LEIGH DISEASE – A RARE MITOCHONDRIAL NEUROMETABOLIC DISORDER

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INTRODUCTION

Leigh disease (Sub-acute necrotizing encephalomyelopathy) is a rare, inherited neurometabolic disorder characterized by degenerative changes in central nervous system [1]. Primary disorder is in the mitochondria of affected cells. There are defects in the enzymes of mitochondrial electrons transport chain. The electron transport chain is responsible for producing energy in the form of adenosine triphosphate (ATP) for proper functioning of body cells. Most commonly involved two enzymes in this disease are Pyruvate dehydrogenase complex and Cytochrome Oxidase. It may be sporadic and three patterns of inheritance have been described in literature, X-linked, autosomal recessive and mitochondrial DNA mutation [3]. Leigh disease typically affects children between three months and two years of age. However, cases are also seen presenting in adolescence or adulthood. The classical presentation is of an infant who presents with central hypotonia, feeding problems, failure to thrive, irritability, developmental regression or arrest and signs of brain stem or basal ganglia involvement which may manifest as ophthalmoplegia, respiratory and bulbar dysfunction and coordination problems [4,5].

Diagnosis is usually confirmed by radiological evidence of symmetrical lesions affecting basal ganglia, brainstem and subthalamic nuclei on computed tomography (CT) or magnetic resonance imaging (MRI) (Magnetic resonance imaging) scans. This is further supported by lactic acidosis and pathological lesions on autopsy [6].

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There is no cure of this disease. However some limited treatment options are available which can relieve some associated symptoms. Most common treatment is administration of thiamine (vitamin B1). In patients having deficiency of Pyruvate Dehydrogenase enzyme complex, a high fat, low carbohydrate diet may be recommended. Oral sodium bicarbonate or sodium citrate may be used for management of lactic acidosis. Overall prognosis of this disease is poor, but a few patient experiences prolonged periods of remission. Disease usually progresses rapidly once first signs and symptoms appear. Death usually occurs by 6 or 7 year of age but some may live up to mid-teens years [3].

Clinical presentation of Leigh's disease can be highly variable. We present here this case which presented with quite bizarre neurological symptoms and signs in early infancy and was suspected on the basis of CT scan findings which was further supported by high serum lactic acid levels.

CASE REPORT

A 04 month old girl presented in outpatient department with parental complains of failure to thrive, excessive irritability, poor feeding and inconsolable cry since later part of neonatal period. She was born at full term by lower segment cesarean section. She was first baby of consanguineous parents after about 2.5 years of marriage. Mother had regular antenatal checkups and no abnormality was detected during this period. Initial neonatal examination was normal. She weighed 2.7 kg and no obvious congenital abnormality was noted. She remained well initially but complaints started in 4th week of life. She was taken to various doctors but complaints kept on worsening. She also started having fits, when she was 02

months old. Fits were mainly tonic type, resulting in generalized stiffness of whole body accompanied by smacking lip movements and shrill cry. Initially duration of each fit was few seconds, which increased with passage of time to 2-3 minutes. Frequency of fits also increased from once or twice to about 10 - 15 times per day.

Family history did not reveal any similar disease in the family. She was exclusively breast fed for initial two weeks only. Since then she was being supplemented with diluted (1:2) buffalo milk also. But due to feeding difficulty, her intake was quite poor. Weaning was not introduced yet.

On examination, she was malnourished, weighing 3.5 kg, length, fronto-occipital circumference (FOC) 35.5 cm. She had no dysmorphic features. She was lethargic, not interested in surroundings. Pupils were mid-dilated having sluggish response to light. However there was no nystagmus, squint, cataract or any other ocular abnormality. Fundoscopy was unremarkable. She had generalized hypotonia with power 2-4/5 in all limbs. Deep tendon reflexes were brisk all over with extensor planter response. There was no scissoring of lower limbs. Neither involuntary movements nor any cutaneous stigmata of neurological disease were noted. Chest auscultation revealed conducted sound with scattered coarse crepitations due to aspiration of secretions and feeds. Rest of systemic examination was unremarkable.

Relevant investigations revealed normal routine hemogram and urine analysis. She had normal blood glucose, liver function tests and cholesterol levels. Serum urea, creatinine, electrolytes and creatinine phosphokinase were within normal limits. Blood for metabolic screening and urine chromatography also did not reveal any abnormality. Arterial blood gases showed metabolic acidosis with pH 7.27, PCO2 33 mmHg, Bicarbonate 15 mmol/l and base excess -11. CT scan brain was performed with and without IV contrast. It revealed bilaterally and symmetrically reduced density of both thalami, basal ganglia extending superiorly to paraventricular portions of both parietal lobes. Patchy area of reduced density of mid brain was also noted. No contrast enhancement of abovementioned hypodense areas was seen.

Based on clinical picture and CT scan findings she was suspected to be a case of acute necrotizing encephalomyelopathy (Leigh disease). For further confirmation, serum lactate levels were sent to laboratory and appointment for MRI was requested. Meanwhile she was managed with broad spectrum antibiotics and general supportive measures including supervised nasogastric feeding NG feeding. Anticonvulsants (Tab Phenobarbitone and Rivotril drops) were started but fits remained poorly controlled.

Her general condition improved. She became slightly active and feeding also improved in a week time. But she had to be discharged due to some domestic problems with advice to continue treatment at home. She was brought back after about ten days, but in very poor condition. She was extremely emaciated, having deep acidotic breathing and bilateral coarse crepitations. Till that time, serum lactate levels report was also received, which revealed it to be raised – 4.8 mmol/l (normal 0.5-2.22 mmol/l) supporting diagnosis of Leigh disease. Due to extreme poor condition she could not be stabilized this time and expired within few hours of second admission. Postmortem examination was suggested to the parents but they refused.

Based on clinical picture, CT scan findings and raised serum lactate levels she was labeled as a case of Leigh disease.

DISCUSSION

Since the description of the first case report of subacute necrotizing encephalomyelopathy by Denis Leigh in 1951 [2]. Leigh disease remains an uncommon disorder. He described findings of symmetrical lesions involving thalamus, midbrain, pons, medulla and posterior column spinal cord in a 07 month old infant on autopsy. Later, involvement of basal

ganglia was highlighted by Richter and others. We are reporting this rare case, which had symmetrical involvement of basal ganglia and thalami bilaterally. Many cases present with atypical features as described by Richard et al in his case series. Clinical presentations are quite variable. Diagnostic criteria set forth by Rahman et al are [3] progressive neurological disease with motor or developmental impairment, [2] signs and symptoms of basal ganglia or brainstem involvement, [3] elevated blood or cerebrospinal fluid (CSF) levels of lactic acid and [4] either radiological or postmortem evidence of basal ganglia, brainstem or spinal cord involvement. In review of 78 cases, Pincus described two groups of patients depending on the age of the onset: those presenting before 12 months versus those with onset after 18 months of age. Psychomotor retardation (64% vs 25%), vomiting (60% vs 12%), weight loss (48% vs 0%) and weakness (48% vs 12%) were more common in former age group, while the later group more often presented with movement disorders (38% vs 2%), coma (12% vs 0%), nystagmus and eye signs (12% vs 0%). The present case had all the features described by Rahman et al and early onset group features mentioned by Pincus [5].

Radiological features are characteristic and help in arriving at ante mortem diagnosis along with relevant clinical features. CT scan typically shows low attenuation areas in basal ganglia (as seen in our case). MRI shows symmetrical hypo intense lesions on T1 weighted image becoming hyper intense on T2, involving basal ganglia and brainstem. However MRI could not be done in this case due to critical condition of patient [6].

Pathological changes are characteristic morphological abnormalities distributed in specific anatomic regions of CNS as reported by Mannan et al [7] in a child of 15 months age on post mortem examination. In this case, postmortem examination could not be done due to unwillingness of parents.

Major biochemical defects elucidated in pathogenesis are defect in mitochondrial chain enzymes, especially Cytochrome Oxidase complex (Cox) and Pyruvate dehydrogenase complex (PDH) deficiency. These abnormalities can be detected by histochemical studies of fresh muscle tissue or cultured skin fibroblasts. We could not do these studies due to lack of facilities. However lactic acidosis, one important criterion of this neurometabolic disorders was documented in this case. Therapeutic modalities have been tried which aim at maximizing the oxidative or bioenergetic ability of patient's mitochondria. Administration of Coenzyme Q, thiamine, ketogenic diet alongwith carnitine as other alternative energy source independent of PDH have been shown to be effective in certain cases. Ghosh and Prdhan from India reported one patient in whom high dose of parentral thiamine resulted in significant improvement of neurological functions. In this case we could not try any specific management measures especially focused on Leigh's disease due to short span of disease.

Although a rare disease, evidence of its existence and with encouraging reports at treating mitochondrial Cytopathies, the importance of ante mortem diagnosis of Leigh's disease can not be overemphasized. To the best of our knowledge, present case may be the first reported case of the Leigh disease in Pakistani literature. Clinical scenarios at presentation may be quite diverse with variety of neurological signs and symptoms affecting all levels of neuraixs and pediatricians should be aware of this possibility. The diagnosis of Leigh disease should be considered in all children presenting with relapsing neurological symptoms with psychomotor retardation, hypotonia and lactic acidosis. Such cases should be subjected to biochemical and / or neuroimaging studies and therapeutic trial with thiamine, Coenzyme Q should be initiated [8,9].

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