Leigh Syndrome - A rare Mitochondrial Disorder

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ABSTRACT

Introduction: Leigh syndrome is a rare progressive neurodegenerative, mitochondrial oxidative phosphorylation disorder of childhood with very few cases documented from India. The clinical presentation is highly variable. Even though, mostly it presents as a progressive neurological disease with motor and intellectual developmental delay and characterstic brain stem and/or basal ganglia involvement. Raised lactate levels in blood and/or cerebrospinal fluid is noted. Magnetic Resonance Imaging (MRI) brain showing characteristic symmetrical necrotic lesions in the basal ganglia and/or brain stem leads to the diagnosis.

Case report: We present a case of 1 year old male child admitted with complaints of regression of attained milestones since 4 month duration. History of previous sibling death at 2 year of age. On examination vitals stable, anthropometry suggests grade III PEM, microcephaly, generalized hypotonia, truncal ataxia, deep tendon reflexes exaggerated. P/A-hepatomegaly present with span of 8 cm. Other systems within normal limits. Ophthalamological and audiological evaluation normal. Serum lactate was found to be normal. MRI brain had shown bilateral symmetric altered signal intensity in basal ganglia, cerebellar and cerebral peduncles and medulla, suggestive of Leigh syndrome. Child was started on Physiotherapy and megavitamin supplements. On 1 month follow up visit, child was found to be achieving head control and able to stand with support.

Conclusion: Leigh syndrome is a rare entity and children with suspected leigh syndrome has to be in detail investigated and treated.

Keywords: Leigh syndrome, Neurodegenerative, mitochondrial oxidative phosphorylation disorder.

INTRODUCTION

Leigh syndrome is a rare progressive mitochondrial neurological disorder of childhood with reported incidence of 1:40,000 births.[1-3] It is characterized by progressive loss of mental and movement abilities which arises in infancy leading to death within a span of several years. The most characteristic neuroradiological findings in Leigh syndrome are bilaterally, symmetrical focal hyper intensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei at different levels on T2- weighted MRI. These high T2 signals on MRI reflect the spongiform changes and vacuolation in the damaged brain structures.[4-6] There is currently no effective treatment.

CASE REPORT

1 year old male child born to a third degree consanguinous married couple admitted to the department of pediatrics, K.S. Hegde Medical Academy with complaints of regression of attained milestones as loss of head control and inability to stand and walk noticed since last 4 month. History of previous sibling death at 2 year of age. History of fever and respiratory distress 4 months back, following that noticed poor tone, increased lethargy. At present no head control, unidextrous grasp + stranger anxiety + can speak one word and on weaning food, immunized as per age. On examination vitals stable, anthropometry suggests grade III PEM, microcephaly, generalized hypotonia, truncal ataxia, Power in neck muscle 0/5, b/l upper limb and lower limb -3/5, exagerrated deep tendon reflex bilateral babinski sign +.P/A-hepatomegaly with span of 8 cm. Other systems were within normal limits. Ophthalamological and audiological examination were normal. Serum lactate was fund to be normal. MRI brain had shown bilateral symmetric altered signal intensity in basal ganglia, cerebellar and cerebral peduncles and medulla, suggestive of Leigh's disease (Figure-1,2). Physiotherapy was advised and child was started on co enzyme Q10, thiamine, and carnitine supplements. On one month of follow up visit, child was found to be achieving head control and able to stand with support.

DISCUSSION

Leigh syndrome, a rare subacute necrotising encephalomyelopathy was first described by Leigh.[2] It is a progressive neurological disorder with variable etiology and clinical presentation seen particularly in pediatric population, even though a few juvenile and adult cases are known.[7-10] The estimated prevalence of Leigh Syndrome was 2.05 cases per 1, 00,000.[11] Mitochondrial as well as nuclear DNA enzyme defects have been known that determine similar clinical pattern but occur at different ages.[9]

Leigh syndrome can be caused by mutations in one of over 30 different genes in mitochondrial DNA (mt DNA) as well as in nuclear DNA (gene SURF1 and some COX assembly factors).[1] The most common mitochondrial DNA mutation in Leigh syndrome affects the MT-ATP6 gene.[5] Clinical symptoms are assessed by which area of the brain is affected. The infantile form usually presents with unspecific symptoms and a delay in psycho motor development. Other symptoms include attention deficit, limb hypotonia, vision abnormalities including nystagmus, poor strength, emesis, refusal to eat, and loss of weight.[9]

The diagnostic criteria include (1) progressive neurological disease with motor and intellectual developmental delay (2) clinical presentation of brainstem and/or basal ganglia disease (3) elevated lactate levels in blood and/or cerebrospinal fluid (CSF) and (4) characteristic symmetrical necrotic lesions in the basal ganglia and/or brain stem.[1]

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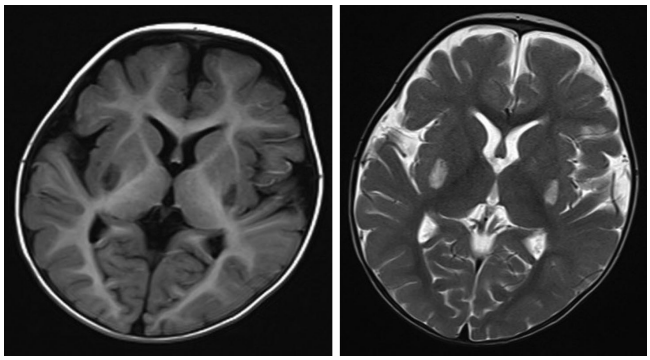

Figure-1,2: MRI brain showing bilateral symmetric altered signal intensity in basal ganglia, cerebellar and cerebral peduncles and medulla.

Neurological symptoms such as ataxia, pyramidal tract symptoms, and myoclonus often develop, followed by ophthalmoplegia and respiratory difficulties as a sign of brain stem damage.[9] Congenital cytochrome-c-oxidase deficiency, pyruvate dehydrogenase deficiency and biotinidase deficiency are known to cause these clinical symptoms. These conditions mostly have an autosomal-recessive inheritance even though mitochondrial and maternal inheritance are being discussed and sporadic cases are known.[10] Genetic irregularities could only be found in around 50% of all patients, showing that there are various biochemical abnormalities which can cause the clinical syndrome of Leigh disease.

Specific biochemical tests are still not available, however lactic acidosis and increased lactate-pyruvate quotient in plasma and CSF are nearly always found. The search for mitochondrial DNA mutations as a common cause for Leigh Disease and biochemical analysis of muscle biopsies still remain the gold standard in diagnosis.

The most characteristic neuroradiological findings in Leigh syndrome are bilateral, symmetrical focal hyper intensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei at various levels on T2-weighted sequence of MRI.[4-6] Similar findings are also seen in Wernicke's encephalopathy, multiple sclerosis, Wilson's disease, amino acidopathies, mitochondrial encephalomyelopathies, and different types of intoxication.[11]

In contrast to Wernicke's encephalopathy mamillary bodies are spared from pathological changes.[10]

A high-fat, low-carbohydrate diet may be preferred if a gene on the X chromosome is implicated. Thiamine (vitamin B1), Ketogenic diet may be supplemented if a deficiency of pyruvate dehydrogenase is suspected. The use of co enzyme Q10, thiamine, and carnitine may cause reduction in severity of symptoms in a few cases.[7,8]

CONCLUSION

The diagnosis of Leigh syndrome may be considered in appropriate clinical and laboratory settings. With appropriate investigations, accurate diagnosis and prompt adequate supportive therapy, symptomatic amelioration can be achieved. Further research aimed at prenatal identification of the probable mutations and prevention of the disease is warranted.

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