

Leigh Syndrome: An Unusual Rare Case Report

P Dinesh¹,
M Madan Raj²,
S Gita³

¹Assistant Professor, Dept. of Ophthalmology, A.I.M.S, B.G.Nagara, ²Post Graduate Dept. of Ophthalmology, A.I.M.S, B.G.Nagara, ³Assistant Professor, Dept. of Ophthalmology, A.I.M.S, B.G.Nagara

Corresponding Author: Dr. P. Dinesh, Assistant Professor, Dept. of Ophthalmology, A.I.M.S, B. G. Nagara. E-mail: drpdinesh@gmail.com

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 movement 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 and unique case of Leigh syndrome seen in a 5 year male child.

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

INTRODUCTION

Leigh syndrome is synonymous with Juvenile subacute necrotizing encephalomyelopathy, 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. It is characterized by progressive loss of mental and movement abilities (psychomotor regression) which typically arises in the first year of life leading to death within a span of several years. Infants with this syndrome have symptoms that include diarrhea, vomiting and dysphagia leading to failure to thrive. Excess lactate may be seen in the urine, cerebrospinal CSF and blood. The muscular system is debilitated throughout the body, as the brain cannot control the contraction of muscles. Hypotonia, dystonia, and ataxia are often seen. Ocular signs include ophthalmoparesis, nystagmus and optic atrophy. Cardiac signs include Hypertrophic cardiomyopathy, ventricular septal defects.¹ Respiratory failure is the most common ultimate cause of death. There are characteristic lesions in the basal ganglia, cerebellum and brainstem, these lesions are often accompanied by demyelination. Leigh syndrome can be caused by mutations in one of over 30 different genes either mitochondrial DNA (mtDNA) or in nuclear DNA (gene SURF1 and some COX assembly factors). There is currently no effective treatment.

CASE REPORT

A five year male child was referred from the pediatric department to the department of ophthalmology to rule out any ocular cause of nystagmus, the informant was the grandmother, she reported unspecific symptoms like attention deficits, decrease in alertness, and history of seizures. The child had a history of second degree consanguineous marriage with an uneventful perinatal history.

On examination the child had delayed developmental milestones, muscular atrophy and dystonia with hypotonia, with Glasgow Coma Scale-6 and afebrile. There was increased tone in the lower limbs. Deep tendon reflexes were exaggerated with bilateral Babinski sign positive. Pupils were dilated and sluggishly reacting to light, funduscopy revealed bilateral optic atrophy, ERG was extinguished, VEP showed reduced amplitude with minimal shift in the latency (Figures 1 and 3). CSF analysis showed significantly raised lactate (9.1 mmol/L), Serum lactate (7.2 mmol/L) and creatinine kinase (347 U/L) levels were abnormally raised. Arterial blood gas analysis indicated metabolic acidosis. MRI showed bilateral, symmetrical abnormal lesions in the basal ganglia and the brain stem, thalamus. The lesions were hyperintense in T2W images.

Supportive therapy in the form of Thiamine infusions and alkali supplementation was given but the condition of the child remained the same for a few weeks and later deteriorated.



Figure 1: Optic atrophy of right eye

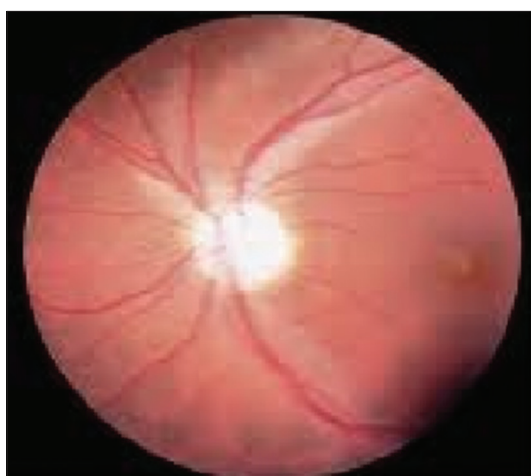


Figure 2: Optic atrophy of left eye

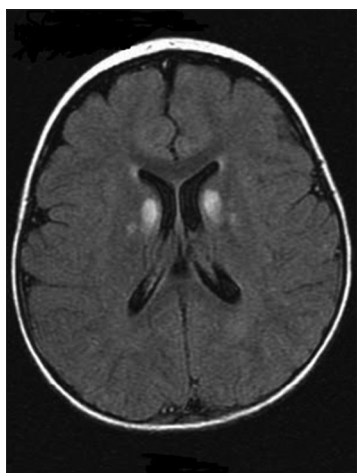


Figure 3: MRI showing bilateral symmetrical lesions in the basal ganglia

DISCUSSION

Leigh syndrome is a rare inherited neurometabolic subacute necrotizing encephalopathy disorder that affects the

central nervous system,¹ occurring in 1 in 40,000 newborns and in certain populations of Saguenay Lac-Saint-Jean region of Quebec, Canada {1 in 2,000 newborns}.² 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.³ It presents early in life with psychomotor regression, abnormal muscle tone, weakness, dystonia, brainstem and cerebellar ataxia, visual loss, missed milestones or regression of the achieved milestones, tachypnea, and seizures.⁴ 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.^{5,6} Laboratory analysis shows metabolic acidosis with elevated blood and CSF lactate and pyruvate concentrations.⁷ 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.⁸ Neuroimaging^{9,10} 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. In the basal ganglia, the putamen is particularly involved.^{11,12}

Leigh syndrome can be caused by mutations in one of over 30 different genes either mitochondrial DNA (mtDNA) or in nuclear DNA (gene SURF1 and some COX assembly factors).¹ 75 to 80% of Leigh syndrome is caused by mutations in nuclear DNA, Disruption of complex IV, also called cytochrome c oxidase or COX, is the most common cause of Leigh syndrome. The most frequently mutated gene in COX-deficient Leigh syndrome is called SURF1 {located on the long arm of chromosome 9}.¹³ Mutations in either mtDNA or in nuclear encoded genes lead to disorders of oxidative phosphorylation which leads to lack of energy in the cells, which leads to cell death of brain stem and basal ganglia. The most common mitochondrial DNA mutation in Leigh syndrome affects the MT-ATP6 gene.⁴ Another nuclear DNA mutation that causes Leigh syndrome affects the protein complex in the mitochondria, pyruvate dehydrogenase complex (PDHC), an enzyme in the glycolysis pathway, which leads to buildup of pyruvate leading to lactic acidosis, PDHC subunit is encoded by an X-linked gene. This syndrome is most commonly inherited in an autosomal recessive pattern, in about 20 to 25 % of people with Leigh syndrome, the condition is inherited in a mitochondrial pattern, which is also known as maternal inheritance. In a small number of affected individuals with

mutations in nuclear DNA, Leigh syndrome is inherited in an X-linked recessive pattern.

The differential diagnosis include perinatal asphyxia, kernicterus, carbon monoxide poisoning, methanol toxicity, thiamine deficiency, Wilson's disease, biotin-responsive basal ganglia disease and some forms of encephalitis.

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.¹⁴ Marked improvement was observed with riboflavin, which nearly normalized the adenosine triphosphate production.^{15,16} Rapid clinical and biochemical improvement was observed in patients with acute central respiratory failure with the use of intravenous soya bean oil (ketogenic emulsion).¹⁷ Ketogenic diet has been found to improve the outcome in those with a deficiency of pyruvate dehydrogenase.¹⁸ The symptoms of lactic acidosis are treated by 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. Nucleus transplantation into enucleated oocyte is emerging as a new option for prevention of mitochondrial disorders. Clinical trials of the drug EPI-743 for Leigh disease are ongoing.

CONCLUSION

Since 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 neurological symptoms whose MRI shows bilateral symmetric hyperintense T2w images of the brain stem and basal ganglia (Figure 4). This should prompt further investigations with measurement for blood/CSF lactate and respiratory chain enzyme activities and if appropriate clinical and laboratory settings are available further enzymatic and genetic study must be performed on the parents.

Even though the 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 adding the extra few years of life to the child.

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Figure 4: Child with Leigh disease having muscular atrophy and rigidity

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