Leigh's Disease: A case Report

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Background:

Leigh disease[1], also termed as Sub Acute Necrotising Encephalopathy (SNP) is a rare, inheritable, progressive neurodegenerative disorder with characteristic pathological features usually presenting in infancy or early childhood. It was first reported in 1951 by Denis Leigh[2], a British neuro pathologist, in a 7 month old infant that progressed rapidly and resulted in death over a 6 week period. Clinically, Leigh disease is characterized by psychomotor delay or regression, muscular hypotonia, brainstem signs (especially strabismus, nystagmus and swallowing difficulties) & ataxia. In late stages pyramidal signs & respiratory insufficiency occurs. In most cases, dysfunction of the respiratory chain enzymes is responsible for the disease. There are several known genetically determined causes of Leigh disease: pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10[1].

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 $E_1\alpha$ deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. About 30% of cases are due to mutations in mtDNA[1]. Despite its considerable clinical, genetic and biochemistry heterogeneity, the basic neuro pathological features in children affected are almost identical; which are focal, bilateral, and symmetric necrotic lesions associated with demyelination, vascular proliferation and gliosis in the brainstem, diencephalon, basal ganglia, and cerebellum[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[4]. We report a rare case which presented clinically as a neurodegenerative disorder and diagnosed as Leigh disease on MRI.

Case Presentation

A 3 years old male child, 2nd issue of non consanguineous marriage, with an uneventful perinatal history, presented to our hospital with status epilepticus, delayed developmental milestones and regression of the achieved milestones. On initial examination, he was unconscious (Glassgow Coma Scale-5) and afebrile. Initial management aimed at controlling the seizures & raised intra cranial tension with anti epileptics & Inj mannitol as per protocol. His pulse was 124 beats per minute, respiratory rate 32 cycles per minute and blood pressure 94/58 mm Hg. His weight was 10 kg and height 84 cms with normal head circumference. CNS examination showed increased tone in the lower limbs. Deep tendon reflexes were exaggerated with bilateral Babinski sign. Pupils were dilated and sluggishly reacting to light. Fundus examination was normal. Routine haemogram revealed haemoglobin 10.2 gm%, packed cell volume 32.3%, total leukocyte count 7,550 cells/mm^3 with 38% neutrophils & 54% lymphocytes. CSF examination showed 6-8 cells, all lymphocytes and normal sugar and protein levels. Gram and ZN staining of the CSF showed no organism and pus cells. Serum lactate was significantly

raised (6.6 mmol/L). Liver function test showed mild derangement with AST- 56 IU/L, ALT- 49 IU/L and ALP- 109 IU/L. Renal function test was within normal limits. Arterial blood gas analysis indicated metabolic acidosis. Blood and urine cultures were negative.

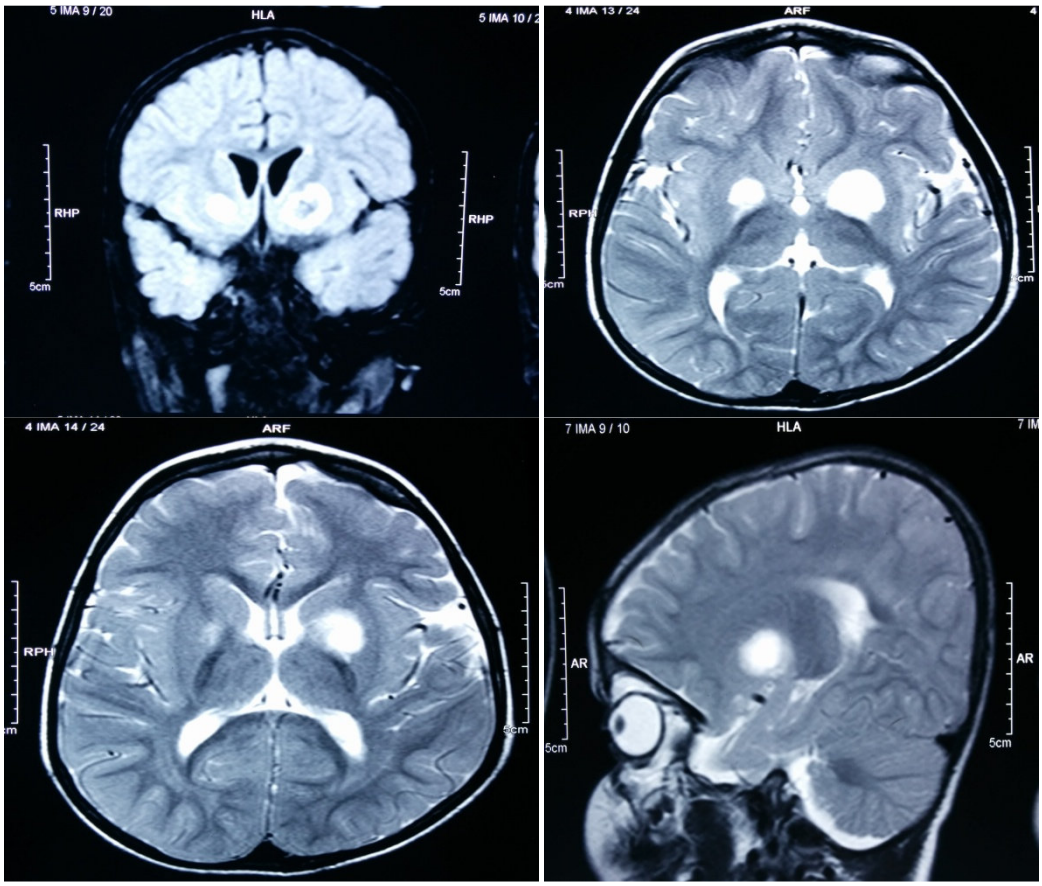

Figure 1: Magnetic Resonance Imaging was done which showed evidence of globular hyper intense areas in bilateral basal ganglia, more on left side with central necrotic / gliotic areas. It reveals hyperintense signals on T2W & FLAIR images & central fluid intensity areas which appear hypo intense on T2W images. Above radiological findings on MRI established the clinical diagnosis of a neurodegenerative disorder as Leigh disease.

Supportive therapy was begun with Tab Thiamine, Carnitine, Folinic acid, Tab Biotin, Tab Levodopa + Carbidopa, Syrup Baclofen, Tab Peciten (trihexyphenydione), Syrup Levetiracetam.

Discussion

Leigh's disease is a rare progressive neurological disorder of the childhood. The estimated prevalence of Leigh disease is 2.05 cases per 100,000[5]. Age of onset of symptoms is usually less than 2 years (infantile form), but milder forms may present in childhood (juvenile form) and unusually in adulthood. It presents early in life with psychomotor regression, abnormal muscle tone, weakness, dystonia, brainstem and cerebellar dysfunction (ataxia), visual loss, regression of the achieved milestones, and seizures[2,6,7]. Occasional findings are tachypnea & respiratory insufficiency. 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. Laboratory analysis shows metabolic acidosis with elevated blood & CSF lactate concentrations.

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[3].

This child presented to us with seizures, regression of developmental milestones and acute exacerbation caused by a trivial respiratory illness. Examination revealed delayed development, hypertonia and disorientation, all of which are recognized features of a neurodegenerative disorder. Serum lactate was elevated. On MR imaging findings suggested a progressive neurodegenerative disorder with the possibility of a mitochondrial encephalopathy (Leigh's Syndrome).

Conclusion

The diagnosis of 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. Our experience suggested that bilateral symmetric T2 prolongation involving multiple brainstem nuclei/structures associated with basal ganglia abnormalities in a child with neurological problems should prompt the clinician to consider Leigh disease and conduct further investigations such as measurement of respiratory chain enzymes activities. Mitochondrial disease cannot be cured completely but 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. Efforts for prevention and prenatal diagnosis are still in the nascent stage. Nucleus transplantation into enucleated oocyte is emerging as a new option for prevention of mitochondrial disorders[8]. Further research aimed at prenatal identification of the responsible mutations and prevention of the disease.

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