

## A Rare Mitochondrial Disorder: Leigh Syndrome –A Case Report

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### Abstract

### Case Report

Leigh syndrome (also called Leigh disease and subacute necrotizing encephalomyelopathy) is a rare inherited neurometabolic disorder that affects the central nervous system. We report a case with hypoactive with paucity of limbs movement, weak crying, poor feeding, developmental delay, decelerated head growth and abnormal eye movement described as oscillatory non rhythmic eyeball movement. Magnetic resonance imaging showing signal intensity changes bilateral in the globus pallidus, thalami and the midbrain, mild Atrophic brain changes that lead to the diagnosis of Leigh syndrome.

**Keywords:** Mitochondrial disorder, Leigh syndrome, necrotizing encephalomyelopathy.

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## INTRODUCTION

Leigh syndrome (also called Leigh disease and subacute necrotizing encephalomyelopathy) is a rare inherited neurometabolic disorder that affects the central nervous system. It is named after Archibald Denis Leigh, a British neuro-psychiatrist who first described the condition in 1951[1].

Most of the time, Leigh's disease is inherited as an autosomal recessive trait but mitochondrial inheritance and X-linked recessive are also exceptions [1]. Clinically characterized by psychomotor delay or regression, hypotonia brainstem signs, ataxia, pyramidal signs, respiratory insufficiency, lactate acidemia and acute deterioration following common infections [3]. The diagnosis is usually done based on clinical features, metabolic abnormalities, mode of inheritance and particularly advanced neuroimaging techniques findings, we report a 4 months old child with clinical and laboratory features of Leigh Syndrome suggested by neuro-imaging.

## CASE REPORT

### Presentation

A 4-month-old up 2-months immunized girl of consanguineous mating parents Admitted into Alyammamh hospital then transferred to King Khalid University Hospital in Riyadh with the complaints of

poor activity described as being of hypoactive with paucity of limbs movement, weak crying, poor feeding for 3 weeks. Also there are 2 other complaints started at 3<sup>rd</sup> month of life (not control her neck and abnormal eye movement described as oscillatory non rhythmic eyeball movement lasting for seconds then resolved spontaneously). She had a history of constipation and decrease urine output for 1 week. No past-medical history. She had no history of convulsion or trauma to the head, no honey ingestion. His perinatal period was uneventful and the growth was normal. No history of intrauterine fetal death or abortion, no smellier condition. Developmental history (no visual fixation on objects but she used to react to sounds which was lost over last 2-3 weeks, lack of head control, no social smile, no cooing).

### Examination

Findings revealed that she was looks lethargic and hypoactive with paucity of spontaneous movements of extremities. Growth parameters: weight 4.5kg 3<sup>rd</sup>%, length 53 cm. 3<sup>rd</sup>%, Head circumference at birth was 36 cm, at present was 38.4 cm. The increment over 4 months is 2.4cm. Vitals signs were normal limit. Hair was brownish in color. Ear-Nose-Throat findings were normal. BCG mark was present. On examination of the nervous system, she was not interesting in surrounding, doesn't fix on objects, having on & off horizontal nystagmus, pupils reactive to light equal, fundus could

not be visualized due to nystagmus, no ptosis, no facial weakness. Weak crying sound but no hoarseness, reaction to sounds was not constant. Has central tongue with no fasciculation. She has normal muscle bulk and consistency, axial hypotonia.

Moving the 4 extremities against gravity with Deep Tendon Reflex +2. Weak primitive reflexes (MORO, planter grasps, other absent).

### Investigations

Showed slightly raised ammonia level (49  $\mu\text{mol/L}$ ). Serum lactate was increased (11  $\text{mmol/L}$ ). Blood glucose level was normal. Complete blood cell: normal Thyroid function test within normal. Urinary ketones were absent. Creatine kinase level was within normal limit. Cerebrospinal Fluid chemistry, cytology, culture unremarkable. Blood gas: PH=7.13 PCO<sub>2</sub>= 43 HCO<sub>3</sub>=12.6, Anion gap=22. IMD panel Transcranial Magnetic Stimulation (TMS) with biotinidase screening was normal. Urinary organic acid analysis showed no

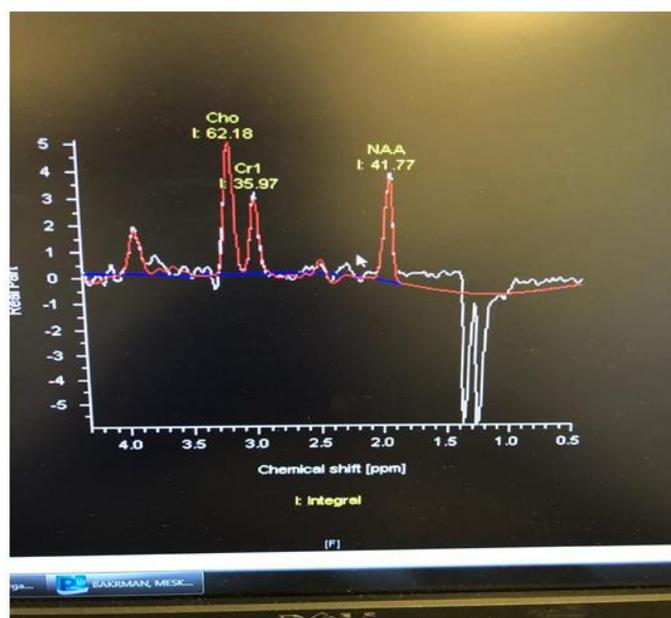
specific findings. Electroencephalography unremarkable. Magnetic Resonance Imaging of brain T2/flair axial sections showing signal intensity changes bilaterally in the globus pallidus, thalami and the midbrain and mild atrophic brain changes (Figure 1). Magnetic Resonance Spectroscopy demonstrates a large lactate high double peak suggestive of subacute necrotizing encephalopathy (Leigh disease; Figure 2). Patient deteriorated, went in progressive encephalopathy with lactic acidosis.

### Treatment

Admitted to PICU connected to cardiopulmonary monitoring, full septic screening done treated with cocktail therapy biotin, thiamin, L-carnitin and Co enzyme Q10. Second day she is deteriorated: bradypnea RR: 10, HR:155. Connected to Mechanical Ventilation. With no improvement and AFTER multidisciplinary team meeting was conducted (metabolic, neurology, PICU and primary team) they decide: DNR, Labs PRN.



**Fig-1: MR imaging of brain T2/flair axial sections showing signal intensity changes bilateral in the globus pallidus, thalami and the midbrain and mild atrophic brain changes)**



**Fig-2: MR spectroscopy demonstrates a large lactate high double peak**

## DISCUSSION

Leigh syndrome (LS) is the most common presentation of a defined mitochondrial disease in pediatrics [2]. The estimated prevalence was affect approximately 1 per 40,000 live births [3]. The classical form develops in less than 2 years (infantile form) accounted for approximately 80 percent of cases. But others may present in childhood (juvenile form) and unusually in adulthood [5]. Affected child usually normal at birth and become symptomatic within the first year of life, progress at a rapid rate, with the earliest signs potentially being poor sucking ability and a loss of motor skills and head control [3].

The term ‘Leigh syndrome’ should be used in cases where the three most characteristic features of the disease are present, these being: (i) a neurodegenerative phenotype; (ii) mitochondrial dysfunction and (iii) bilateral CNS lesions is accompanied by a broad range of neurologic manifestations, including psychomotor delay/regression, strabismus, muscular hypotonia, nystagmus, swallowing difficulty, ataxia, respiratory insufficiency, pyramidal signs, acute deterioration following common infections and lactate academia[6]. Respiratory failure is usually responsible for mortality [4]. Respiratory chain enzymes defect is the responsible in Leigh disease, due to deficiency of cytochrome-c-oxid oxidase, pyruvate dehydrogenase and biotinidase[1].

The differential diagnosis include perinatal asphyxia, kernicterus, carbon monoxide poisoning, methanol toxicity, thiamine deficiency, Wernicke’s encephalopathy, Wilson’s disease, biotin-responsive basal ganglia disease and some forms of encephalitis. In contrast to Wernicke’s encephalopathy mamillary bodies are spared from pathological changes. A differentiation to Wilson’s disease is possible through laboratory studies of the blood [1].

No specific therapy for mitochondrial disorders in children is available. The aim of symptomatic treatment is to improve the ATP production and to lower the lactate levels. Treatment generally involve variation of vitamin and supplement therapies, often in “cocktail” combination, and are only partially effective. Thiamine, a cofactor of pyruvate dehydrogenase has been reported to be improving the neurological status in some patients. Marked improvement was observed with riboflavin, which nearly normalized the ATP. Coenzyme Q and carnitine have also been found to be effective. Physical therapists

many times help with exercises that can assist the person to maintain strength and range of motion. As Leigh’s disease progresses, an occupational therapist can provide the person with positioning devices for their comfort [1].

## CONCLUSION

The diagnosis of Leigh syndrome should be considered in a child with the diagnostic criteria: (1) Progressive neurological disease with motor and intellectual developmental delay. (2) Signs and symptoms of brain-stem 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. The most characteristic neuroradiological findings are bilateral, symmetric focal hyperintensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei. Proton spectroscopy demonstrates elevated brain lactate levels in the basal ganglia, occipital cortex, and brainstem. Specific therapy for mitochondrial disorders in children is not available. These patients are usually treated symptomatically with multivitamin therapy and other supportive treatment.

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