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# Case Reports

## Leigh Syndrome: A Rare Mitrochondrial Disorder

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**Abstract**

*Leigh syndrome is a rare inherited neurometabolic subacute necrotizing encephalopathy mostly involving brainstem and basal ganglia, seen in the early childhood. It is characterized by progressive loss of mental and motor abilities associated with abnormal muscle tone, weakness, visual loss and respiratory failure. There is no effective treatment for this condition, as such the prognosis of this condition is very bad with death occurring within the first few years of life most commonly due to respiratory failure. Here we present a rare case of Leigh syndrome seen in a 3 and half years male Bangladeshi child with clinical and laboratory features of Leigh Syndrome suggested by neuro-imaging.*

***Keywords:*** *Brainstem, Basal Ganglia, Inherited Neuro-metabolic, Necrotizing Encephalopathy*

### Introduction

Leigh syndrome is synonymous with Leigh disease, infantile subacute necrotizing encephalomyelopathy, and subacute necrotizing encephalomyelopathy (SNEM). It is a rare inherited neurometabolic disorder that affects the central nervous system. It is named after Archibald Denis Leigh, a British neuropsychiatrist who first described the condition in 1951.

Clinically, Leigh disease is characterized by psychomotor delay or regression, muscular hypotonia, brainstem signs (especially strabismus, nystagmus and swallowing difficulties) & ataxia. In late stages pyramidal signs & respiratory insufficiency occurs. In most cases, dysfunction of the respiratory chain enzymes is responsible for the disease. There are several known genetically determined causes of Leigh disease: pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10.[1]

These defects may occur sporadically or be inherited by autosomal recessive transmission, as in the case of COX deficiency; by X-linked transmission, as in the case of pyruvate dehydrogenase E1á deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. About 30% of cases are due to mutations in mtDNA [1]. Despite its considerable clinical, genetic and biochemical heterogeneity, the basic neuro pathological features in children affected are almost identical; which are focal, bilateral, and symmetric necrotic lesions associated with demyelination, vascular proliferation and gliosis in the brainstem, diencephalon, basal ganglia, and cerebellum.[2] It is possible to come to a diagnosis of SNE (subacute necrotizing encephalopathy) on the basis of clinical signs and symptoms, mode of inheritance, metabolic abnormalities, and neuro imaging findings [3]. We report here a rare case which presented clinically as a neurometabolic disorder and diagnosed as Leigh disease based on clinical and neuroimaging findings.

### Case Report

A 3 and half years old male child, 3rd issue of consanguineous parents (2nd degree), with an uneventful perinatal history, developmentally age

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appropriate till $2^{1/2}$ years of age presented to our hospital with gradual regression of the achieved milestones (motor and speech), Bilateral strabismus for last 1 year and chest deformity for last 3 months. He had history of recurrent vomiting, feeding and swallowing difficulty since infancy and failure to thrive. History of a sibling death was present who died with similar features at the age of 9 yr. On examination, he was active, alert, vital signs were normal. His weight was 9.8kg (Z score: -5.2) and height 80cms (Z score: -4.7) with normal head circumference. On skin survey hypertrichiosis was present. CNS examination showed generalised hypotonia, deep tendon reflexes were exaggerated with bilateral Babinski sign positive. Pupils were dilated and sluggishly reacting to light, horizontal nystagmus present in lateral gaze also convergent squint in both eyes. Fundus examination showed chorio-retinal changes. In view of the above a clinical possibility of a mitochondrial disorder was considered and he was investigated accordingly.

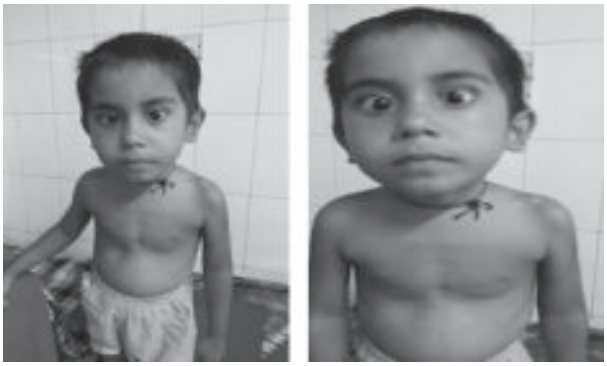

**Figure 1&2:** *showing bilateral convergent strabismus with chest deformity*

MR Imaging of the brain revealed bilaterally almost symmetrical T1W1 hypointense and T2W1/Flair hyperintense signal changes noted at both basal ganglia, thalami, supra ventricular and brain stem regions. The involved regions showed restriction of diffusion on diffusion-weighted imaging. The imaging findings were consistent with a progressive neurodegenerative disorder and suggested the diagnosis of a mitochondrial encephalopathy. Serum lactate was significantly high 7.1mmol/l(2.5-5.5). There was mild metabolic acidosis. Serum ammonia was normal. CSF Lactate could not be done. Enzymology, histology and functional fibroblast ATP synthesis rate, molecular studies were not performed due to the absence of facilities and financial constraints. Child was given supportive treatment with Tab. Thiamine, Carnitine,Tab. Folinic acid, Tab. Biotin and kept in regular follow up.

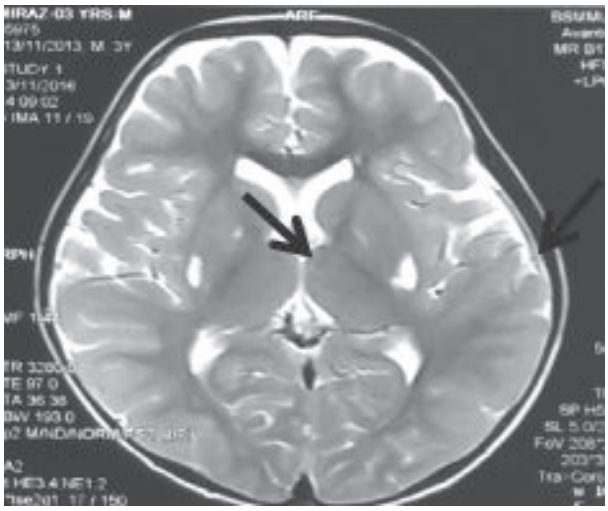

**Fig.-3:** *MRI of brain T2 image showing bilateral symmetrical lesions in the basal ganglia*

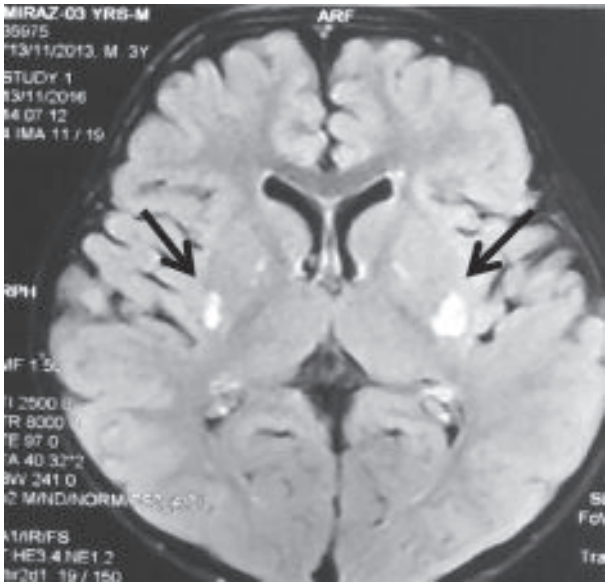

**Fig.-4:** *MRI of brain T1 image with Flair showing bilateral symmetrical lesions in the basal ganglia*

**Discussion**

Leigh's disease or SNE is a rare progressive neurological disorder of the childhood. The estimated prevalence of Leigh Syndrome was 2.05 cases per 1, 00,000 [4]. The preschool incidence of Leigh syndrome was 1 out of 32000 [5]. Age of onset of symptoms is usually less than 2 years (infantile form), but others may present in childhood (juvenile form) and unusually in adulthood.

There are several genetically determined causes of Leigh Syndrome causing enzyme deficiencies such as Pyruvate dehydrogenase complex deficiency, ATPase deficiency , these enzymes, when defective, are known to disturb oxidative phosphorylation and lead to failure of organs with high oxidative metabolic demand such as neuro-muscular system. The mutations can arise sporadically or be inherited by autosomal recessive transmission (COX deficiency) or X linked transmission (PDHE1ádeficiency) or by maternal transmission (complex V deficiency ATPase6 nt 8993 mutation). Maternal inheritance accounts for 20 % of the cases [6]. Mutation studies have shown T8993C mutation was found to be associated with a slower clinical progression and more frequent sensory neuronal involvement.[7] Also Preliminary studies have proven the utility of mutation analysis in prenatal diagnosis and of Leigh Syndrome.[8,9]

Affected children presents in early life with psychomotor regression, abnormal muscle tone, weakness, brainstem and cerebellar ataxia, nystagmus, external ophthalmoplegia, ptosis, optic atrophy and decreased visual acuity, even visual loss, tachypnea, and seizures[10]. Affected children usually become symptomatic within the first year of life with feeding difficulties, vomiting and failure to thrive. Death usually occurs within a few years after onset of symptoms, typically from progressive respiratory failure [10]. Laboratory analysis shows metabolic acidosis with elevated blood and CSF lactate and pyruvate concentrations[11]. Our patient had similar presentation of psycomotor regression, hypotonia, opthalmological findings in the form of squint and nystagmus along with failure to thrive. He even had history of vomiting and feeding difficulties since infancy. Laboratory findings were also in favour of the leigh syndrome with high blood lactate level and metabolic acidosis.

Neuroimaging[10,12-15] plays an important role in diagnosis of patients with Leigh syndrome. The most characteristic neuro-radiological findings are bilateral, symmetric focal hyperintensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei at various levels on T2-weighted MRI. These high T2 signals on MRI reflect the spongiform changes and vacuolation in the affected brain structures [16,17]. In the basal ganglia, the putamen is particularly involved. In one series, 100% of the patients with proven SNE had putaminal involvement.[10]

The diagnostic criteria are: (1) Progressive neurological disease with motor and intellectual developmental delay; (2) Signs and symptoms of brainstem and/or basal ganglia disease; (3) Raised lactate levels in blood and/or cerebrospinal fluid; (4) Characteristic symmetric necrotic lesions in the basal ganglia and/or brainstem.[12] All of which were compatible with the findings of this case.

As the child presented to us with, history of regression of developmental milestone, strabismus and feeding difficulty, these symptoms pointed towards a neurodegenerative disorder. Examination revealed developmental regression (motor and speech), hypotonia, hypertrichiosis, failure to thrive, nystagmus, bilateral convergent squint, tremor, all of which are recognized features of Leigh Syndrome. Serum lactate was markedly elevated and the imaging findings suggested a progressive neurodegenerative disorder with the possibility of a mitochondrial encephalopathy. This is consistent with the neuro-radiological findings in previous reports of Leigh Syndrome. Also history of sibling death who had delayed neurodevelopment history and similar MRI findings also goes in favour of Leigh disease.

The differential diagnosis includes other mitochondrial myopathies and neuro-metabolic disorders including Wilson's disease but presentation at this age is uncommon. Another differential may be Biotinidase deficiency but with high serum lactic acid it is unlikely.

There is currently no effective treatment, a high-fat, low-carbohydrate diet may be followed if a gene on the X chromosome is implicated. Thiamine (vitamin B1) may be given if a deficiency of pyruvate dehydrogenase is known or suspected [18]. Marked improvement was observed with riboflavin, which nearly normalized the adenosine triphosphate production.[19] Ketogenic diet, supplementing the diet with sodium bicarbonate or sodium citrate and Dichloroacetate, Coenzyme Q10 and Carnitine supplements have been seen to improve symptoms in some cases. In this case child was given supportive treatment with Tab Thiamine, Carnitine, Folinic acid and Biotin. Nucleus transplantation into enucleated oocyte is emerging as a new option for prevention of mitochondrial disorders.

**Conclusion**

As this is a rare condition and since many conditions present with similar symptoms, the diagnosis of Leigh syndrome should be considered in a child with

neurodevelopment delay / gradual neurodevelopment regression and signs / symptoms of brain stem and/ or basal ganglia involvement whose MRI shows bilateral symmetric hyperintense T2w images of the brain stem and basal ganglia. This should prompt further investigations with measurement for blood/CSF lactate and respiratory chain enzyme activities. If appropriate clinical and laboratory settings are available further enzymatic and genetic study must be performed on the parents.

Though prognosis of this condition is very bad with death occurring within the first few years of life, with appropriate investigations and accurate diagnosis, adequate supportive therapy can be given to smoothen the years of his life.

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