

CASE REPORTS

**A RARE MITOCHONDRIAL DISORDER
LEIGH SYNDROME - A CASE REPORT**

A Rare Mitochondrial Disorder: Leigh Syndrome - A Case Report

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Abstract

Introduction

Leigh syndrome is a rare, progressive neurodegenerative disorder of mitochondrial origin that predominantly affects infants and young children. Only a limited number of cases have been reported from India. The disease exhibits marked clinical heterogeneity but typically presents with developmental delay, neuroregression, and signs of brainstem and/or basal ganglia dysfunction. Elevated lactate levels in blood and/or cerebrospinal fluid reflect impaired oxidative phosphorylation, while characteristic neuroimaging findings are crucial for diagnosis.

Case presentation

A 7-month-old female infant presented with status epilepticus, delayed developmental milestones, and regression of previously achieved milestones. There was no significant perinatal history. Clinical evaluation raised suspicion of an underlying neurodegenerative disorder. Laboratory investigations revealed elevated lactate levels. Magnetic resonance imaging of the brain demonstrated symmetrical necrotic lesions involving the basal ganglia and brainstem, which are classical radiological features of Leigh syndrome. Based on the clinical, biochemical, and radiological findings, a diagnosis of Leigh syndrome was established.

Discussion and conclusion

Leigh syndrome poses a diagnostic challenge due to its variable presentation and overlap with other neurodegenerative conditions. Neuroimaging, particularly MRI, remains a cornerstone in diagnosis, especially in resource-limited settings where genetic confirmation may not be readily available. Early recognition of the disease allows for timely supportive management, seizure control, and appropriate genetic counselling of families. This case underscores the importance of considering Leigh syndrome in infants presenting with seizures, developmental delay, and neuroregression, and highlights the pivotal role of MRI in facilitating early and accurate diagnosis.

Keywords: Leigh syndrome, mitochondrial disorder, infantile encephalopathy, subacute necrotizing encephalopathy, basal ganglia lesions, lactic acidosis, paediatric mitochondrial disease, MRI findings, status epilepticus, case report

Introduction

Leigh syndrome, also known as subacute necrotising encephalopathy[1], is a rare inherited neurologic disorder that typically affects children under two years old. The first case of Leigh syndrome was reported by Denis Leigh in 1951, when a 7-month-old child developed quickly and died after only six weeks of worsening illness.[2] Leigh syndrome is diagnosed primarily by the clinical features of the syndrome, such as developmental delays or regression, brainstem dysfunction, hypotonia, ataxia, and respiratory failure, in conjunction with metabolic evidence of lactic acidosis[3]. Most cases of Leigh syndrome will have abnormal findings on neuroimaging, specifically bilateral symmetric necrotic lesions in the basal ganglia[4]; therefore, it is possible to make a probable diagnosis of Leigh syndrome based only on clinical and metabolic findings and MRI findings.[5]

Case Presentation

A female child aged 7 months who was born from a second-degree consanguineous Marriage, presented with Status Epilepticus with delay in Developmental Milestones. Her Perinatal History was uneventful. Initially, she was found to be unconscious (Glasgow Coma Scale 5) and afebrile. For the control of Seizures, Diazepam IV was given at a

Her vital signs were Pulse of 154/min, Respiratory Rate of 36/min, Blood Pressure of 84/46 mmHg, Weight of 5 kg, Height of 62 cm. Neurological findings included increased tone of the lower limbs, exaggerated deep tendon reflexes and Bilateral Babinski signs, and dilated, sluggish pupils. The fundus was normal and Visual evoked potentials were normal. An hour later, the child went into apnoea and was put on a ventilator.

Laboratory Tests showed that the child was Anemic (Hb 8.8 g/dL, PCV 28.6%) and had a Leukocytosis (TLC 26,800/mm³, 85% Neutrophils) and that her Cerebrospinal Fluid (CSF) contained 4 Lymphocytes with Normal Sugar and Protein levels and that

dose of 0.3 mg/kg IV Stat, and Phenytoin was administered at a dose of 20 mg/kg IV Stat and subsequently at a rate of 5 mg/kg IV every 12 hours. After Seizures were controlled, she developed decerebrate posturing and increased Intracranial Pressure (ICP). Mannitol IV was given at a dose of 5 mg IV Stat.

her CSF Lactate levels were Markedly Elevated (8.8 mmol/L), her Serum Lactate was Elevated (6.8 mmol/L), her Serum Creatine Kinase (320 U/L) level was Elevated, her Liver Function tests were mildly elevated (AST 54 IU/L, ALT 49 IU/L, ALP 109 IU/L), her Renal Function was Normal, and Arterial Blood Gases were consistent with metabolic acidosis. blood and urine cultures were negative.

MRI revealed bilateral symmetrical lesions located in the basal ganglia, thalamus, cerebral peduncles, dorsal medulla and periaqueductal grey as well as hyperintense areas on T2W images, FLAIR images and Diffusion Weighted imaging

(Figure 1A, 1B & 1C). On the images, we also noted extensive extracerebral CSF located in the fronto-temporal-parietal areas, which had similar appearances (Figure 1D). The frontal lobe was noted to be atrophic, and myelination appeared normal for a child of this age. Together these MRI imaging findings supported a principal diagnosis of Leigh syndrome.

The child diagnosed with a suspected mitochondrial disorder was given intravenous administration of thiamine, carnitine, migraine alkaloids, and oral coenzyme Q10 (ubiquinone); she did well initially, was extubated after two days; but, as she continued to be treated, there was further deterioration with subsequent coma (GCS of 4), no oculocephalic reflex, and required to be re-intubated. The child died after ten days in intensive care.

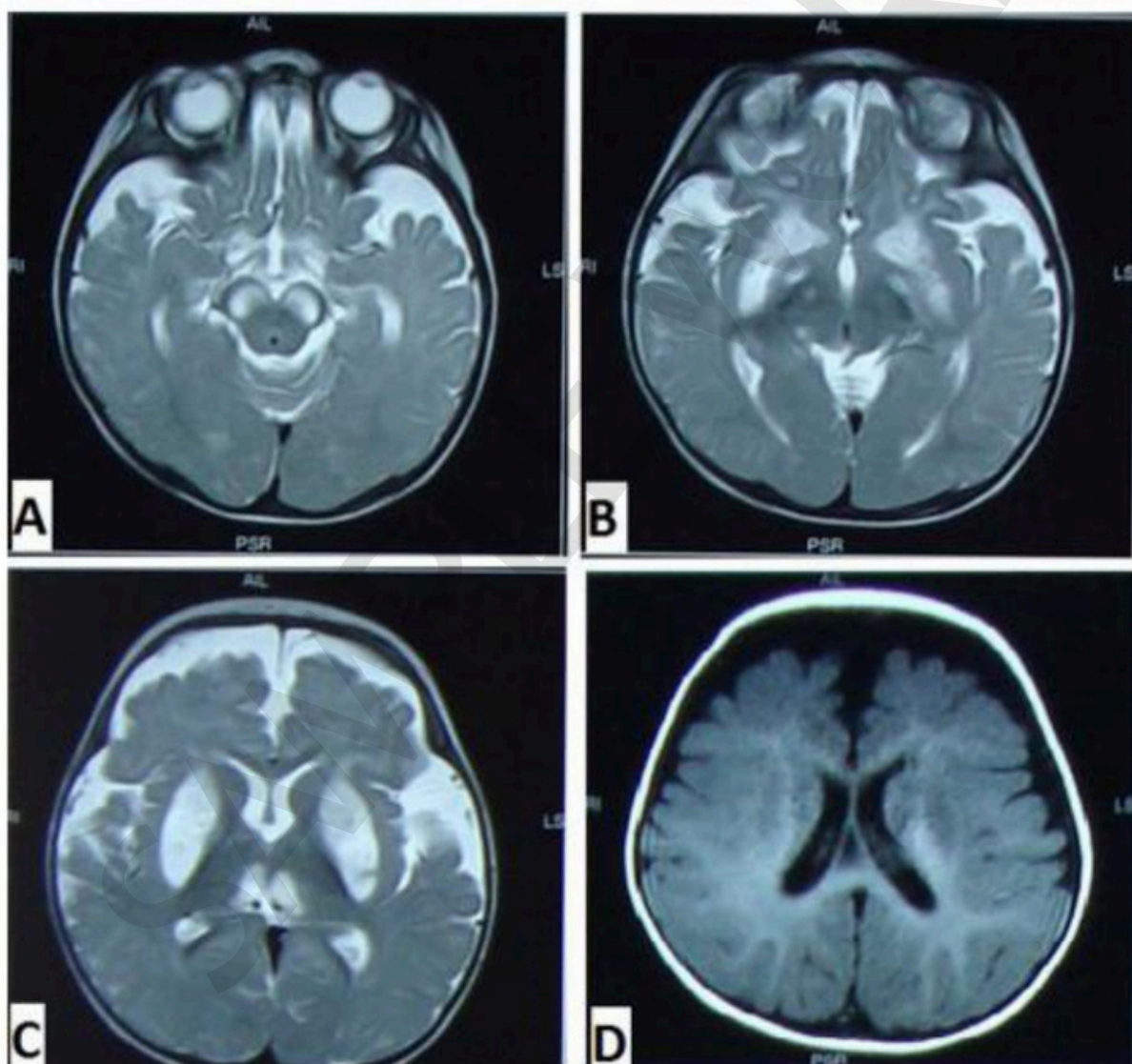


Figure 1 MRI Findings of Leigh Syndrome. A & B: T2W image showing bilateral symmetrical abnormal signal intensities, seen in cerebral peduncles, dorsal medulla and peri aqueduct grey matter. C: T2W image showing bilateral symmetrical abnormal signal intensities, seen involving basal ganglia and thalami. D: T2W image showing prominent extracerebral CSF spaces in front-temporo-parietal region on both sides depicting signs of frontal atrophy

Discussion

Leigh syndrome (often referred to as subacute necrotizing encephalopathy or SNE) is an extremely uncommon and progressive childhood neurodegenerative illness that affects children at an early age. The estimated prevalence rate is approximately 2.05 cases per 100,000 individuals [6]. The incidence of Leigh syndrome among preschool children is estimated to be 1 in every 32,000 children. Most of the patients who develop Leigh syndrome will do so by the time they are 2 years of age; however, there are also juvenile and rare adult-onset forms of Leigh syndrome that can develop at other ages. Some of the clinical signs and symptoms associated with Leigh syndrome include abnormal muscle tone, weakness, psychomotor regression, visual loss, lost or regressed developmental milestones, dystonia, tachypnea (rapid breathing), seizures, and cerebellar, or brainstem involvement [7]. Feeding difficulties, vomiting, and failure to thrive are usually the first signs and symptoms that appear during the first year of life in children with Leigh syndrome; therefore, most children with Leigh syndrome die due to progressive respiratory failure within a few years of developing the disease [8].

Laboratory findings obtained from routine blood tests show that children with Leigh syndrome typically have a metabolic acidosis because of an elevated level of lactic acid and pyruvic acid in their blood or cerebrospinal fluid. Most cases of Leigh

syndrome are inherited as an autosomal recessive genetic condition that results from defects in mitochondrial enzymes (i.e., Pyruvate Dehydrogenase, Pyruvate Carboxylase, Cytochrome C Oxidase, and Complex I [NAD-Coenzyme Q]) function [8,10]. Diagnostic criteria for Leigh syndrome include: (1) progressive neurological disease that is associated with motor and cognitive delay; (2) evidence of brainstem and/or basal ganglia involvement; (3) elevated lactate concentration in blood or CSF; and (4) characteristic bilateral necrotic brain lesions involving the basal ganglia or brainstem.

Neuroimaging is a key diagnostic tool in mitochondrial disorders [9]. The most commonly used neuroimaging method is T2-weighted MRI, which typically shows bilateral, symmetric hyperintensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei, which may indicate spongiform changes and vacuolation [10]. The putamen has the highest incidence of involvement, with a reported incidence of 100% in one series. Many of the earlier reports of mitochondrial disorders from India have emphasized the importance of CT and MRI as diagnostic tools [11]. A definitive therapy does not yet exist for mitochondrial disorders and the prognosis varies widely. Symptomatic treatment has the goal of improving ATP production and decreasing lactate levels. Some patients have shown neurological improvement with thiamine, which is a cofactor in the reaction of pyruvate to acetyl-CoA. Riboflavin has been shown to

normalize ATP production and improve the outcome in many cases of pyruvate dehydrogenase deficiency. The use of a ketogenic diet and fewer ketone emulsions has improved outcomes for both children and adults with pyruvate dehydrogenase deficiency [12]. Coenzyme Q10 and Carnitine supplementation have also been reported to be beneficial to both types of mitochondrial disorders. The use of botulinum toxin to relieve dystonic symptoms has been studied. Transplantation of the nucleus has been proposed as a potential preventive measure [13].

A neurodegenerative disorder is suspected in our patient due to seizure activity, regression in milestones, and an acute decline in neurological function after a mild upper respiratory infection. During our patient's

examination at the time of consult, we found signs of developmental delay, hypertonicity (increased muscle tone), and confusion or disorientation [1]. Cerebrospinal fluid (CSF) lactate level was found to have a very high elevation, but serum lactate was within normal limits. This finding correlates with earlier work, which shows that although serum lactate may be within normal limits in Leigh syndrome, there are very clear neuroimaging findings consistent with that diagnosis [14]. MRI findings were completely compatible with previously published reports from India, as well as other countries, that support the diagnosis of mitochondrial encephalopathy. We did not perform advanced enzymology testing, histology analysis, or molecular assays because we had no access to the necessary laboratory equipment or funds.

Conclusion

Clinicians should consider Leigh syndrome as a possible diagnosis for a child when CT reveals symmetric hypodensity in the putamen and midbrain. The next steps in the diagnostic process would be to perform an MRI for further evaluation and perhaps to measure the lactate level in either blood or CSF in addition to respiratory chain enzyme activity, if there were bilateral symmetric increased T2 signal intensity in the brainstem nuclei and basal ganglia on the MRI. The neuro-radiological pattern seen would help guide the clinician to conduct the appropriate enzyme and gene testing. Presently there are no cures available for mitochondrial disease, and the ability to prevent these diseases/conditions is very limited. Nevertheless, recognition and treatment in a timely fashion can enhance symptom relief and as a result, increase meaningful survival; future research needs to be focused on prenatal diagnosis and prevention strategies.

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SAMPLE WORK