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*RESEARCH ARTICLE*

# "A CASE SERIES ON VARIED CLINICAL PRESENTATION IN LEIGH'S SYNDROME IN A TERTIARY CARE HOSPITAL"

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## *Abstract*

**Background:**Leigh syndrome (LS) is a hereditary neurometabolic disease, also known as subacute necrotizing encephalomyelopathy, and was described by the British neuropathologist and psychiatrist Denis Leigh in 1951. It is a neurodegenerative disease with variable symptoms that occurs due to a mitochondrial dysfunction caused by a hereditary genetic defect, associated with bilateral central nervous system lesions. Although it is a rare disease, with an approximate incidence of 1: 40,000 live births, it is the most frequent mitochondrial disease in the first year of life.

**Clinical Scenario: Case 1**

Baby Nikshitha, a 6-and-a-half-month old female child born to a multigravida mother in a non-consanguineous marriage with previous 2 abortions and 1 intrauterine death. The baby was born through LSCS (oligohydramnios) and cried immediately at birth with a weight of 2.5kgs with uneventful antenatal periods.Excessive Vomiting x 1 month, increased over 5 days, Inability to gain weight over the past 3 months, Abnormal Posturing - 2 days prior to admission

**Mri Brain:** Symmetric areas of altered intensity in bilateral caudate nucleus relatively sparing Globus pallidi showing diffusion restriction.

**Clinical Scenario: Case 2**

Baby of suhasini, a 3 months old female child born to a primi mother in a non-consanguineous marriage with previous 1 sibling death. The baby was born through NVD and cried immediately at birth with a weight of 2.5kgs with uneventful antenatal periods.Child presented to the hospital at 3months of life with the chief complaints of - FEVER x 4 days, Noisy breathing since 4 days, Abnormal Posturing – since yesterday nightInitial Septic workup to rule out meningitis – NORMAL. ABG done in view of failure to thrive with recurrent vomiting –

**Metabolic Acidosis.Mri Brain:** Symmetric areas of altered intensity in bilateral caudate nucleus relatively sparing Globus pallidi showing diffusion restriction. No blooming to suggest haemorrhage or calcification. Myelination is consistent with age

**Clinical Scenario: Case 3**

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Shobhakumari, 2Y old female child born to a multigravida mother in a non-consanguineous marriage with h/o sibling death at 5 years of age (leighs disease). The baby was born through NVD and cried immediately at birth with a weight of 2.5kgs with uneventful antenatal periods.Child presented to the hospital at 2 years with the chief complaints of - Excessive Vomiting since 6daysInability to gain weight over the past 3 months MRI brain :T2/Flair hyperintense signal with restricted diffusion in deep grey matter of b/l cerebellar hemisphere and periaqueductal grey matter of midbrain caudate nucleus and putamen

**Clinical Scenario: Case 4**

B/o Afreen 4 year male born to a primi mother through normal vaginal delivery in a non-consanguineousmarriage with birth weight of 2.7 kg . Child presented to a hospital with History of regression of milestones and rhythmic repetitive movement of upper limb since 15 months of age. Serum lactate was high and MRI brain showed symmetrical B/l T2/FLAIR caudate and putamen nucleus hyperintensity with restriction on DW1 images

**Discussion:**Several studies showed significant heterogeneity in the clinical findings of Leigh syndrome. Sofou K et al., revealed in a study that 69% of the cases presented before 2 years of age, while three patients presented with ataxia or seizures at 8,10 and 21 years of age.

**Conclusion:**The diagnosis of Leigh's disease should be considered in appropriate clinical and laboratory settings whenever symmetrical hypo densities are encountered in the putamen and midbrain on.



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## Introduction:-

Leigh syndrome (LS) is a hereditary neurometabolic disease, also known as subacute necrotizing encephalomyelopathy, and was described by the British neuropathologist and psychiatrist Denis Leigh in 1951. It is a neurodegenerative disease with variable symptoms that occurs due to a mitochondrial dysfunction caused by a hereditary genetic defect, associated with bilateral central nervous system lesions. Although it is a rare disease, with an approximate incidence of 1: 40,000 live births, it is the most frequent mitochondrial disease in the first year of life.[1 – 4)]

There are several genetically determined causes of Leigh disease that result from nuclear DNA mutations. Pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10. 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 E, deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. Approximately 30% of cases are caused by mutations in mtDNA.

The heterogeneous functional nature of the mitochondria is responsible for the broad spectrum of clinical manifestations that characterize LS. A dysfunction is present in a restricted but vital area of mitochondrial metabolism, oxidative phosphorylation, in which most cellular adenosine triphosphate (ATP) is produced. Thus, any organ can be affected, but tissues with higher oxygen needs, such as the skeletal muscle, the heart and the nervous system, are usually the most affected.[5,6)]

Neurological manifestations may include delayed psychomotor development, muscle weakness, hypotonia, dystonia, spasticity, epilepsy, ataxia, intentional tremor, nystagmus, ophthalmoparasia, optic atrophy, dysphagia, respiratory impairment, deafness, paralysis of peripheral cranial nerves, polyneuropathy and myopathy. The most frequent non-neurological manifestations include dysmorphic and endocrine (short stature, hypertrichosis, diabetes), cardiac (dilated or hypertrophic cardiomyopathy) or gastrointestinal abnormalities (diarrhea, vomiting). [2,4,7)]


The biochemical markers that are suggestive of LS are high plasma lactate levels (by glucose overload) and increased lactate/pyruvate ratio; however, their absence does not exclude the diagnosis. [1, 8] Neuroimaging plays an important role in diagnosis of patients with Leigh syndrome. The most characteristic neuroradiological findings are bilateral, symmetric focal hyper intensities in the basal ganglia, thalamus, substantianigra, 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. In the basal ganglia, the putamen is particularly involved.Other frequently involved areas are the thalamus, substantianigra, red nucleus, brainstem, cerebellum, cerebral white matter, or spinal cord.[2,8,9]

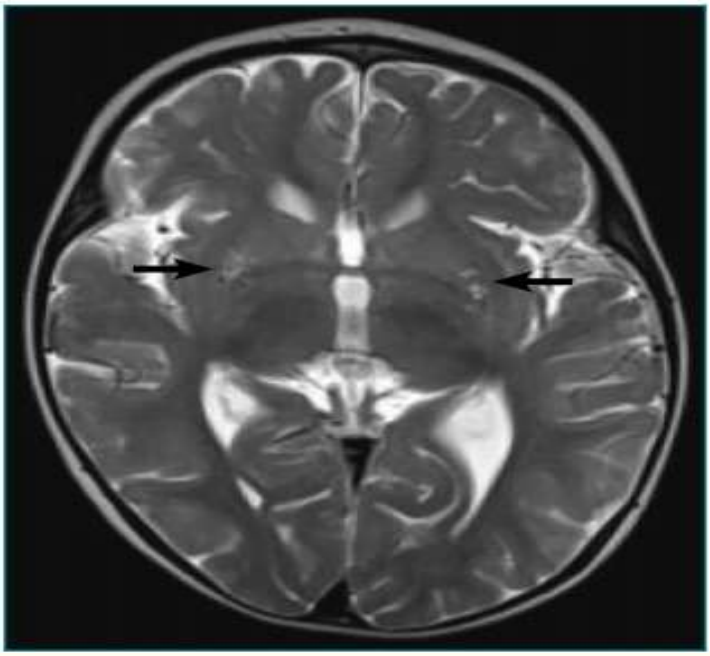


**Figure 1:-** Axial cut of the cranioencephalic magnetic resonance (T2) of the patient with Leigh syndrome and 8993T>G mutation. The arrows show the bilateral lenticular hyper signal.

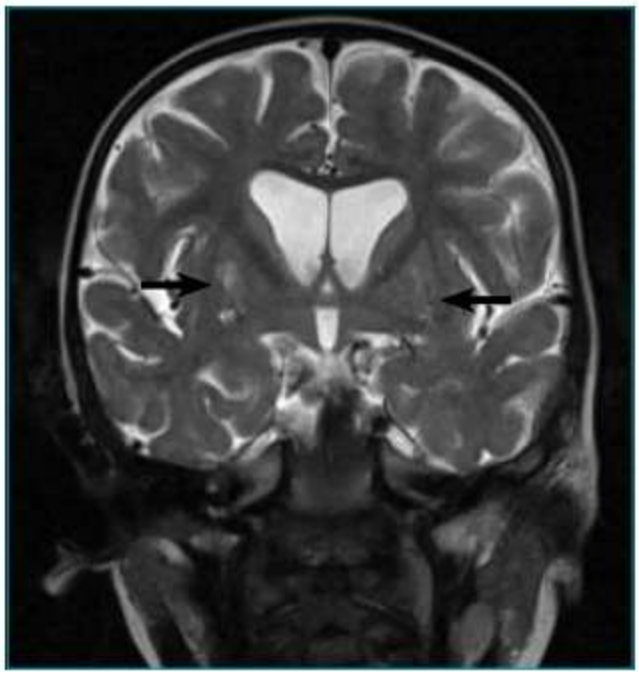


**Figure 1:-** Coronal cut of the cranioencephalic magnetic resonance (T2 weighting) of the patient with Leigh syndrome and 8993T>G mutation. The arrows show the bilateral lenticular hyper signal.

The prognosis of LS is reserved and there is no specific treatment, and multidisciplinary palliative care should be performed.NO complete cure has been identified for mitochondrial diseases. Aim of treatment is to lower lactate levels and to increase ATP production. Thiamine, Riboflavin, Coenzyme Q and Carnitine can be given.

**Clinical Scenario: Case 1**

Baby Nikshitha, a 6-and-a-half-month old female child born to a multigravida mother in a non-consanguineous marriage with previous 2 abortions and 1 intrauterine death. The baby was born through LSCS (oligohydramnios) and cried immediately at birth with a weight of 2.5kgs with uneventful antenatal periods. Child presented to the hospital at 6 months of life with the chief complaints of - Excessive Vomiting x 1 month, increased over 5 days, Inability to gain weight over the past 3 months, Abnormal Posturing - 2 days prior to admission.

Vomiting - curdy white, non-bilious, non-projectile, small quantities most probably regurgitation. Inability to gain weight - static weight noted (5 kgs) since 4 months of life in spite of adequate feeding, adequate milk output, no bottle feeds and no structural abnormalities affecting feeds. Dystonic posturing: not associated with LOC or loss of tone or posture. History of delay and currently neuroregression observed on follow up. On admission, the baby was encephalopathic with vitals being stable. Dystonic posturing noticed in the hospital lasting for almost half an hour. General examination revealed no dysmorphisms or neurocutaneous markers. CNS examination revealed developmental delay in all 4 domains. Other systems were within normal limits.

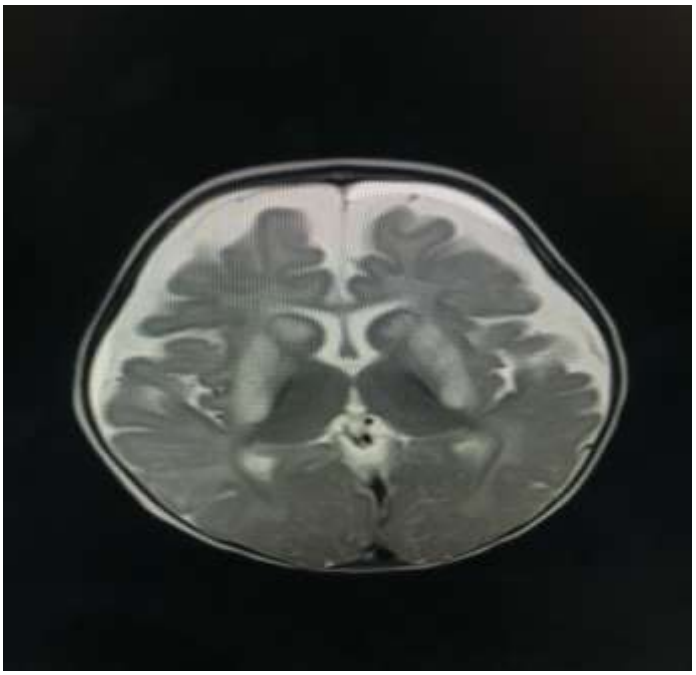
Development assessment revealed a mild delay in all the 4 domains with regression of milestones over the past 3 weeks. Chronological age - 7 months. Developmental age - 4-5 months.

**Investigations:**

Initial Septic workup to rule out meningitis – NORMAL, ABG done in view of failure to thrive with recurrent vomiting – NORMAL, Blood, urine and CSF cultures were normal.

**Mri Brain:**

Symmetric areas of altered intensity in bilateral caudate nucleus relatively sparing Globus pallidi showing diffusion restriction. No blooming to suggest haemorrhage or calcification. Myelination is consistent with age, **SUGGESTIVE OF LEIGH'S SYNDROME.**



**Management:**

Pediatric Neurologist opinion sorted and child initiated on the following Thiamine, riboflavin, biotin, INJ Vitamin B12, haloperidol, levipil. Child is currently 7 months old and is on regular follow up and close watch for development and neurological outcome.

**Clinical Scenario: Case 2**
Baby of suhasini, a 3 months old female child born to a primi mother in a non-consanguineous marriage with previous 1 sibling death. The baby was born through NVD and cried immediately at birth with a weight of 2.5kgs with uneventful antenatal periods.

Child presented to the hospital at 3months of life with the chief complaints of - FEVER x 4 days, Noisy breathing since 4 days, Abnormal Posturing – since yesterday night.Fever low grade intermittent no diurnal variation. c/o noisy breathing since 4 days. Abnormal jerky movements of the head around 10.30 pm with movements of both the lower limb lasting for 10 minutes not associated with loss of consciousness pre ictally child was playing postictally no loss of consciousness similar episode at 5am and 8am.

Baby was breast fed after 45mins of delivery and was given top feeds for 7days. Development :normal.

Family history: non consanguineous marriage born to a primi mother.

On admission, the baby was encephalopathic with gasping Baby was actively seizuring with uprolling of eyes noticed in the hospital lasting for almost half an hour. Anthropometry showed failure to thrive General examination revealed no dysmorphisms or neurocutaneous markers. CNS examination child was encephalomathic. Other systems were within normal limits.

**Investigations:**
Initial Septic workup to rule out meningitis – NORMAL. ABG done in view of failure to thrive with recuTrrent vomiting – METABOLIC ACIDOSIS. Blood, urine and CSF cultures were normal. TMS –NORMAL. Plasma lactate 80mg/dl.

**Mri Brain:**
Near Symmetric acute ischaemic infract of b/l basal ganglia,caudate nuclei and lateral aspect of the left cerebral hemisphere likely secondary to acute profound hypoxic ischemic event. T1w sequence lack of hyperintense signal intensityin anterior limb of internal capsule t2w sequence reveals lack of hypointense signal intensity in the optc tract **SUGGESTIVE OF LEIGH'S SYNDROME.**

In view of the above findings, child was further evaluated for LEIGH'S syndrome. Serum Lactate elevated to 80mg/dl. TMS evaluation to rule out IEM was normal. EEG showed recurrent episode of generalized seizure with buried polyspikes to look for classical myoclonus infantile seizure.

**Management:**
Pediatric Neurologist opinion sorted and child initiated on the following, Thiamine, riboflavin, biotin, INJ Vitamin B12, haloperidol, levipil. Child is currently 1y5m months old and is on regular follow up and close watch for development and neurological outcome.

**Clinical Scenario: Case 3**
Shobhakumari, 2Y old female child born to a multigravida mother in a non-consanguineous marriage with h/o sibling death at 5 years of age (leighs disease). The baby was born through NVD and cried immediately at birth with a weight of 2.5kgs with uneventful antenatal periods. Child presented to the hospital at 2 years with the chief complaints of - Excessive Vomiting since 6days. Inability to gain weight over the past 3 months. Vomiting – white in colour post feeds contains food paticles non bilious non projectile non blood stained. c/o refusal to feeds since 4 days and excessive cry since one day. History of development delay and currently neuroregression at admission.

On admission, the baby was severly dehydrated with shock. General examination revealed no dysmorphisms or neurocutaneous markers. Anthropoemetry showed severe acute malnunitrition with microcephaly. CNS examination revealed developmental delay in all 4 domains with qudriparesis with choreoathetosis. Other systems were within normal limits.Development assessment revealed a gdd in all the 4 domains with regression of milestones over the past 3weeks. Chronological age – 2years. Developmental age – 9m.

**Investigations:**
Initial Septic workup - NORMAL. ABG done showed high anion gap acidosis. Blood, urine cultures were normal.

**Mri Brain:**
T2/Flair hyperintense signal with restricted diffusion in deep grey matter of b/l cerebellar hemisphere and periaqueductal grey matter of midbrain caudate nucleus and putamen. Glotic areas in deep periventricular white mater of b/lfrontoparietal and occipital lobes caudate nucleus putamen subthalamic nucleus crus of midbrain ventral midbrain centrum semi ovale and corona radiate. Features suggestive of leighs disease. In view of the above findings, child was further evaluated for LEIGH'S syndrome. TMS evaluation to rule out IEM was normal.

**Management:**
Pediatric Neurologist opinion sorted and child initiated on the following, t.Seranace, syp.carnitine, t.zubitine,t.tiam. Child was on regular follow up and died at the age of 3y6m came with c/o fever respiratory distress abgwith showed respiratory alkalosis.

**Clinical Scenario: Case4**
B/o Afreen 4 year male born to a primi mother through normal vaginal delivery born out of a non-consanguineous marriage with birth weight of 2.7 kg . Child presented to a hospital with History of regression of milestones and startle response along with rhythmic repetitive movement of upper limb since 15 months of age.

EEG was normal with generalized spike at the time of sound induced startle. Biochemical examination revealed increased serum lactate.

MRI showed symmetrical B/L T2/FLAIR caudate and putamina nucleus hyperintensity with restriction on DWI images.

## Discussion:-

Leigh's syndrome, a mitochondrial disorder, is a rare progressive neurodegenerative disorder presenting in the infancy or childhood.Neuroimaging with MRI along with MR spectroscopy of the affected area has proved to be of great importance in the early diagnosis. MR Spectroscopy is a non-invasive method to measure and monitor the biochemical changes in various lesions. Each metabolite in the brain affects specific cellular and biochemical processes and appears at a specific ppm. Hence the observed MR spectroscopy finding oflesion as along with MRI finding correlation gives more information about the disorder being evaluated.

Sub-acute Necrotizing Encephalomyelopathy (SNE) presents broadly in two forms, infantile and juvenile form. Within two years of life, most of the cases of infantile form of Leigh's syndrome has characteristic clinical features of breathing dysfunctions, ataxia, seizures, regression of neuro-psychomotor development and hypotonia[11,12].

Several studies showed significant heterogeneity in the clinical findings of Leigh syndrome. Sofou K et al., revealed in a study that 69% of the cases presented before 2 years of age, while three patients presented with ataxia or seizures at 8,10 and 21 years of age [13]. In the index case, the child presented at the age of 7 years with ataxia, gait disturbances and neuroregression. Adult onset Leigh disease is designated to patients who survive longer than 18 years. Adult onset Leigh disease has lesser incidence of serum lactate elevation, basal ganglia lesion, COX deficiency and developmental delay. The patients present with cranial nerve disorders, pyramidal signs and cerebellar dysfunction [14].

Diagnosis of this syndrome is suspected by MRI in most of the cases, especially in late or atypical forms. Basal ganglia and brain stem are the most commonly affected areas. MRI findings include symmetric hyperintense lesions of basal ganglia especially putamen and globuspallidus, brain stem and thalamus on T2W images. The neuroimaging alterations found, along with hyperlactacidemia and hypocitrulinaemia, reinforced the diagnostic hypothesis. For this reason, the genetic investigation focused on the mitochondrial panel of genes, with the 8993T>G mutation. Although more studies are needed, this mutation should be considered early in the diagnostic evaluation of childhood mitochondrial diseases with hypocitrulinaemia, which minimizes the need for invasive procedures, such as muscle biopsies, associated with a small but not negligible risk of complications. (15)

Pathologically, the changes in the Leigh syndrome is characterised by multifocal spongiform lesions with relative preservation of neurons associated with degeneration and gliosis through the brain, including basal ganglia, brain stem, thalami, cerebellum, spinal cord and optic nerve[16] .MR imaging helps in differentiating the other pathological conditions affecting the basal ganglia manifesting in the childhood which are not well differentiated on CT brain [17].

Barkovich AJ et al., reported an increase in lactate from the affected areas of patients, on MR spectroscopy [18]. MR Spectroscopy findings, clinical symptoms and laboratory findings are altogether important for diagnosing Mitochondrial Encephalopathies.

Specific treatment for the Leigh syndrome is not available and available therapeutic options are limited. Symptomatic treatment is usually given to improve the ATP production and to lower the lactate levels. Ketogenic diet is found to improve the clinical features [19]. Supplements with thiamine and physiotherapy are recommended for the neuromuscular concerns. Anti-seizure medication is suggested for seizure control. Response to the treatment can be monitored by MRI Brain and MRS.

## Conclusion:-

The diagnosis of Leigh's disease should be considered in appropriate clinical and laboratory settings whenever symmetrical hypodensities are encountered in the putamin and midbrain on MRI. Mitochondrial disease cannot be cured completely. symptomatic amelioration can be achieved. Magnetic resonance imaging with modern imaging techniques and MR spectroscopy is a valuable investigation for the extent of the disease and diagnosis of subacute necrotizing encephalomyelopathy and for the evaluation of its outcome.

**Conflicts of interest:**
None.

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