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Case Report

Leigh Syndrome in a 3-Year-Old Boy with Unusual Brain MR Imaging and Pathologic Findings

Meral Topçu, Isil Saatci, R. Anil Apak, Figen Sylemezoglu, and Zuhall Akc,ören

Summary: We report unusual MR serial imaging and electron microscopy findings in a 3-year-old boy who had Leigh syndrome with cytochrome-c oxidase (cox) deficiency. The MR imaging findings included periventricular white matter involvement, posteroanterior progression, and extension through the corpus callosum and internal capsule; however, no basal ganglia or brain stem abnormality was found, which was suggestive of leukodystrophy. The most noteworthy findings were the cystic foci with contrast enhancement in the affected white matter.

Leigh syndrome, or subacute necrotizing encephalomyelopathy, is an inherited, progressive, neurodegenerative disease of infancy or early childhood with variable course and prognosis. (1, 2). The typical MR imaging findings include symmetrical putaminal involvement, which may be associated with the abnormality of the caudate nuclei, globus pallidi, thalami, brain stem, and, less frequently, the cerebral cortex (3). Few cases of white matter involvement have been reported (4). Pathologic examination of Leigh syndrome reveals spongiform degeneration, demyelination, astrocytosis, microglial reaction, vascular proliferation, and cystic cavitation of the cerebral white matter (5–7).

We report the unusual findings on serial MR images and histopathologic examinations in a 3-year-old boy with Leigh syndrome caused by cytochrome-c oxidase (cox) deficiency.

Case Report

A 3-year-old boy, who was healthy until 6 months earlier, when he presented with intermittent lateral deviation of the left eye and progressive mental and motor deterioration. He had no seizures.

He was the third living child of a sixth pregnancy from second-generation, consanguineous parents, and had brothers who died within their first week of life because of respiratory failure.

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At admission, he was uncooperative and disoriented. His weight and height were below the third percentile, but his head circumference was normal. He had marked spasticity, having flexor posture on the upper and extensor posture on the lower extremities, with hyperactive deep tendon reflexes, bilateral positive extensor plantar response, and Clonus. Gag reflex and swallowing were absent. Eye movements were normal, with no nystagmus. The fundus examination was unremarkable.

Laboratory data included normal complete blood count, urinalysis, liver and renal functions, with normal triglyceride, cholesterol, and uric acid levels. He had mild metabolic acidosis, with normal anion gap. Serum amino acid screening, blood ammonia, lactate, and pyruvate levels were normal; however, urine amino acid assay showed increased glycine, alanine, and glutamine. CSF analysis was normal, including lactate and pyruvate levels, with lactate to pyruvate ratio measured at 1200:100 mmol/L. EEG showed slowing on background rhythm and no epileptic activity.

Brain MR imaging showed bilateral, symmetrical involvement of the parieto-occipital periventricular white matter, the posterior aspect of the posterior crus of the internal capsules, and abnormality of the corpus callosum at the genu and splenium, with T2 hyperintensity and T1 hypointensity (Fig 1A–B). There were cystic foci within the involved periventricular white matter. Foci of contrast enhancement, mostly located at the periphery of the abnormal areas, were present (Figure 1C). The basal ganglia, thalami, brain stem, and cerebellum were not involved, and the cortex appeared normal. There were no associated atrophic changes. Other tests, including nerve-conduction velocities, electro- and echocardiographies, and lysosomal enzyme and organic acid analysis, revealed no abnormality.

His symptoms were progressively increasing during his clinical course. Follow-up brain MR imaging at 3 months revealed markedly increased periventricular white matter abnormality, with lesions extending anteriorly and involving the entire periventricular white matter, including the frontal and temporal regions. The U-fibers remained unaffected (Figure 2A). Again noted were the cystic changes located particularly in the posterior periventricular white matter. Foci of contrast enhancement were still present at the periphery of the abnormal white matter. The external capsule was partially involved. The basal ganglia, thalami, and the brain stem remained unaffected. On the other hand, the involvement of the corpus callosum was striking (Figure 2B). New lesions appeared in the cerebellar hemispheres. Mild atrophy developed during this interval.

Histochemical investigation of the muscle biopsy specimen revealed no abnormalities except for the absence of cox activity. Mitochondrial DNA analysis, performed by polymerase chain reaction technique, did not show any known mutation.

Histopathologic examination of the brain biopsy specimen revealed thickening of leptomeninges and prominent spongiosis, nonspecific macrophage infiltration, and variable degrees of astrogliosis, where the astrocytes appeared swollen within the white matter. Cerebral cortex had relatively preserved layering. Electron microscopic examination revealed

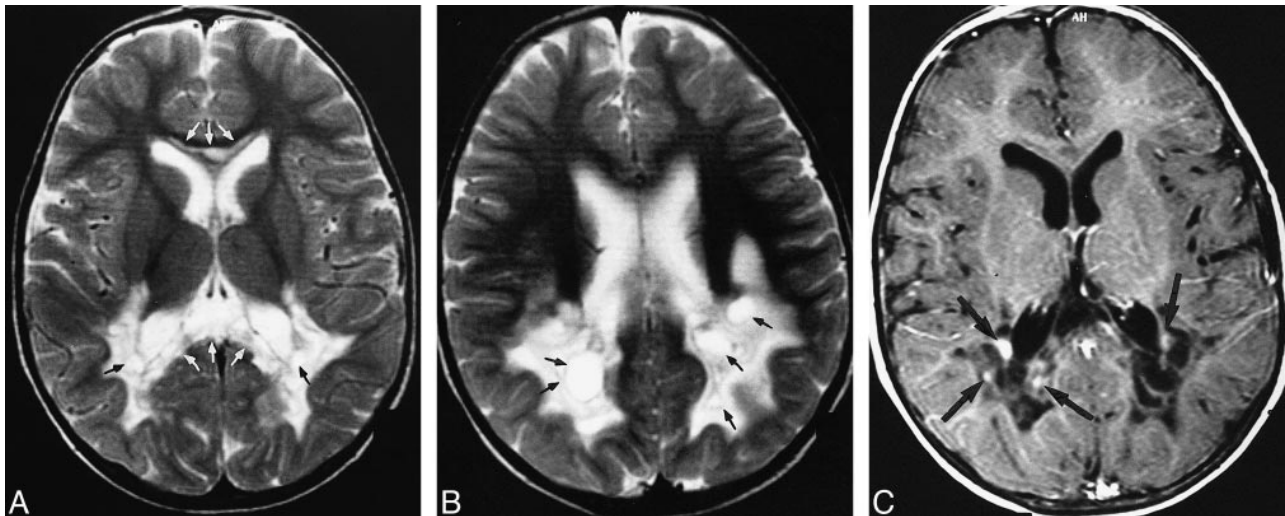


FIG 1. Initial MR examination.

A and B, T2-weighted (3500/98 [TR/TE]) axial turbo spin-echo images showing involvement of the posterior periventricular white matter, symmetrical bilaterally (A and B), with the abnormal signal intensity in the genu and splenium of the corpus callosum (white arrows, A). The hyperintensity extends to the posterior crus of the internal capsule (A). There are well-marginated cystic areas within the abnormal white matter (black arrows). Note the basal ganglia are not affected.

C, Contrast-enhanced T1-weighted (600/14 [TR/TE]) axial image, corresponding to figure A, showing the cystic nature of the periventricular white matter with foci of contrast enhancement mostly at the periphery of the abnormal area (black arrows).

diffusely scattered foam cells within the cerebral white matter (Fig 3).

The patient was diagnosed with Leigh syndrome resulting from cox deficiency based on clinical presentation and laboratory findings. Mitochondrial cocktail therapy, including coenzyme Q, thiamine, riboflavin, and vitamin C, was started. He showed mild improvement at 6-month follow-up, with spasticity mildly reduced, swallowing function regained, and normal background activity re-established on EEG.

Discussion

The imaging findings of Leigh syndrome have been reported in a number of publications and typical imaging findings have been considered to be the diagnostic hallmark (8, 9). Putaminal involvement has been reported to be the constant feature, and several reports have supported this statement

(10, 11). Putaminal lesions have showed increased T2 signal intensity that might be associated with swelling in the acute-subacute phase or shrinkage in the late stage. The other abnormalities were foci of increased T2 signal involving the medulla, substantia nigra, cerebral peduncles, decussation of superior cerebellar peduncles, brachium of inferior colliculi, subthalamic nuclei, thalami, periaqueductal region, globus pallidus, and caudate nuclei. Cortical involvement might also accompany the basal ganglia and brain stem lesions. Involvement of cerebral white matter has only been reported in a few cases (12).

In the presented case, Leigh disease has found to be resulting from cox deficiency. The initial MR examination, obtained at 3 years of age, revealed an appearance of leukodystrophy with increased T2

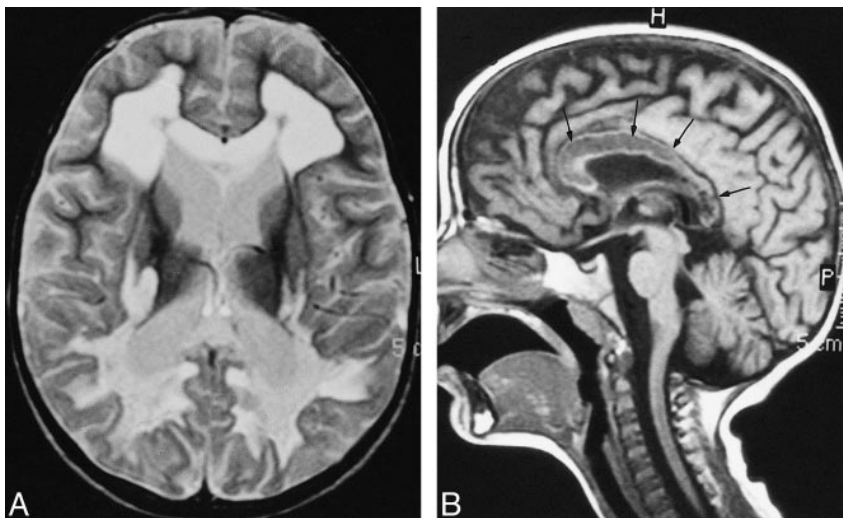


FIG 2. Repeat MR examination at 3 months

A, T2-weighted (2340/90 [TR/TE]) axial turbo spin-echo image through the same level as 1A, showing the progression of periventricular white matter abnormality. Corpus callosum appear swollen and hyperintensity extends further through the internal capsule as well as in the external capsule. Note that the U-fibers are spared.

B, Unenhanced T1-weighted (550/15 [TR/TE]) midsagittal image showing diffuse involvement of the corpus callosum, with decreased signal intensity (arrows).

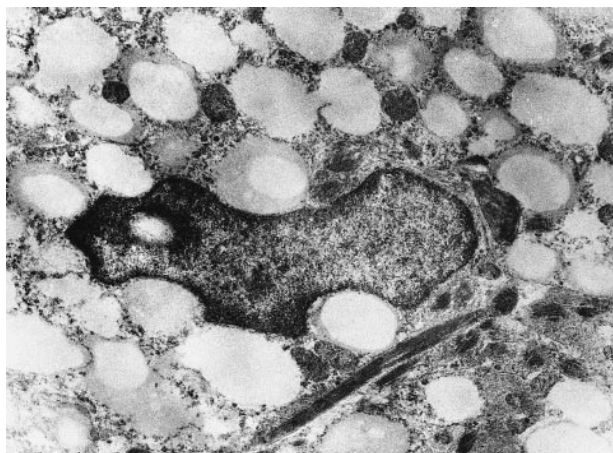


FIG 3. Electron microscopic findings of the brain tissue showing foam cells within the cerebral white matter.

signal intensity confined to periventricular white matter, particularly at the posterior region, internal capsule, and corpus callosum. The basal ganglia and brain stem were intact. There were well-defined cystic areas within the abnormal white matter and foci of contrast enhancement. The parenchyma appeared swollen with mild mass effect on the ventricles and sulcal effacement. The MR imaging findings were suggestive of primary white matter disease with a "leukodystrophy pattern" rather than gray and white matter involvement. The patient showed rapid deterioration within 3 months. The follow-up MR examination showed significant extension of the white matter abnormality, involving the entire periventricular region and associated parenchymal loss, which was evident by ventricular dilation and, to a lesser degree, by a widened cortical sulci. The sparing of U-fibers was noteworthy. The brain stem and basal ganglia remained intact. Additional involvement of cerebellar white matter, however, was noted. There was still some contrast enhancement, seemingly at the periphery of the abnormal regions.

The diffuse involvement of white matter in the absence of basal ganglia abnormality is uncommon in Leigh syndrome. Harpey et al (12) reported a similar case in which cox deficiency was detected and their patient also presented with isolated diffuse leukodystrophy; however, the entire cerebral white matter was affected, unlike our case, in whom the peripheral white matter was spared. Zafeiriou and colleagues (4) reported two siblings with Leigh disease with clinical and radiologic features suggestive of leukodystrophy. Interestingly, deficient enzyme again was cox. These two patients, however, had pons involvement in addition to diffuse abnormality of the cerebral white matter, and dorsal pons involvement has been previously reported in the cox deficiency. In both reports, the white matter was affected both anteriorly and posteriorly. In our patient, however, the initial examination provided a clue that the white matter involvement preferably started posteriorly, then

extended to result in diffuse white matter involvement and the U-fibers remained spared, at least at the onset. In the series of Barkovich et al (11), one patient in a group of seven, had diffuse white matter involvement, but that particular patient also had putaminal and caudate lesions. In the group of Vallanne et al (10), three patients had white matter abnormality. One also had cyst-like changes, with involved parenchyma appearing swollen. Frontotemporal white matter was preferentially affected in this patient, unlike the posterior involvement in ours. The remaining patients had diffuse white matter signal intensity change. Moreover, our patient showed prominent symmetrical lesions in the cerebellar white matter, and this has not been reported in any of these previous publications.

The appearance of the abnormal white matter at the periventricular region was peculiar in that there were cystic foci with well-defined margins and small nodular contrast enhancement, primarily at the periphery of the involved parenchyma. This appearance can easily be attributed to characteristic pathologic findings in Leigh syndrome; ie, cystic cavitation and spongiform degeneration in addition to demyelination, astrocystosis, and microglial reaction. The vascular proliferation may possibly be accounted for the contrast enhancement. The electron microscopic finding of diffusely scattered foam cells within the cerebral white matter detected in our patient has not been reported previously. This finding may also have contributed to the appearance of milimetric cystic foci present within the cerebral white matter, in addition to the above-mentioned light microscopy findings.

In conclusion, absence of putaminal involvement does not rule out the diagnosis of Leigh syndrome. Diffuse white matter abnormality, with the appearance of leukodystrophy, may occur in the absence of basal ganglia lesions, the hallmark of the disease. Cox deficiency may present with symmetrical periventricular posteroanterior white matter abnormality, with cystic changes, contrast enhancement, and diffuse corpus callosum involvement on MR images.

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Clinical NMR Imaging of the Brain: 140 Cases

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Cranial nuclear magnetic resonance (NMR) scans were performed on 13 healthy volunteers and 140 patients with a broad spectrum of neurologic disease and compared with x-ray computed tomography (CT) scans. The NMR scans included a variety of sequences reflecting proton density, blood flow, T_1 , and T_2 as well as transverse, sagittal, and coronal images. White matter, gray matter, and cerebrospinal fluid were clearly distinguished in the normal brain with inversion-recovery (IR) sequences, and normal progressive myelination was demonstrated in infants and children.

Acute hemorrhages displayed short T_1 values, but other pathologic processes such as infarction, infection, demyelination, edema, and malignancy were associated with long T_1 values. Cysts had very long T_1 values (about that of cerebrospinal fluid). Spin-echo (SE) sequences showed increased values of T_2 in a variety of conditions and highlighted lesions against the relatively featureless background of the remaining brain. With inversion-recovery scans, different stages of infarction were recognized in the hemispheres. NMR was more useful than CT in demonstrating brainstem infarction.

The white matter lesions in demyelinating diseases were well demonstrated with NMR scans. Many more lesions were observed in multiple sclerosis with NMR than with CT. Benign tumors were well seen and usually had shorter T_1 values than malignant tumors. Mass effects from tumors were generally better demonstrated with NMR than with CT, including more subtle mass effects such as displacement of the external capsule. Abnormalities were seen in diseases of the basal ganglia, including marked atrophy of the head of the caudate nucleus in Huntington chorea.

Advantages of NMR imaging include the high level of gray-white matter contrast, lack of bone artifact, variety of possible sequences, transverse, sagittal, and coronal imaging, sensitivity to pathologic change, and lack of known hazard. Disadvantages include lack of bone detail, limited spatial resolution, lack of contrast agents, and cost. Promising directions for future clinical research include developmental neurology, tissue characterization with T_1 and T_2 , assessment of blood flow, and the development of contrast agents. Much more detailed evaluation will be required, but NMR seems to be a potentially important addition to existing techniques of neurologic diagnosis.

Although NMR imaging was initially proposed in the United States [1, 2], much of the early development was carried out by small groups of physicists and engineers in Britain based at the Department of Bio-medical Physics in Aberdeen [3], the Department of Physics in Nottingham [4], and the Central Research Laboratories of Thorn-EMI Ltd. The hitherto published results of NMR imaging of the brain largely reflect the activities of these groups, although major contributions are expected from other centers in the near future. Head images were produced by the Thorn-EMI group in 1978 [5], and a series of brain scans was published by the Nottingham group during 1980 [6-10]. The Aberdeen group produced normal head images in 1980 [11] and have described abnormal cases during 1981 [12]. Nevertheless the total volume of published cerebral cases remains small. Fewer than 40 cases have been described with the largest series a group of 10 patients with multiple sclerosis [13].

In previous studies we have emphasized the high level of gray-matter contrast

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