Case Report: 

Leigh's Syndrome (Subacute Necrotising Encephalomyelopathy): A Case Report

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Abstract:
Leigh syndrome or sub-acute necrotizing encephalomyelopathy (SNE) is a rare progressive neurodegenerative, mitochondrial disorder of childhood. It was first reported in 1951 by Denis Leigh in, a British neuropathologist, in a 7 months old infant that progressed rapidly and resulted in death over 6-week period estimated prevalence is 1 in per 40,000 births. Our patient 18 months male child 3rd issue of 2nd degree consanguineous marriage with uneventful perinatal history presented to our hospital with multiple convulsions, respiratory distress, delayed developmental milestones and regression of achieved milestones and malnutrition. On initial examination child was drowsy (Glasgow coma scale:10) and febrile. On examination table, child had generalized tonic clonic type of convulsion which were treated by Diazepam (i.v.0.3 mg/kg stat) and Phenytoin (i.v.20 mg/kg stat followed by 5 mg/kg 12hourly). Laboratory analysis showed metabolic acidosis. His pulse rate was 160/min; respiratory rate 50/min. CNS examination showed increased tone in the lower limb, deep tendon reflexes were exaggerated with bilateral Babinski sign. Pupils were mid dilated with sluggishly reacting to light. Fundus examination and visual evoked potential were normal. His weigh was 8 kg and height 94 cms. The above clinical findings were highly suggestive of a neurodegenerative disorder and the patient was further investigated. Our experience suggested that bilateral symmetric T2 prolongation involving multiple brain stem nuclei/structures associated with basal ganglia abnormalities in a child with neurological problem should prompt the clinician to consider Leigh syndrome and conduct further investigations such as measurement of blood and/or CSF lactate, and respiratory chain enzymes activities.

Background:
Leigh syndrome or sub-acute necrotizing encephalomyelopathy (SNE) is a rare progressive neurodegenerative, mitochondrial disorder of childhood. It was first reported in 1951 by Denis Leigh in, a British neuropathologist, in a 7 months old infant that progressed rapidly and resulted in death over 6-week period estimated prevalence is 1 in per 40,000 births. The onset is usually early in infancy and patient manifest a heterogeneous set of symptoms, such as regression or psychomotor delay, weakness, hypotonia, brainstem sign, ataxia, pyramidal sign, respiratory insufficiency, lactate acidosis in the blood, cerebrospinal fluid, urine and acute deterioration following common infection. The prognosis is poor and, in most cases patient die before age of 5 years. In most cases, dysfunction of respiratory chain enzyme is responsible for the disease. It may be due to defects in genes for the pyruvate dehydrogenase complex, cytochrome-c oxidase, ATP synthase subunit 6 or subunits of mitochondrial complex 1. Patterns of inheritance include X-linked recessive, autosomal recessive and mitochondrial. However the genetic cause of number of cases of Leigh syndrome remains unknown, despite the presence of specific biochemical defect in...
many of them. Despite its considerable clinical genetical and biochemistry heterogeneity, the basic neuropathological features in children affected are almost affected identical;which are focal, bilateral and symmetrical necrotic lesions associated with demyelination, vascular proliferation and gliosis in the brainstem, diencephalon, basal ganglia, and cerebellum. It is possible to come to diagnosis of probable SNE during life of on the basis of clinical signs and symptoms, mode of inheritance, metabolic abnormalities, and neuroimaging findings. We report a rare case which presented clinically as neurodegenerative disorders and diagnosed as Leigh syndrome on MRI.

**Case Presentation**

Our patient 18months male child 3rd issue of 2nd degree consanguineous marriage with uneventful perinatal history presented to our hospital with multiple convulsions,respiratory distress,delayed developmental milestones and regression of achieved milestones and malnutrition. On initial examination child was drowsy(Glasgow coma scale:10) and febrile. On examination table, child had generalized tonic clonic type of convulsion which were treated by Diazepam(i.v.0.3 mg/kg stat)and Phenytoin (i.v.20 mg/kg stat followed by 5 mg/kg 12hourly). Laboratory analysis showed metabolic acidosis.His pulse rate was 160/min;respiratory rate 50/min.CNS examination showed increased tone in the lower limb, deep tendon reflexes were exaggerated with bilateral Babinski sign. Pupils were mid dilated with sluggishly reacting to light.Fundus examination and visual evoked potential were normal.His weigh was 8 kg and height 94 cms. The above clinical findings were highly suggestive of a neurodegenerative disorder and the patient was further investigated. Routine haemogram revealedhaemoglobin 9.1gm%, packed cell volumes 30%,total leucocytes counts 20,000 cell per mm3 with marked neutrophilia (85%)and lymphocytes counts 10%. Cerebrospinal examination showed 2 cells,all lymphocytes and normal sugar and protein levels.CSF lactate was significantly raised (9.4mmol/L).Gram and ZN staining of the CSF showed no organism and pus cells. Serum Lactate (7.2mmol/L) and creatinine kinase levels were raised. Liver function and renal function were within normal limit. Blood and urine culture were negative. Magnetic Resonance Imaging was done which showed bilateral symmetric area of altered signal intensities noted involving basal ganglion (putamen, caudate nucleus, globus pallid) , brain stem, substantianigra andperi-aqueductal white matter appearing hyperintense T2W and FLAIR images(Image 1-3). There were prominent extracerebral CSF spaces in the fronto-temporo-parietal region on both the sides. Atrophy with myelination normal for age was noticed. MR SPECTROSCOPY: single voxel spectroscopy of the lesion shows elevated choline peak and NNA peak and elevated choline/creatine (1.55) and choline/NNA (1.54) ratios. Multi-voxel spectroscopy shows elevated lactate values (Image 4). The above radiological findings on MRI BRAIN WITH MR SPECTROSCOPY established the clinical diagnosis of a neurodegenerative disorder as Leigh syndrome.

Supportive therapy for Leigh disease was begun with intravenous Thiamine infusion,Carnitine, oral coenzyme Q10 (Ubiquinone) and alkali supplementation. Over the next 4 days, he improved clinically.He was discharged home after 11th day. Enzymology, histology and functional fibroblast ATP synthesis rate, molecular studies were not performed due to the paucity of facilities and financial constraints.
Discussion
Leigh disease or SNE is a rare progressive neurological disorder of the childhood. The estimated prevalence of Leigh syndrome in infancy (1: 40,000)⁶. 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. 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 E1α deficiency⁷. Approximately 30% of cases are caused by mutation in mtDNA. The clinical diagnosis of the disease becomes difficult because of the variability of the symptoms and lack of specific biochemical investigations. It usually presents early in life with abnormal muscle tone, weakness, dystonia, brainstem or cerebellar dysfunction (ataxia), missed milestones or regression of achieved milestones, tachypnea, and seizures. Affected children usually become symptomatic within a few years of life with feeding difficulties, vomiting, and failure to thrive or malnutrition¹. Symptoms are made worse by intercurrent infection or ingestion of heavy carbohydrate meal. Elevations in serum lactate are characteristic. Death usually occurs within few years after onset of symptoms.

There are four diagnostic criteria’s:
(1) Progressive neurological disease with motor and intellectual development delay;
(2) Sign and symptoms of brain stem and/or basal ganglia disease:
(3) Raised lactate levels in blood and/or CSF;
(4) Characteristic symmetric necrotic lesions in the basal ganglia and or brainstem

Neuroimaging plays important role in diagnosis of patient with Leigh syndrome⁸⁻¹². MRI appears to be superior to CT in identifying lesions of Leigh syndrome. The most characteristic neuro-radiological findings are bilateral, symmetric focal hyperintensities 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. Low attenuation in the putamina on CT is considered to be characteristic of the disease.

There is no cure for Leigh syndrome. Specific therapy for mitochondrial disorders in children is not available. Treatment generally involve variation of vitamin and supplement therapies, often in “cocktail” combination, and are only partially effective. The aim of symptomatic treatment is to improve the ATP production and to lower the lactate levels. Thiamine, a cofactor of pyruvate dehydrogenase has been reported to be improving the neurological status in some patients¹³. Marked improvement was observed with riboflavin, which nearly normalized the ATP. Coenzyme Q and carnitine have also been found to be effective.

Conclusion
Our experience suggested that bilateral symmetric T2 prolongation involving multiple brain stem nuclei/structures associated with basal ganglia abnormalities in a child with neurological problem should prompt the clinician to consider Leigh syndrome and conduct further investigations such as measurement of blood and/or CSF lactate, and respiratory chain enzymes activities. Neuro-radiological discriminative observation is very useful in guiding the clinician for the most appropriate enzymatic and genetic study in their patients. Leigh syndrome has no cure. 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.

Consent
Written informed consent was obtained from the father of the patient for publication of this case report and any accompanying images.

List of abbreviations
MRI: Magnetic Resonance Imaging; SNE: Subacute necrotizing encephalopathy; DNA: Deoxyribonucleic acid; i.v: intravenous; CSF: Cerebrospinal fluid; AST: Aspartate transaminase; ALT: Alanine transaminase; ATP: Adenosine triphosphate; CT:Computed Tomography; NAD: Nicotinamide adenine dinucleotide.
References


Image 4: Single voxel spectroscopy of the lesion shows elevated choline peak and NNA peak and elevated choline/creatine and choline/NNA ratios. Multi-voxel spectroscopy suggestive of elevated lactate values.