Case Report

# A rare pediatric neurometabolic disorder: Leigh syndrome

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## ABSTRACT

Subacute necrotizing encephalomyelopathy called Leigh Disease is a rare inherited pediatric neurological disorder generally involving infants. The condition primarily involves the central nervous system and the most involved structures are basal ganglia, thalamus, and brainstem. In this disorder, there is a progressive loss of mental and movement abilities associated with abnormal muscle tones, weakness, visual loss, respiratory failure, and strikingly, we got raised lactate levels in the blood, cerebral spinal fluid, and other body fluids. The prognosis of this condition is bad as there is no effective treatment and finally, the patient succumbs to death mostly due to respiratory failure. Here, we present a case of Leigh disease in an 8-month-old boy having chief complaints of delayed motor (weakness), and cognitive development with a previous history of recurrent respiratory infection. Upon recent radiological imaging, gross neurological abnormalities were seen which suggested the possibility of Leigh disease which was further confirmed by raised body fluid lactate levels.

**Key words:** Body fluid lactate level, Leigh disease, Respiratory failure, Subacute necrotizing encephalomyelopathy

Leigh disease is a rare congenital disease of infants. The disease is fatal in prognosis and leads to early death of the patient, mostly due to respiratory failure. It is also known as subacute necrotizing encephalomyelopathy (SNE) and has a characteristic pathological feature of progressive neurodegeneration and muscular weakness presenting in infancy or early childhood [1]. The incidence is about 1 in 40,000 live births [2]. A British neuropsychiatrist named Archibald Denis Leigh first described this condition in a 7-month-old infant in 1951 who eventually died of the disease over a period of 1½ months [3]. The main clinical change is a progressive deterioration of mental and muscular activities which is typically noted in the infantile age and culminates in death within a short period of life, mostly the first few years of age. In rare cases, the patient could survive to their teenage years depending on the severity of the disease. Other symptoms of the disease include diarrhea, vomiting, and dysphagia causing failure to thrive. Muscular weakness is noted throughout the body in the form of hypotonia, dystonia, and ataxia. Ophthalmological signs are also frequently present and include ophthalmoparesis, nystagmus, and optic atrophy. Cardiac signs are hypertrophic cardiomyopathy and ventricular septal defect. Excessive lactate levels in different body fluids such as blood, cerebral spinal fluid (CSF), and urine are a striking feature of this disease. The diagnosis of Leigh's disease depends collectively on clinical findings, metabolic changes, and neurological imaging findings [4]. The characteristic MRI findings of the brain show symmetrical basal ganglia involvement (Globus pallidi, putamen, and caudate nucleus abnormality), thalamic changes, brain stem abnormality, and less frequently, the cerebral cortex [5].

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## CASE REPORT

An 8-month-old male was referred to pediatrics OPD for delayed motor and cognitive development and gross abnormalities in radiological scans. On inquiry, the child had a high-grade fever for 3 days 2 months back which was diagnosed as pneumonia and treated for the same. The child is a fourth-order male born to unrelated parents with an unremarkable perinatal history. At present, he cannot sit and has not even attained neck holding.

The baseline blood investigations which included a complete blood count picture, liver function test, renal function test, random blood sugar, and thyroid-stimulating hormone were within normal limits. The electroencephalogram study appeared normal.

The non-contrast computed tomography head showed hypodense foci in bilateral basal ganglia and thalami, and the midbrain with cerebral atrophy, more prominent in bilateral frontotemporal regions (Fig. 1). Brain MRI with spectroscopy was advised which revealed multiple foci of altered signal intensities in the rostrum of the corpus callosum, bilateral caudothalamic groove and posteromedial thalami, midbrain and periaqueductal gray and posterior part of pons and medulla

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which were hypointense on T1WI, hyperintense on T2 (Fig. 2), and FLAIR WI, and showed restriction on DWI (Fig. 3). There was mild thinning of bilateral superior cerebellar peduncles. Mild diffuse cerebral atrophy with prominent subarachnoid spaces in bilateral frontotemporal regions was also noted. A spectroscopy study revealed an increased lactate peak (at 1.36 ppm) and reduced N-acetyl aspartate (NAA) peak in the regions of altered signal intensities.

After evaluating the MRI brain findings, some metabolic neurodegenerative changes were suspected and the patient's blood and urine levels of lactate were examined and found to be significantly raised. Thereafter, lactate level in CSF was also examined and here again found to be raised (7.6 mmol/L). The patient was discharged once investigation and probable diagnosis was made as Leigh disease with proper advice including vitamin supplements, thiamine, riboflavin, coenzyme and carnitine, diet with maximum fat (ketogenic food), and less carbohydrate. Regular follow-up and consultation with doctors are also advised to know the status of the patient.

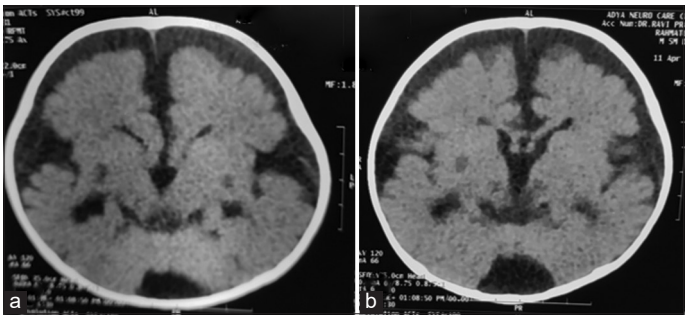

**Figure 1: (a and b) Non-contrast computed tomography head showing hypodense foci in bilateral basal ganglia and thalami and in periaqueductal grey region with cerebral atrophy more prominent in bilateral fronto-temporal regions causing marked widening/ enlargement of sylvian fissures and interhemispheric fissure**

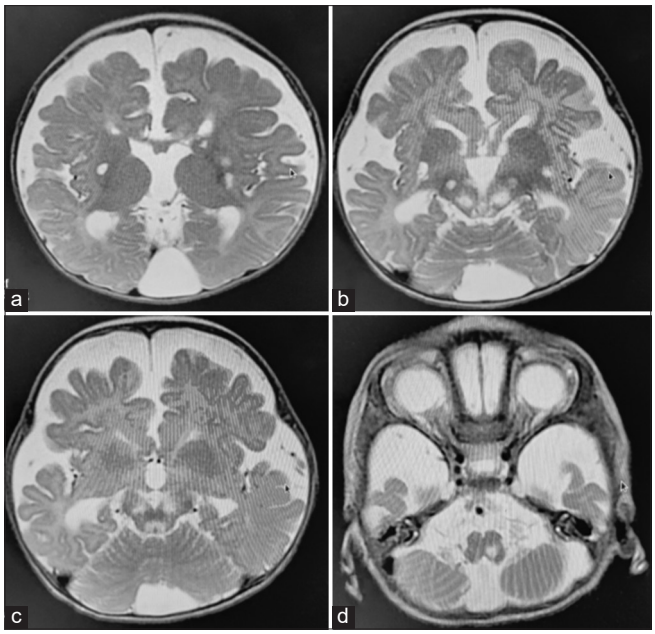

**Figure 2: (a-d) T2 WI showing hyperintense areas in bilateral basal ganglia and brain stem with diffuse cerebral atrophy. Posterior fossa cisterna magna is evident**

## DISCUSSION

SNE, or Leigh syndrome (LS), is a rare disorder characterized by progressive neurodegenerative disorder with onset usually in infancy or early childhood that occurs before the age of 2 years due to mutations in mitochondrial OXPHOS subunit genes that aid in energy production. It typically results in death within 2–3 years, usually due to respiratory failure. LS was named after Denis Leigh, the first man to describe this rare neuropathology, with an incidence of about 1 in 40,000 births [2]. Nuclear DNA mutations are more common (~75%) and are inherited in a Mendelian fashion with both autosomal recessive and X-linked inheritance encountered including *SURF1*. Less commonly, it occurs due to mitochondrial DNA (25%) and is only inherited from the mother including *MT-ATP6*. The pattern of inheritance of the disease is either X-linked recessive, autosomal recessive, and mitochondrial [6].

Clinically, LS is characterized by psychomotor delay or regression, muscular hypotonia, brainstem signs (especially strabismus, nystagmus, and swallowing difficulties), ataxia, pyramidal signs, respiratory insufficiency, lactate acidemia, and acute deterioration after common infections [7] Delayed development is important in cases of early age of onset, and motor weakness or ataxia is important in cases of late age of onset. In general, LS in adulthood is rare [7] which usually presents with intellectual decline and vertical gaze paralysis, headache, memory loss, and visual hallucinations. LS should be considered when symptoms related to gross motor function such as delayed development, motor weakness, and ataxia are among the presenting symptoms [8]. However, the time interval from the first clinical presentation to the diagnosis of LS, follow-up

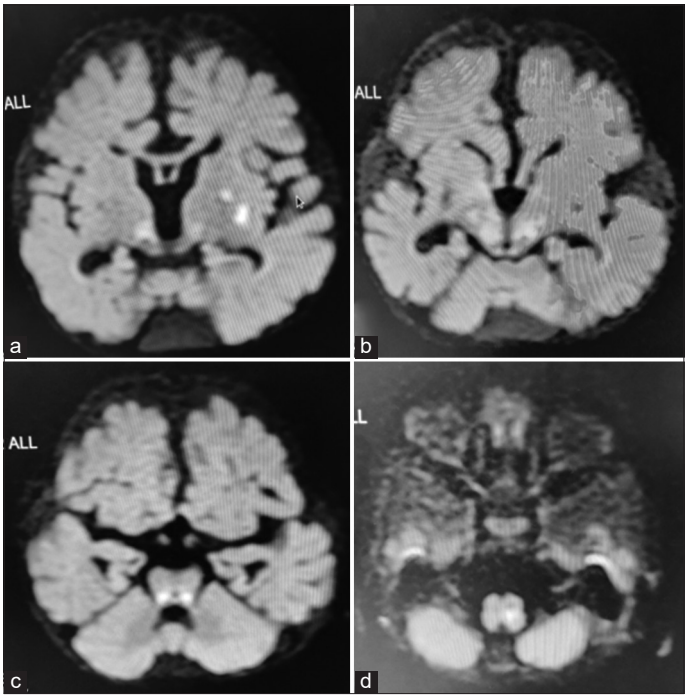

**Figure 3: (a-d) DWI images showing areas of restricted diffusion in basal ganglia, thalami, and brain stem**

duration, birth history, family history, and organ involvement are not statistically significant.

As the first approach to a suspicion of LS, it is reasonable to evaluate the possible affected pathways, considering energy supplies and metabolic intermediates generated in response. As so, blood gas analysis, lactate and pyruvate, glucose, and electrolyte profile are the main metabolic basis. LS includes normal/raised lactate/pyruvate levels in plasma and/or CSF and may present with metabolic acidosis and hypoglycemia in decompensation status. The most characteristic neuroradiological findings in LS are bilateral, symmetric focal hyperintensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei at various levels on T2-weighted MRI. Lesions of the lower brain stem are always present in patients with near-fatal respiratory failure. However, upper brain stem lesions are transient and are found in parallel to reversible respiratory disorders [9]. Brainstem and subthalamic nuclei lesions are present in LS SURF-1 patients. These patients die soon, probably because of lower brainstem involvement. Basal ganglia abnormalities are common in LS non-SURF-1 patients [10]. 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 [11]. Magnetic resonance proved to be superior to CT in establishing other areas of involvement: tectum and tegmentum, and medullary olive [12]. The presence of cerebral or cerebellar white matter lesions is unusual. Reversibility of lesions is seen in some patients. MR Spectroscopy shows a decreased level of NAA peak due to neuronal loss and an elevated lactate peak due to dysfunctional OXPHOS. The diagnostic criteria include a progressive neurological deficit in the form of motor and cognitive developmental delay, signs, and symptoms of brainstem and/or basal ganglia disease, lactic acidosis in body fluids (CSF and/or blood), typical symmetric necrotic lesions in basal ganglia and/or brainstem on MR neuroimagings [13].

Since the disease is a mitochondrial-based enzyme abnormality, specific therapy for Leigh's disease is still not available [7]. Significant change in the state of disease is seen in patients undergoing treatment with riboflavin, intravenous thiamine infusion, carnitine, and oral coenzyme Q (Ubiquinone), as all these improve ATP production. The result and prognosis depend upon the severity of the disease. The main aim of treatment is to increase the level of ATP in the body and reduce the level of lactate production. The use of thiamine is found to improve the neurological status in some patients [14].

Intravenous use of soya bean oil emulsion is proven to give a rapid clinical and biochemical improvement in patients with acute central respiratory failure [15]. A ketogenic diet improves the condition of the patients as it supplements the enzyme pyruvate dehydrogenase.

## CONCLUSION

SNE (Leigh disease) should be considered in infant patients presenting with delay in developmental milestones, muscular weakness, or signs and symptoms of basal ganglia and/or brainstem disorders with lactic acidosis in body fluids. As the prognosis of the disease is not good, the patients mostly die of respiratory failure at very early ages. This mitochondrial disease treatment cannot be possible completely, and prevention and prenatal diagnosis of Leigh disease is still under research. With early clinical identification of the condition and proper investigations, accurate diagnosis, and early prompt treatment with adequate supportive therapy we can possibly improve the limited years of survival of these patients.

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