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Case Report

Leigh's disease, a fatal finding in the common world: A case report [☆]

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ABSTRACT

Leigh syndrome is a neurodegenerative mitochondrial disorder of childhood characterized by symmetrical spongiform lesions in the brain. The clinical presentation of Leigh's syndrome can vary significantly. However, in the majority of cases, it usually presents as a progressive neurological disease involving motor and cognitive development. It is common to see signs and symptoms of the midbrain and brainstem involvement. Limited data are present on the brain processes occurring in Leigh's syndrome which can be attributed to fatal respiratory failure. Raised lactate levels in the blood and/or cerebrospinal fluid are noted. Magnetic resonance imaging (MRI) findings such as necrotic, symmetrical lesions in the BG/brain stem are helpful in arriving at the diagnosis of Leigh's syndrome. It's of utmost importance to determine whether fatal respiratory failure can be predicted based on clinical characteristics and findings on MRI. In our report, we presented 3 cases from rural India, including a 2-year-old male child presenting with UMN lesion signs, a 3-month-old female infant with delayed developmental milestones with lab results suggestive of Leigh's disease, and a 12-year-old female child with epistaxis and generalized weakness. As discussed above, all 3 cases presented differently with a variety of signs and symptoms and would

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have gone undiagnosed without the use of brain imaging. The study concluded with the impression that while MRI is essential to the initial diagnosis of Leigh's disease, MRI alone cannot be used to predict fatal respiratory failure in patients with Leigh's disease. In any dilemma regarding diagnosis even with MRI, molecular studies remain the gold standard.

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Introduction

Leigh's disease, more aptly termed subacute necrotizing encephalomyelopathy, is a degenerative disorder affecting the central nervous system. The disease is named after Leigh in 1951 [1]. The disease classically presents with regression of milestones occurring early in childhood with typical imaging features. Certain occasions also present later in adulthood as well [2]. In this article, we present 3 cases of Leigh's disease with different clinical presentations. Patients were included with the criteria being raised lactate levels in the blood and/or cerebrospinal fluid with clinical suspicion of Leigh's syndrome. Any other patient without raised lactate levels/other mitochondrial disorders (Kearns Sayre syndrome/MELAS)/metabolic encephalopathy were excluded.

With this study, we aim to determine whether life-threatening respiratory failure can be predicted based on clinical characteristics and findings from magnetic resonance imaging (MRI).

Saito et al., in 2019, concluded that CEST imaging can be used as a biomarker for intracerebral levels of lactate in mitochondrial diseases, which was also verified in their study, using imaging modalities [3].

Case presentation

Case 1: A 2-year-old male child with a normal institutional vaginal delivery presented with delayed developmental milestones and excessive irritability for the past 3 months. Examination of the child revealed bilateral lower limb hypertonia and extensor plantar reflexes. Laboratory analysis showed elevated serum lactate. MRI brain of the child revealed symmetrical altered signal intensities in bilateral caudate nuclei (predominantly involving the body), lentiform nuclei, midbrain (Fig. 2), posterior aspect of the pons, anterior aspect of the medulla (Fig. 4), bilateral dentate nuclei, and vermis which appear hypointense on T1 and hyperintense on T2 & FLAIR sequences. The lesions in the midbrain and medulla demonstrate mild diffusion restriction. In addition, altered signal intensities are noted in the bilateral deep white matter of the parietal and occipital lobes (Fig. 5). The definite diagnosis of Leigh's disease was made after detection of mutation in the exon of the MT-ND5 gene (G12622A), following PCR amplification.

Case 2: A female child of age 3 months presented with delayed milestones and involuntary movements since birth. The child had a history of birth asphyxia with an APGAR score at 1 minute, of 6. Laboratory analysis showed elevated serum lac-

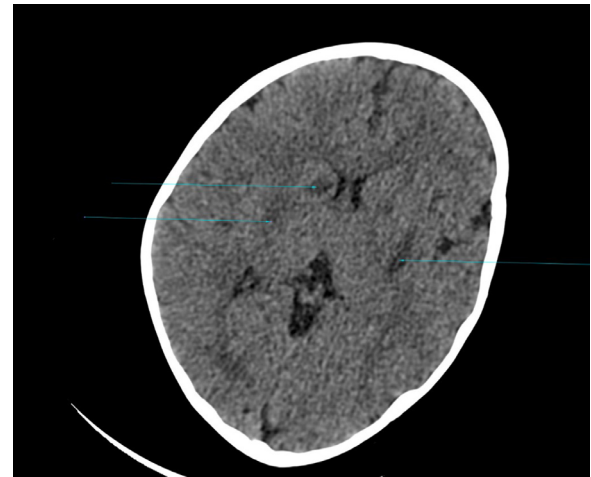


Fig. 1 – Axial CT brain—symmetrical hypodensities in the bilateral caudate nuclei and lentiform nuclei.

tate and metabolic acidosis. MRI brain of the child revealed altered signal intensities in the head and anterior body of caudate nuclei, bilateral lentiform nuclei, midbrain, and right centrum semiovale which appear hypointense on T1 and hyperintense on T2 sequences. The lesions in the midbrain demonstrate diffusion restriction (Fig. 6). The definite diagnosis of Leigh's disease was made after detection of mutation in the exon of the MT-ATP6 gene (T9191C), following PCR amplification.

Case 3: A 12-year-old female child presented with epistaxis and generalized weakness for 6 months. Laboratory analysis showed elevated serum lactate. On imaging, bilateral caudate and lentiform nuclei showed symmetrical hypodensities on plain computed tomography (CT) of the brain (Fig. 1). On MRI brain, symmetrical altered signal intensities (Fig. 3) in bilateral caudate and lentiform nuclei, which appear hypointense on T1 and hyperintense on T2 & FLAIR sequences were noted. However, there was no evidence of diffusion restriction in these lesions. In this particular instance, genetic testing was deferred because neither of the patient's parents agreed to provide their consent for genetic testing. Hence, the clinical and MRI findings were used to arrive at a conclusive diagnosis of Leigh's disease.

Discussion

Leigh's disease is the clinical result of heterogeneous biochemical abnormalities in the mitochondria [4]. It is known to

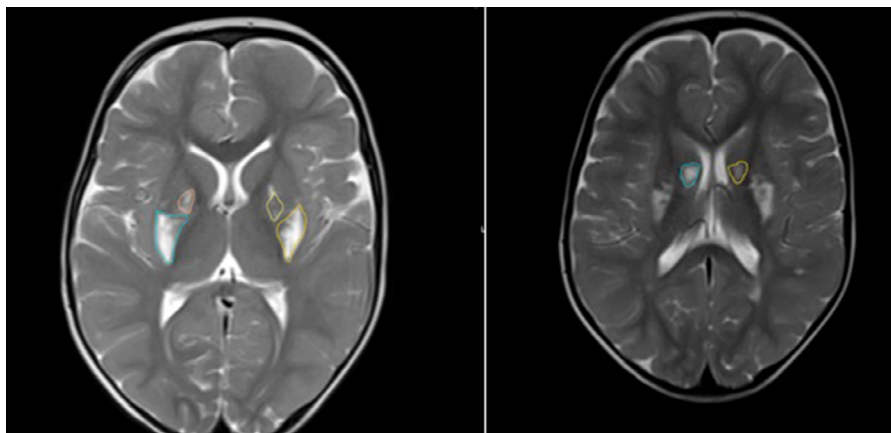


Fig. 2 – T2W axial image—symmetrical altered signal intensities are noted in the bilateral caudate nuclei (predominantly involving the body), and lentiform nuclei (putamen and globus pallidus).

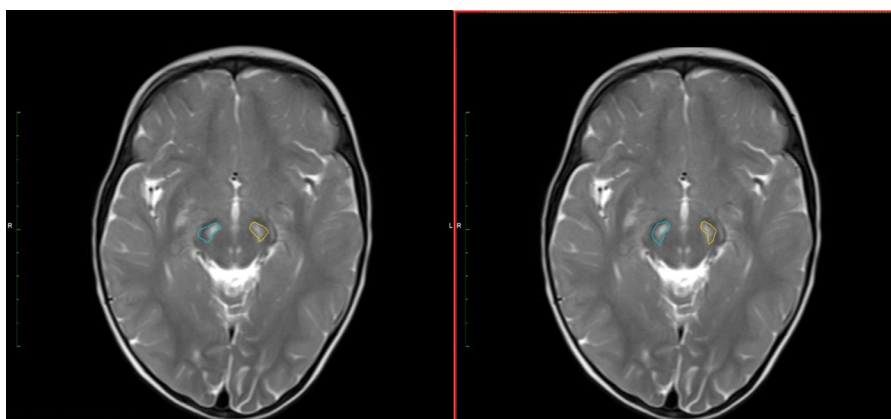


Fig. 3 – T2W axial image—symmetrical altered signal intensities are noted in the midbrain (bilateral substantia nigra).

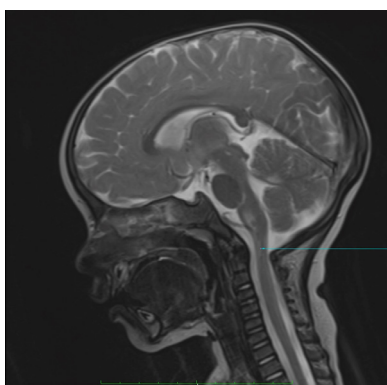


Fig. 4 – T2W sagittal image—hyperintensity in the brainstem (posterior aspect of pons, anterior aspect of medulla).

affect about one in every 40,000 live births around the world [5]. Though the exact etiology is still debatable, numerous mutations have been described in the various enzymes of the respiratory chain. The involvement of pyruvate dehydrogenase

complex, cytochrome oxidase, complex V, thiamine deficiency, succinate dehydrogenase deficiency, and complex I deficiency are some of the causes of Leigh's disease [6].

Most of the patients present chronically with a possible acute presentation during metabolic decompensation. Affected infants and children present typically toward the end of the first year of life. Hypotonia and psychomotor deterioration is the usual presentation. Ataxia, ophthalmoplegia, ptosis, dystonia, and swallowing difficulties are the usual sequelae. Pathologic abnormalities described in Leigh's include neuronal loss, vascular proliferation, microcystic cavitation, and demyelination in the midbrain, basal ganglia, cerebellar dentate nuclei, and cerebral white matter [7]. Some patients also present later in childhood or adulthood [2].

On imaging, Leigh's disease has predominant gray matter involvement with associated white matter involvement. The typical sites of involvement include deep gray matter, cerebellum, and brainstem. Some rare cases of cortical involvement have also been described. But the predominant site is the striatum. MRI is the imaging investigation of choice for all the metabolic and developmental disorders involving the brain as it can characterize the lesion with more confidence than neurosonography and CT. CT of the affected patients

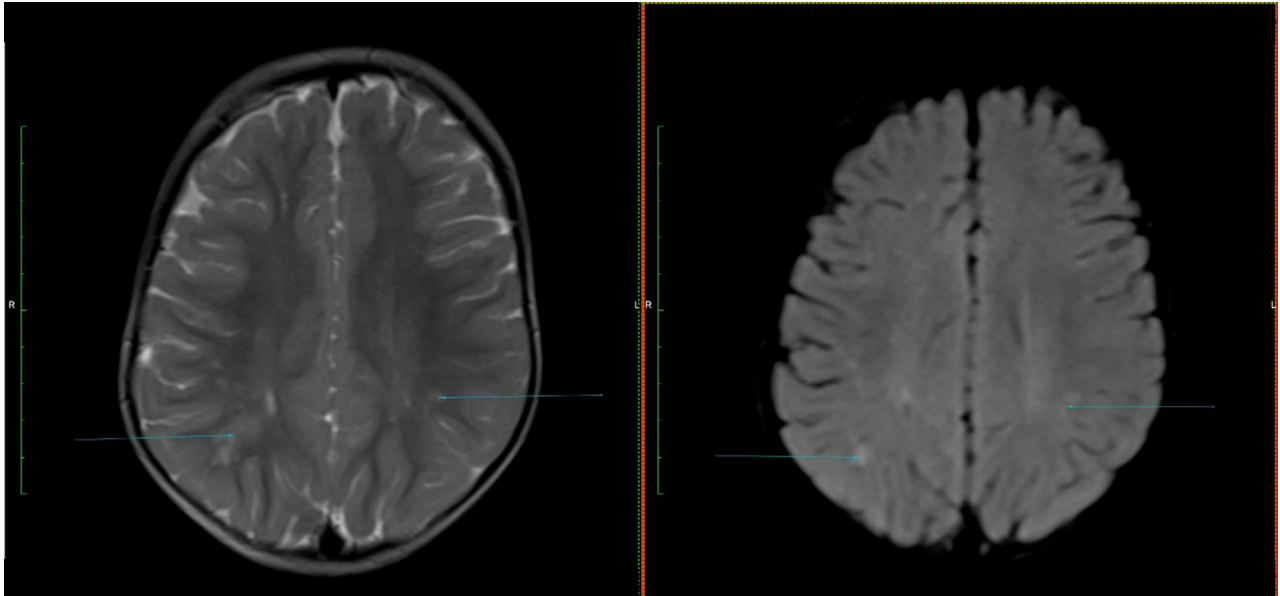


Fig. 5 – T2 and FLAIR axial images—altered signal intensities in the bilateral deep white matter of the parietal and occipital lobes.

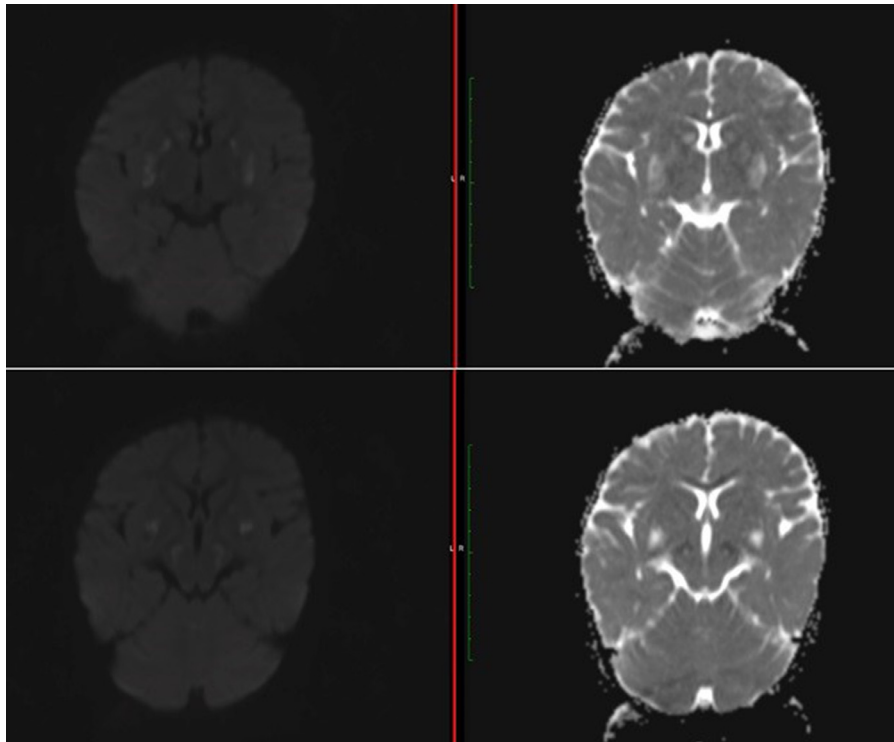


Fig. 6 – Restricted diffusion with corresponding low values on ADC in bilateral lentiform nuclei.

shows hypodense lesions in the affected regions which do not enhance on contrast [8]. Calcification and hemorrhage are not described in Leigh's disease. The imaging findings tend to vary with the mutation that is the cause of the syndrome. Diffusion characteristics vary with the stage of the disease. MRI of the brain is useful to rule out other related conditions and diagnose Leigh's disease with more confidence. The affected re-

gions show hypointense lesions on the T1-weighted sequence and corresponding hyperintensity on T2 and FLAIR sequences [8]. In the acute stage, water diffusivity will be reduced (due to acute impairment of mitochondrial function). Diffusivity may return to normal later. But if significant necrosis ensues in the injured area, diffusivity will be increased. Magnetic resonance spectroscopy has shown decreased N-acetyl aspartate and el-

evated lactate peaks. MR spectroscopy findings are more associated with more severe lesions [9].

Even with an accurate diagnosis, there is no complete cure for Leigh's disease to date [10]. All the available treatment options are mostly symptomatic. General management strategies include vitamin and other supplementation therapies, often in combination cocktails including thiamine, riboflavin, biotin, succinate, and idebenone. Thus, counseling of the parents remains the centerfold of management.

Our conclusion suggested that symmetrical T2 prolongation involving multiple brainstem structures associated with basal ganglia abnormalities in a child with neurological problems should alarm the physician to rule in Leigh's syndrome and further investigate the patient using modalities such as blood and/or cerebrospinal fluid lactate, and respiratory chain enzymes' activities. Our results suggest that fatal respiratory failure is unpredictable from clinical or neuroradiologic findings.

Vigilant monitoring of patients for signs respiratory failure combined with institution of suitable tests may allow us to tackle sudden death in patients with pre-established diagnosis of Leigh's syndrome. With use of relevant investigations, diagnosis, and early management with adequate supportive therapy, symptomatic improvement can be achieved, thereby adding years to the limited survival of these children.

The prognosis of Leigh's disease is generally considered poor. All 3 cases were diagnosed with Leigh's disease. Though most cases present with typical clinical features, the pathognomonic imaging findings are the key to suspicion of diagnosis with molecular diagnosis being the present gold standard. Thus, in any suspicion of an inborn error of metabolism, an MRI of the brain is ideal to rule out any organic cause and to rule out other metabolic disorders with similar presentation. Most cases typically live between a few months to a couple of years after diagnosis. There are possibly certain milder cases that present later in adulthood and seem to live longer with a better prognosis.

Patient consent

Informed written consent was obtained from the patients for publication of their case.

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