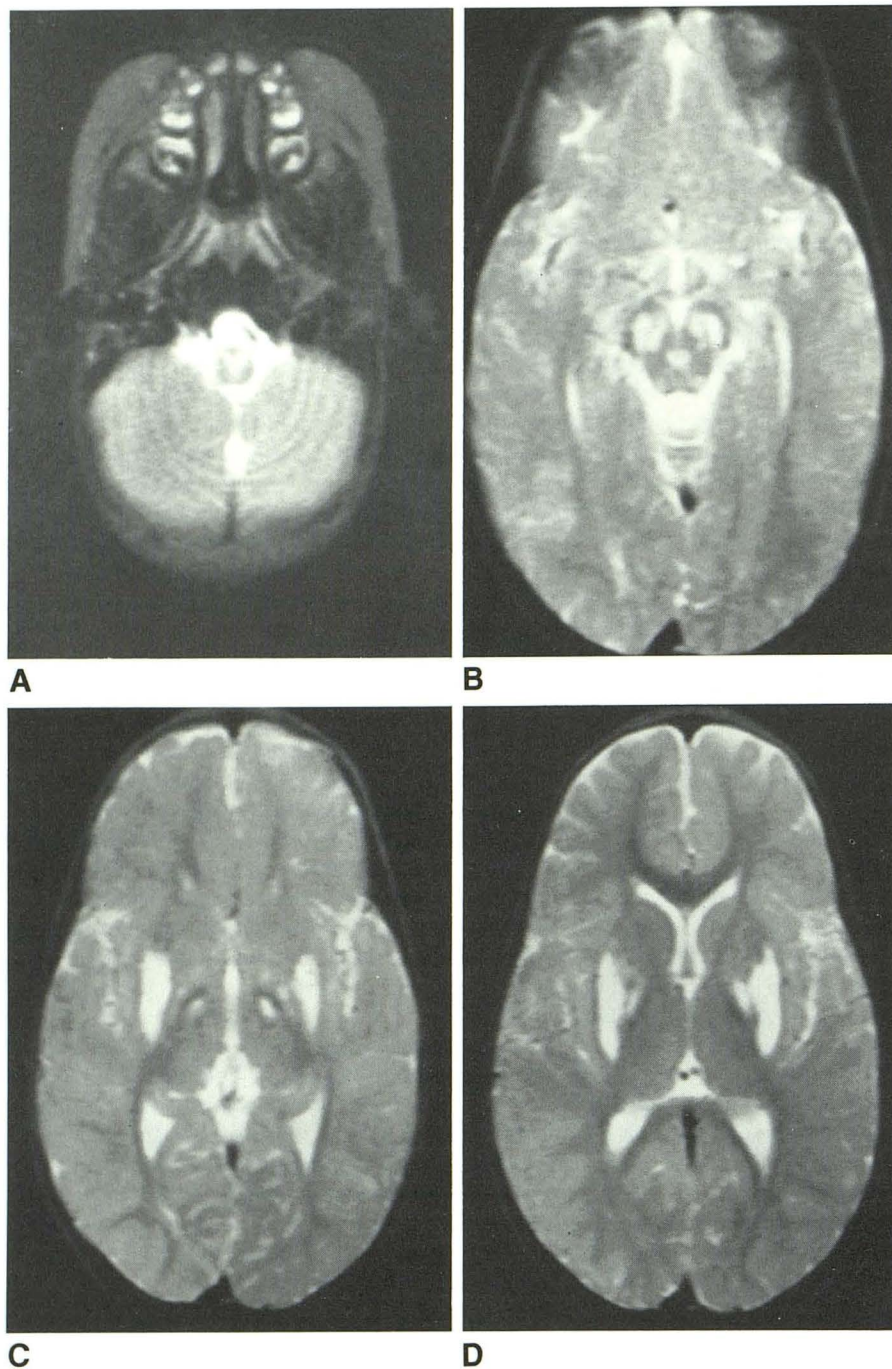


Fig. 1.—Case 1: T2-weighted axial MR images in 6-month-old patient with Leigh syndrome and cytochrome c oxidase deficiency.

A, Abnormal high signal involvement of medulla.

B, Abnormal high signal involvement of bilateral cerebral peduncles, substantia nigra, decussation of superior cerebellar peduncles, and periaqueductal region.

C, Symmetrically abnormal high signal involvement of putamina and, more medially, globus pallidi and subthalamic nuclei.

D, Higher section more clearly shows involvement of bilateral globus pallidus and putamen.

The differential diagnosis of disease entities with involvement of the basal ganglia manifesting in childhood include various toxic conditions such as carbon monoxide poisoning, cyanide poisoning, and a rare complication of viral encephalitis [11, 16, 17]. Such chronic conditions as familial striatal necrosis [18] (one case included in our study), Wilson disease, and Hallervorden-Spatz disease also have been noted to involve

the basal ganglia. Wilson disease tends to occur in older children and has specific laboratory abnormalities [19–21].

In conclusion, a pattern of symmetrical, hyperintense lesions on T2-weighted images involving the basal ganglia and brainstem, with predominant involvement of the putamen, is highly specific for SNE. In these patients further attempts

Fig. 2.—Case 2: T2-weighted axial and coronal MR images in 16-month-old patient with Leigh syndrome and pyruvate dehydrogenase deficiency.

A and B, Axial (A) and coronal (B) images show abnormal high signal involving substantia nigra and periaqueductal region.

C and D, Axial (C) and coronal (D) images show high signal foci in putamen bilaterally.

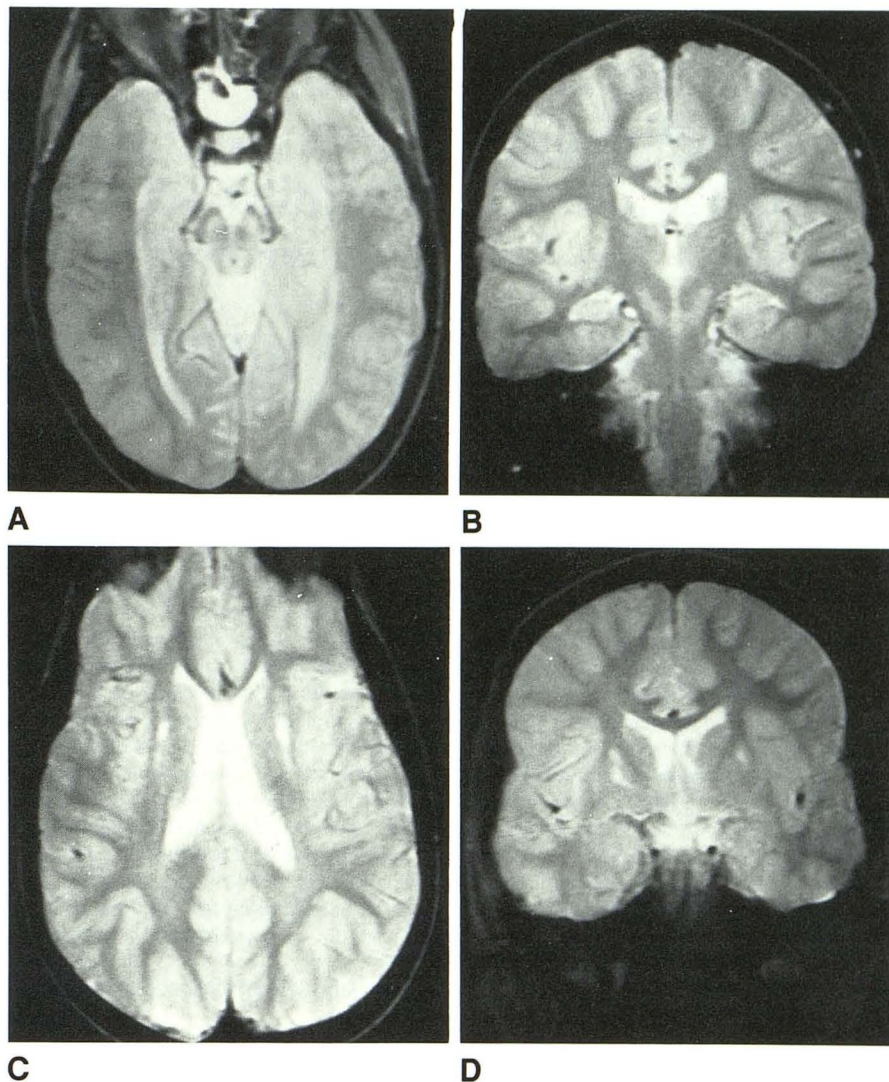


TABLE 3: Clinical, Laboratory, and MR Findings in Patients Without Subacute Necrotizing Encephalomyelopathy

| Patient No. | Age at Onset | Clinical Findings | Laboratory Findings | MR Findings (T2-Weighted Images) |
|-------------|--------------|--|---|---|
| 8 | 4 months | Delayed neurologic development; spasmus mutans; nystagmus | Increased serum lactate; normal enzymes | Increased SI in temporal lobes, paraventricular white matter of occipital region, and centrum semiovale |
| 9 | 6½ years | Hypotonia; dystonia; family history for familial bilateral striatal necrosis | Normal serum lactate; normal enzymes | Increased SI in bilateral globus pallidus |

Note.—SI = signal intensity.

should be made to identify a specific mitochondrial enzyme deficiency that has been associated with the diagnosis of subacute necrotizing encephalomyelopathy.

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