ABSTRACT

Leigh’s disease is a rare inherited neurometabolic subacute necrotizing encephalopathy (SNE) mostly involving brainstem and basal ganglia is a rare entity affecting the central nervous system generally of infants, incidence being 1 in 40,000. It is characterized by progressive loss of mental and movement abilities associated with abnormal muscle tone, weakness, visual loss, respiratory failure and raised lactate levels in blood and/or cerebrospinal fluid. 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 8-month-old boy, who was healthy until 2 months earlier when he was brought to the hospital by his parents with chief complaints of fever, cough and cold since 3 days and rapid breathing for a day. After performing the various examinations the physicians were confirmed the diagnosis as Leigh’s disease. The therapy should be given for 12 days, and finally the patient was discharged on 13th day. Leigh’s disease cannot be cured completely. Nucleus transplantation into enucleated oocyte is emerging as a new option for prevention of mitochondrial disorders. Further research aimed at prenatal identification of the responsible mutations and prevention of the disease.

KEYWORDS: Leigh’s disease, Sub acute Necrotizing Encephalopathy (SNE), lactate, cerebrospinal fluid, respiratory failure.

INTRODUCTION

Leigh syndrome is synonymous with Juvenile subacute necrotizing encephalomyelopathy, Leigh disease, infantile subacute necrotizing encephalomyelopathy, and subacute necrotizing encephalomyelopathy(SNEM). Leigh Syndrome is a rare, inherited progressive neurodegenerative disorder with characteristic pathological features usually presenting in infancy or early childhood.[1]

It was first reported in 1951 by Denis Leigh, a British neuropathologist, in a 7 month old infant that progressed rapidly and resulted in death over a 6-week period.[2]

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]

It is possible to come to a diagnosis of SNE on the basis of clinical signs and symptoms, mode of inheritance, metabolic abnormalities, and neuro imaging findings.[3] The typical Magnetic resonance imaging (MRI) findings include symmetrical putaminal involvement, which may be associated with the abnormality of the caudate nuclei, globus pallidi, thalami, brain stem, and, less frequently, the cerebral cortex.[4] We report a rare case which presented clinically as a neurodegenerative disorder and diagnosed as Leigh syndrome on MRI.

CASE REPORT

A 8-months-old boy, who was healthy until 2 months earlier, when he was brought to the hospital by his parents with chief complaints of fever, cough and cold since 3 days and rapid breathing since 1 day. His history of present illness states that fever was high grade, intermittent not associated with chills and rigors, temporarily relieved on taking medications. Cough and cold was productive, more in supine position and no
diurnal variation. Past history reveals that the baby had convulsions 1 month back and is on treatment i.e., Syp.Phenytoin and also known case of Leigh’s disease. He was the fourth living child of non-consanguineous parents, and had two older sisters and one brother. Birth history, developmental history, immunization history and family history was normal.

At the time of admission, he was uncooperative and disoriented. The fundus examination was unremarkable. Laboratory data included Routine haemogram revealed haemoglobin 6 gm%, packed cell volume 32.3%, total leukocyte count 5,400 cells/mm3 with 51% neutrophils and 46% lymphocytes, urinalysis, liver and renal functions, with normal triglyceride, cholesterol, and uric acid levels. MP smear was positive for Plasmodium Vivax. Serum amino acid screening, blood ammonia, lactate, and pyruvate levels were normal; however, urine amino acid assay showed increased glycine, alanine, and glutamine. Cerebrospinal fluid examination showed 4 cells, all lymphocytes and normal sugar and protein levels. CSF lactate was significantly raised (8.8 mmol/L). EEG showed slowing on background rhythm and no epileptic activity.

From the above examinations, the physician was diagnosed as LEIGH’s disease with Malaria and the baby was on treatment with IV Fluids (1/2 DNS + Kcl), Inj. Amoxyclav 200mg IV BD, Syp.Zinc 5ml PO OD, Salbutamol nebulisation (0.3cc + 3cc NS + O2) QID, Syp.Phenytoin 1.8ml PO OD, Tab.Biotin ½ tab PO OD, Tab.Coenzyme-Q ½ tab PO OD, Tab.Levocarnitine ½ tab PO OD, Multivitamin drops 5½ BD, Ultra-D3 drops 1ml PO OD, Syp.Chloroquine 4ml PO OD (1 day), Tab.Thiamine ½ tab PO OD, Tab.Pyridoxine ½ tab PO OD and Syp.Luminarx 5ml PO BD. The above mentioned therapy was continued until all the symptoms were resolved completely. The treatment was given for 12 days, on 13th day the patient was discharged.

DISCUSSION

Leigh’s disease is a rare inherited neurometabolic disorder that affects the central nervous system. This progressive disorder begins in infants between the ages of three months and two years. Rarely, it occurs in teenagers and adults.[5] The Synonyms of Leigh Syndrome are: Leigh Syndrome, Leigh necrotizing encephalopathy, Leigh’s disease, Necrotizing encephalomyelopathy of Leigh’s, Subacute necrotizing encephalomyelopathy (SNE), Subacute necrotizing encephalopathy. It is also known as Infantile subacute necrotizing encephalopathy and Juvenile subacute necrotizing encephalopathy.[7]

Leigh syndrome is an early-onset progressive neurodegenerative disorder with a characteristic neuropathology consisting of focal, bilateral lesions in one or more areas of the central nervous system, including the brainstem, thalamus, basal ganglia, cerebellum, and spinal cord. The lesions are areas of demyelination, gliosis, necrosis, spongiosis, or capillary proliferation. Clinical symptoms depend on which areas of the central nervous system are involved. The most common underlying cause is a defect in oxidative phosphorylation.[8]

Clinically, Leigh syndrome is characterized by psychomotor delay or regression, muscular hypotonia, brainstem signs (especially strabismus, nystagmus and swallowing difficulties), ataxia, pyramidal signs, respiratory insufficiency, lactate acidemia and acute deterioration following common infections. In most cases, dysfunction of the respiratory chain enzymes 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 I. Patterns of inheritance include X-linked recessive, autosomal recessive, and mitochondrial.[9] Oxidation of pyruvate is dependent on a multienzyme complex (the pyruvate dehydrogenase complex); it is likely that a number of apoenzyme and coenzyme deficiencies could lead to this disorder.[10]

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.[2] 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.[11,12]

Leigh’s disease 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]

The signs and symptoms of Leigh syndrome are caused in part by patches of damaged tissue (lesions) that develop in the brains of people with this condition. A medical procedure called magnetic resonance imaging (MRI) reveals characteristic lesions in certain regions of the brain. These regions include the basal ganglia, which help control movement; the cerebellum, which controls the ability to balance and coordinates movement; and the brainstem, which connects the brain to the spinal cord and controls functions such as swallowing and breathing.[13]

It is possible to come to a diagnosis of probable SNE during life on the basis of clinical signs and symptoms, mode of inheritance, metabolic abnormalities, and neuroimaging findings.[3]

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.\textsuperscript{[14]}

Specific therapy for mitochondrial disorders in children is not available. The results and prognosis are variable. The aim of symptomatic treatment is to improve the ATP production and to lower the lactate levels. Thiamine, a cofactor of pyruvate dehydrogenase complex has been reported to improve the neurological status in some patients.\textsuperscript{[15]} 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.\textsuperscript{[16]}

Improvement was observed with riboflavin, which nearly normalized the adenosine triphosphate production.\textsuperscript{[17,18]} Supportive therapy for the suspected mitochondrial disorder was begun with intravenous Thiamine infusions, Carnitine, alkali supplementation and oral coenzyme Q10(Ubiquinone).Rapid clinical and biochemical improvement was observed in patients with acute central respiratory failure with the use of intravenous soya bean oil (ketogenic emulsion).\textsuperscript{[19]} Ketogenic diet has been found to improve the outcome in those with a deficiency of pyruvate dehydrogenase.\textsuperscript{[19]} Coenzyme Q and carnitine have also been found to be effective.\textsuperscript{[20]}

Respiratory infection was managed with intravenous antibiotics (Amoxicillin – clavulanic acid), salbutamol nebulisations and supplemental oxygen. He was also commenced on antiepileptics (phenytoin and valproate). Phenytoin was gradually tapered off and stopped. Specific supportive therapy for the suspected mitochondrial disorder was begun with oral thiamine, levocarnitine, biotin and coenzyme Q (ubiquinone). In view of the persistent fever, paracetamol was given and chloroquine on 3\textsuperscript{rd} and 4\textsuperscript{th} day of admission to treat malaria. Over the next 9 days, his fever defervesced and the choreoathetoid movements showed a significant improvement. Supplemental Oxygen was gradually weaned and stopped. He was discharged home after 13 days.

**CONCLUSION**

Leigh’s disease should be considered in a child presenting with neurodevelopment delay / progressive neurodevelopment regression and signs / symptoms of brain stem and/or basal ganglia involvement with raised lactate levels in blood and cerebrospinal fluid.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.

Mitochondrial disease cannot be cured completely. Nucleus transplantation into enucleated oocyte is emerging as a new option for prevention of mitochondrial disorders. Further research aimed at prenatal identification of the responsible mutations and prevention of the disease.

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