CASE REPORT

# IMAGING BASED DIAGNOSIS OF LEIGH'S SYNDROME IN A RURAL SETUP

Sushil Kachewar, Meera Sachin Patil

Rural Medical College (RMC), Pravara Institute of Medical Sciences, Loni, Maharashtra, INDIA

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## ABSTRACT

Leigh's syndrome (LS) or Sub acute necrotizing encephalomyelopathy is a progressive neurodegenerative disorder characterized by symmetrical spongiform lesions in the brain with onset usually in infancy or early childhood. We report a case of Leigh's syndrome in a 7 month old female first suspected on Magnetic Resonance Imaging (MRI) of brain and confirmed on MR spectroscopy (MRS).

**Keywords:** Leigh's syndrome, spongiform lesions, spectroscopy, mitochondrial disorder, mutation.

## Introduction

Leigh's syndrome (LS) is a rare, progressive neurodegenerative disorder and the case reports in literature are scanty. Nevertheless, it is one of the few neurometabolic disorders where supportive treatment is found to ameliorate clinical symptoms, at least partially. Apt use of neuro-imaging and genetic analysis needs to be emphasized if the disease is to be diagnosed at the earliest presentation. This case report discusses the magnetic resonance imaging features and MR spectroscopy findings of Leigh's syndrome.

## Case Report

A female child of 7 months age who was a product of consanguineous marriage was brought to Pravara Rural Hospital with history of delayed milestones and one episode of generalized tonic-clonic convulsions on the day of admission. Her clinical examination showed delayed milestones in the form of inability to hold her neck and inability to sit without support. Her fine motor, social and language milestones were within fairly normal limits. On auscultation there were bilateral grunting sounds. Later on she became drowsy and was intubated and put on ventilator. After the patient became stable the patient was extubated and sent for MRI.

MRI brain images (Fig.1) show bilateral symmetrical

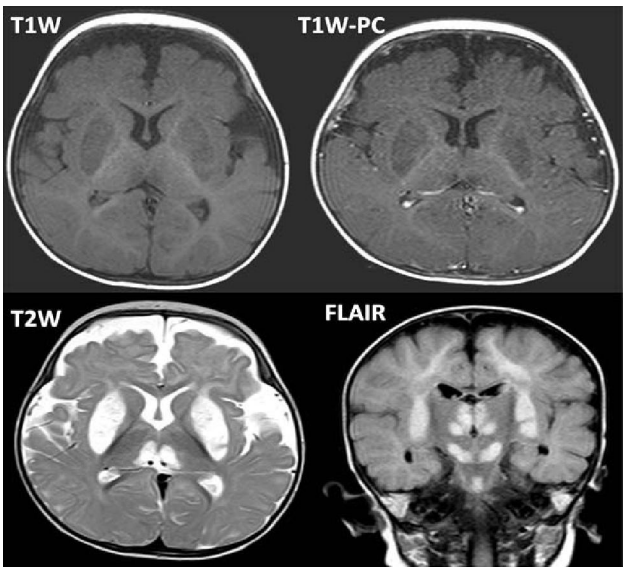


**Figure 1:** MRI brain images show bilateral symmetrical abnormal signal intensities involving basal ganglia, thalami, cerebral peduncles, dorsal medulla and peri-aqueductal grey matter appearing hyperintense on T2W, FLAIR and DW images. No significant enhancement was seen in post contrast study (TIW-PC).

**Correspondence :** Dr. Sushil Kachewar
Rural Medical College,
Pravara Institute of Medical Sciences,
Loni, Maharashtra, India.
Email: sushilkachewar@hotmail.com

abnormal signal intensities involving basal ganglia, thalami, cerebral peduncles, dorsal medulla and peri-aqueductal grey matter appearing hyperintense on T2W (T2 Weighted), FLAIR (Fluid Attenuated Inversion Recovery) and DW (Diffusions Weighted) images. No significant enhancement was seen in post contrast study (TIW-PC). MR spectroscopy (Fig. 2) from areas of abnormal signal intensities showed increased lactate peak which is confirmative of Leigh's syndrome.

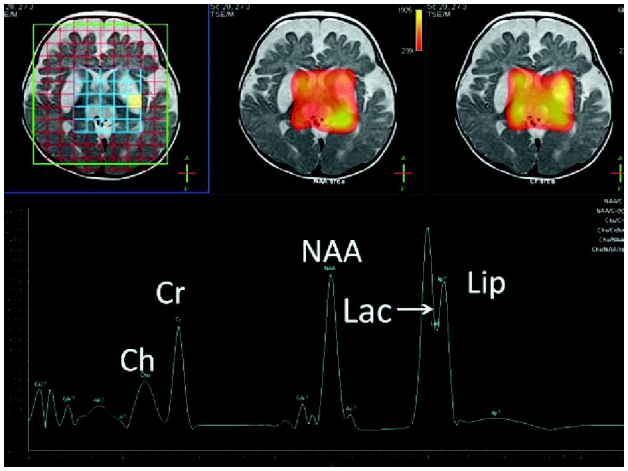


**Figure 2:** MR spectroscopy from areas of abnormal signal intensities showed increased lactate peak which is confirmative of Leigh's syndrome.

## Discussion

Leigh's syndrome[1] is a rare, inherited neuro-degenerative disorder with characteristic pathological features usually presenting in infancy or early childhood. It was first reported by Denis Leigh[2, 3] in 1951 in a 7 month old infant. The estimated prevalence of Leigh syndrome was 2.05 cases per 1,00,000.[4] The pre-school incidence of Leigh syndrome was 1 in 32,000.[5] In India, Bhavsar VM, Kumta NB[6] described the role of CT scan of the brain in the diagnosis of Leigh Syndrome in 1991. Ghosh and Pradhan[7] reported two children with Leigh's syndrome suspected clinically and confirmed by MRI in 1996. The children showed partial response to parenteral thiamine and MRI lesions showed partial improvement with time over one year of follow up. In one of their patients, medulla and spinal cord were involved which is extremely rare. In 2004, Mannan and Sharma et al[8] reported autopsy proven Leigh's syndrome in a 15 month old girl admitted with cough and hyperventilation. In 2005, Hombal and Narvekar[9] reported Leigh's syndrome in a 3 year old child with regression of milestones and involuntary movements. The diagnosis in their case was based on neuroimaging.

There are at least four genetically determined causes of Leigh's syndrome:[10,1] Pyruvate dehydrogenase complex deficiency, complex I deficiency, complex IV deficiency (COX), and complex V (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. All the five complexes except complex II are heterogeneous in their origin i.e. components of all the four complexes are encoded by both nuclear and mitochondrial genomes. ND 5 and ATPase 6, which are mitochondrial component of complex I and complex V respectively, are one of the frequent genetic causes for occurrence of Leigh's syndrome. The activity of these complexes can be detected by histochemical studies of fresh muscle tissues or cultured skin fibroblasts.

The mutations can arise sporadically or be inherited by autosomal recessive transmission (COX deficiency) or X linked transmission (PDHE 1 ∝deficiency) or by maternal transmission (complex V deficiency ATPase 6nt 8993 mutation). Maternal inheritance accounts for 20 % of the cases.[11] Mutations in other mitochondrial genes ND 4 and ND 6 and nuclear genes such as SURF-1 are also reported to be associated with Leigh's syndrome.[10,12] Yang and Sun et al reported A8344G, T8993G, T8993C, A3243G, G604C and SURF-1 mutations in a retrospective study of 65 patients with Leigh`s Syndrome.[12] NARP (neurogenic weakness, ataxia, and retinitis pigmentosa) and Leigh's syndromes are associated with a T8993G mutation when the percentage of mutant mitochondrial DNA is low (60-90%) or high (>90%), respectively. Leigh's syndrome is also caused by a second mutation in the same position T8993C4.[9] T8993C mutation was found to be associated with a slower clinical progression and more frequent sensory neuronal involvement.[5,7] Thus mutation analysis may be useful for prognostication also. Akagi, Inui et al detected a T-to-G transition at nucleotide 9176 (T9176G) in the mitochondrial adenosine triphosphate 6 gene (MTATP 6) in two siblings with Leigh's syndrome.[11] Preliminary studies have proven the utility of mutation analysis in prenatal diagnosis of Leigh's syndrome.[10,11]

Affected children usually become symptomatic within the first year of life with feeding difficulties, vomiting and failure to thrive.[1,2] Motor and language milestones

may be delayed. They can have seizures, hypotonia, ataxia, tremor, pyramidal signs, nystagmus, external ophthalmoplegia, ptosis, optic atrophy and decreased visual acuity. Intermittent sighing respirations may be found secondary to brainstem dysfunction. Rarely can it present in the childhood (juvenile form). Respiratory failure is usually responsible for mortality. Biochemical abnormalities include elevated blood and CSF lactate and pyruvate.[12]

Neuroimaging[6,7,9,10,13] plays an important role in diagnosis as well as follow up of patients with Leigh's syndrome. CT scans may reveal bilateral symmetric areas of low attenuation involving the basal ganglia. On MR imaging, signal changes characterized by low signal on T1 weighted images and high signal on T2 weighted images, have been most commonly reported in the basal ganglia, thalamus and brainstem. Variable involvement of the cerebral and cerebellar cortex, cerebral and cerebellar white matter and the spinal cord has also been reported. The affected regions show restriction of diffusion in the acute phase. MR spectroscopy of the basal ganglia typically demonstrates high lactate levels, decrease in NAA/Creatine levels and elevation of Choline/Creatine ratio. These metabolites are useful indicators of prognosis and response to therapy.[14,15] Abnormality of diffusion-weighted imaging of the white matter may be apparent before clinical onset.[16,17] Thus neuroradiological examination can be quite discriminative in a child with neurological problems and should the referring doctor to go for the most appropriate enzymatic and genetic study in their patients.[18]

Autopsy findings[8,11] include focal symmetric areas of necrosis in the thalamus, basal ganglia, tegmental gray matter, periventricular and periaqueductal regions of the brainstem and posterior columns of the spinal cord. These lesions show cystic cavitation with neuronal loss, demyelination and vascular proliferation. Demyelination with relative preservation of neurons and axon differentiates these lesions from those of hypoxic or ischemic origin.[8]

Leigh's disease is a very rare disorder, and there is currently no cure. A high-fat,  may be recommended. It is currently treated with  (vitamin B1), but even with treatment, infants rarely live longer than two or three years after the onset of the disease. In cases of older people, the disease takes longer, but is still almost always fatal. Mitochondrial disease cannot be cured completely. Efforts for prevention and prenatal diagnosis are still in the nascent stage. With appropriate investigations, accurate diagnosis and prompt institution of adequate supportive therapy, symptomatic amelioration can be achieved, thereby adding life to the limited years of survival of these children. Further research aimed at prenatal identification of the responsible mutations and prevention of the disease is warranted.

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