Leigh disease (subacute necrotizing encephalomyelopathy): MR documentation of the evolution of an acute attack.

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Leigh Disease (Subacute Necrotizing Encephalomyelopathy): MR Documentation of the Evolution of an Acute Attack

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Summary: The radiologic evolution of Leigh disease is documented with sequential brain MR in the acute phase of the illness, at 3 weeks, and at 3 months. High-signal-intensity lesions seen on T2-weighted images in the first week resolved by 3 months, whereas new lesions appear during the chronic stage. Putamenal involvement is not a pathognomonic radiologic finding. Brain stem tegmentum, particularly the mesencephalon, is characteristically involved on MR in the early and late phases of the illness.

Index terms: Degenerative spinal cord disease; Degenerative brain disease; Brain, magnetic resonance; Pediatric neuroradiology

Leigh disease or subacute necrotizing encephalomyelopathy (SNE) is an inherited neurodegenerative disease with an episodic or chronic progressive clinical course. The defect is caused by deficiency of either the mitochondrial enzyme cytochrome *c* oxidase or pyruvate decarboxylase or by pyruvate dehydrogenase complex (PDHC) (1–3). Radiologic abnormalities in the brain stem on magnetic resonance (MR) during the early stages make the diagnosis probable while awaiting confirmatory laboratory results.

We report a patient with juvenile-onset SNE caused by PDHC deficiency. During the early phase of the disease, characteristic as well as unusual features on MR were seen. As the disease progressed, subsequent radiologic studies chronicled the evolution of the lesions.

Case Report

This 13-year-old girl presented with vomiting and ataxia that lasted 5 days. A cranial computed tomographic (CT) scan was normal. A second episode of nausea, vomiting, and ataxia occurred 9 months later when the patient was admitted to our hospital for investigation. Examination revealed an alert girl with minor calculation difficulties. Conjugate eye movements revealed abnormal smooth pursuit and gaze-evoked horizontal nystagmus. There was mild to moderate motor weakness, predominantly in the proximal muscles of the upper and lower limbs, with reduced tendon jerks. A sensory examination was normal. Coordination in the limbs was impaired, and her gait was ataxic.

The significant biochemical abnormalities were elevated serum lactate (6.9 mmol/L; normal, 0.8 to 1.7) and pyruvate (238 μmol/L; normal, 40 to 80) levels. The cerebrospinal fluid was normal. CT brain scan was again normal. Nerve conduction studies showed no evidence of a motor or sensory neuropathy, and an electrocardiogram was normal.

A skin fibroblast culture was grown from a skin biopsy and showed normal pyruvate carboxylase activity (cell-free assay) by a modified method of Bartlett et al (4). PDHC activity (whole-cell assay) by a modified method of Sheu et al was measured three times with different matched control fibroblasts (5). The PDHC activity was 30 to 40% of the matched control fibroblasts. "Total" PDHC activity was established after pretreatment of the fibroblasts with dichloroacetate. The control fibroblasts increased their activity by threefold, whereas the patient's fibroblasts were unchanged; hence, the "total" PDHC enzyme gave a residual activity of only 15%.

The patient developed generalized tonic-clonic seizures and a deterioration in consciousness. She was stuporous on day 4 and comatose on day 7. A CT head scan on day 5 was again normal. An MR study on day 7 revealed discrete, bilateral, symmetrical lesions of increased signal intensity on the T2-weighted images (2000/80 [repetition time/echo time]) in the cortical-subcortical junction of the frontoparietal region, extending to the vertex (Fig 1a). Bilateral, symmetrical high-signal-intensity foci were also seen on T2-weighted images around the walls of the third ventricle, medial thalamic nuclei, rostral substantia nigra, periaqueductal region, midbrain, pontine tegmentum, and dentate nuclei. Bright "target" lesions were seen symmetrically in the region of the red nuclei on T2-weighted images (Fig 1b). Early pontine and midbrain atrophy caused widening of the encompassing cisterns and were best shown on the T1-weighted images (600/27).

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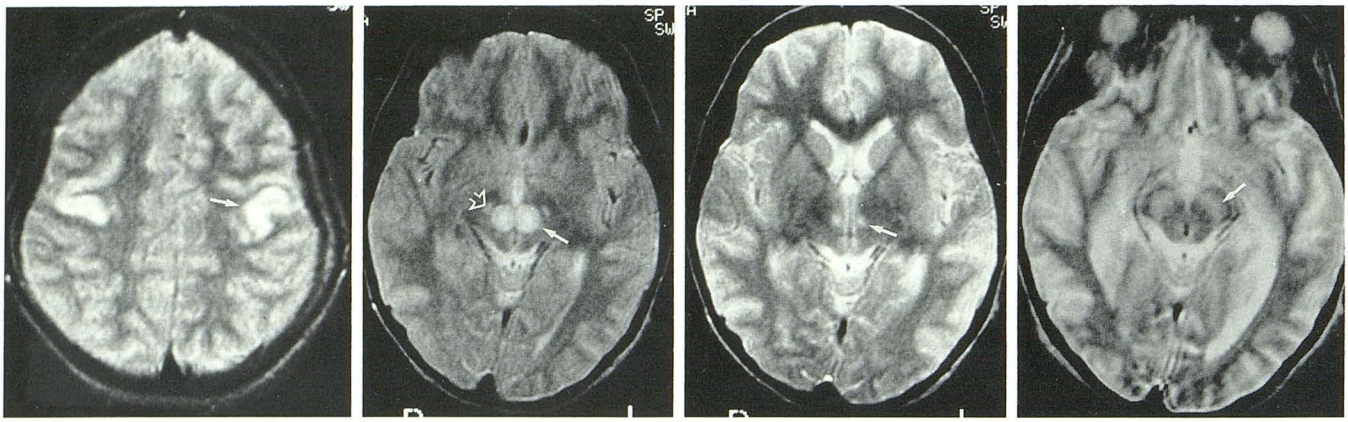

Fig. 1. *A*, T2-weighted images (2000/90) showing discrete symmetrical lesions of increased signal intensity at the cortical-subcortical junction of the frontoparietal region (*arrow*) (day 7).

B, Bright symmetrical "target" lesions (2000/90) in the region of the red nuclei on T2-weighted images (day 7) (*closed arrow*). Increased-signal-intensity lesions are seen in the rostral substantia nigra (*open arrow*).

Fig. 2. Partial resolution of "target" lesions (*arrow*) in the region of the red nuclei on T2-weighted images (day 20) (2000/90).

Fig. 3. Progression of increased-signal-intensity lesions on the T2-weighted images (2000/90) in the substantia nigra (*arrow*) (day 63).

Deterioration continued with complete external ophthalmoplegia, areflexia, and no response to painful stimuli on day 8. On day 11, a modest clinical improvement was noted with the development of spontaneous horizontal eye movements and mild facial grimacing to painful stimuli. During the succeeding weeks, the patient developed increasing spasticity and dystonic posturing of the limbs.

A second MR on day 20 showed partial resolution of the "target" lesions in the region of the red nuclei (Fig 2). The cortical-subcortical lesions showed a brighter signal on T2-weighted images. There was partial resolution of the lesions in the dentate nuclei. Subsequently, the lactate level in blood fell over the next 2 weeks to a level within the upper limits of normal (1.5 mmol/L). The patient developed an akinetic mute state with marked dystonic contractures and assumed a fetal posture.

Although there had been no further clinical relapse since the initial deterioration, a third MR done on day 63 showed high-signal-intensity lesions of the T2-weighted images in both globi pallidi. Extension of the lesions in the substantia nigra was also noted (Fig 3). The other previously mentioned lesions showed complete resolution. There was gross atrophy of the cerebral hemispheres. Marked brain stem atrophy was also evident with pontine, medullary, and ambient cisternal enlargement.

Discussion

The pathology in SNE has been shown to consist of bilateral, symmetrical lesions in subcortical structures including brain stem, basal ganglia, thalamus, and optic nerves (6–10). Histopathology includes neuronal, myelin, axonal, and dendritic damage with capillary proliferation and, if severe, neuronal necrosis and cavitation. Characteristically, the lesions are centered around the tegmentum of the brain stem and caudal portion of the walls of the third ventricle (6), as seen in our patient. The most common pathologically demonstrated sites in order of decreasing frequency are the pontine, medullary and midbrain tegmenta, substantia nigra, ventral medulla, putamen, cerebellum, optic nerves, and thalami (6). The substantia nigra has been shown to be involved in more than 50% of pathologically verified cases of Leigh syndrome (4), and was involved radiologically in our patient (Fig 3). Cortical involvement (Fig 1a) is a variable finding both radiologically and pathologically (6, 11).

The first MR (Fig 1b) in our patient also showed involvement of the red nuclei with "target" high-signal-intensity lesions. Kissel et al state that the red nuclei are characteristically spared (11), although others have found the nuclei to be involved in eight of 50 pathologically proved cases (6). It is of interest that the symmetrical lesions in the dentate nuclei, red nuclei, thalami, and discrete cortical-subcortical regions seen on the T2-weighted images on the first two MR scans (days 7 and 20) showed complete resolution on the third MR scan (day 63), indicating that lesions seen on MR are dependent on the timing of the study (12). The marked T2 signal changes in the dentate and red and thalamic nuclei on the first MR suggest involvement of the dentatorubrothalamic tract, rather than discrete lesions. The increasing T2-weighted signal seen in the sub-

stantia nigra on earlier sequential scans is interestingly followed by mild signal changes in the globi pallidi on the MR of day 63. Presumably, this delayed involvement of the pallidum is caused by Wallerian degeneration in the nigropallidal afferents.

Striatal involvement, particularly putamenal, has been documented radiologically as characteristic of SNE (11, 13, 14). Medina et al (15) state that the absence of putamenal lesions in an otherwise characteristic case casts doubt on the diagnosis. Those authors report seven patients with radiologic features suggestive of this syndrome, all of whom share putamenal involvement, but do not specify disease duration in their patients. DiMauro and associates (10), however, report no putamenal involvement in five pathologically confirmed cases caused by cytochrome *c* deficiency, with the brunt of the disease falling in the brain stem. A large autopsy series found basal ganglia involvement in 67% and brain stem tegmentum involvement in 98% of cases (6).

Neither a short duration nor an episodic course, as in our patient, bears any relation to the absence of putamenal involvement. Three of eight previously reported cases of chronic progressive SNE had no putamenal involvement on MR after, respectively, 8 months, 21 months, and 7.5 years (7). Another case of an adult with an episodic disease course was reported to develop putamenal lesions after a disease duration of only 3 months (11).

In conclusion, we have reported a case of juvenile-onset Leigh disease, caused by PDHC deficiency, with episodic ataxia. The absence of putamenal lesions on MR in early (11; this case) or late (7, 10) disease does not exclude the diagnosis. Symmetrical, high-intensity brain stem lesions on T2-weighted images, particularly mesencephalic, are characteristically seen in these metabolic encephalopathies, irrespective of duration.

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