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CASE REPORT

Clinical insights and challenges: A rare case report of Leigh syndrome

Hini J. Patel, Khunt Vishwash Hareshbhai and S. P. Srinivas Nayak*

Department of Pharmacy Practice, PIPR, Parul University, Vadodara, India

***Correspondence:**
S. P. Srinivas Nayak,
spnayak843@gmail.com

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Leigh syndrome is a severe neurological disorder that impairs mobility and respiration, among other bodily functions. Progressive brain deterioration is what makes it distinctive. This case report describes a 10-month-old female child who displayed symptoms such as vibratory movements in the right upper and left lower limbs, failure to thrive, decreased activity, and vomiting after consuming supplemental feeds. Multiple clinical signs of Leigh syndrome, including missed developmental milestones and mild acute malnutrition, were identified during a physical examination. So the symptoms that led to the diagnosis of Leigh syndrome were quadriparesis, dystonia, intermittent stridor (laryngeal dystonia), and bulbar weakness. This was supported by various laboratory results and diagnostic procedures, including brain imaging. The treatment included pacitane, thiamine, biotin, l-carnitine, calcium + vitamin d3, and sodium benzoate as well as dietary assistance and other medicines. Leigh syndrome is an incredibly rare disorder that has major effects on those affected and often manifests in infancy or early childhood. It is characterized by things like vomiting, feeding issues, neurological impairments, and delays in development. Sadly, because Leigh syndrome is a degenerative condition, the outlook for those who have it is frequently bleak. In cases with Leigh syndrome, this case emphasizes the value of early diagnosis and interdisciplinary treatment. The patient was instructed to have additional testing such as an EEG and a disability evaluation. Healthcare professionals must be aware of the clinical manifestation and treatment of Leigh syndrome in order to give affected people and their families the right care and support.

Keywords: Leigh syndrome, neurodegenerative disorder, quadriparesis, dystonia, failure to thrive, case report

Introduction

Leigh syndrome is a very rare and serious neurological disorder that mainly affects children. It is caused by a problem in the mitochondria, which are tiny structures in our cells responsible for producing energy. Due to this mitochondrial dysfunction, the brain and nervous system gradually deteriorate over time. Leigh syndrome is exceptionally rare, and there have been only a few reported cases in India and worldwide. Subacute necrotizing encephalopathy, which is also called Leigh Syndrome, is a rare inherited brain disorder. Specific brain abnormalities that cause respiratory difficulties, muscle weakness, and developmental delays often first appear in infancy or early

Abbreviations: CNS: Central Nervous System; CVS: Cardiovascular System; RS: Respiratory System; GIT: Gastrointestinal Tract; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; TDS: Three Times a Day; BD: Twice a Day; QDS: Four Times a Day; OD: Once a Day; NICU: Neonatal Intensive Care Unit; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW: Red Cell Distribution Width; WBC: White Blood Cell; RBC: Red Blood Cell; PCV: Packed Cell Volume; CNS: Central Nervous System; S. Sodium: Serum Sodium; S. Potassium: Serum Potassium; S. Urea: Serum Urea; S. Creatinine: Serum Creatinine; S. ALT (SGPT): Serum Alanine Aminotransferase; S. AST (SGOT): Serum Aspartate Aminotransferase; S. Inorganic Phosphorus: Serum Inorganic Phosphorus; S. Magnesium: Serum Magnesium; EEG: Electroencephalogram; LS: Leigh Syndrome; ATP: Adenosine Triphosphate; OXPHOS: Oxidative Phosphorylation; DNA: Deoxyribonucleic Acid; mtDNA: Mitochondrial DNA; OMIM: Online Mendelian Inheritance in Man Database.

childhood. The first instance was described by British neuropathologist Denis Leigh in 1951 and involved a 7-month-old baby who rapidly deteriorated and passed away within six weeks (1). The prevalence of Leigh Syndrome, a rare illness, is roughly 1 in 40,000 live births. It is the most frequent mitochondrial illness to strike children in their first year of life, despite its rarity. The mitochondria, which are tiny structures inside our cells, have various important functions. In Leigh Syndrome, there is a problem specifically in one critical aspect of mitochondrial function called oxidative phosphorylation, which produces energy (ATP) for the cell. The brain system, heart, and muscles, which require more oxygen than other organs, are often the most affected by this failure. As a result of the varying effects on various body areas, people with Leigh Syndrome experience a wide range of clinical symptoms. In around 50% of cases of Leigh Syndrome, the cause can be traced back to genetic factors. Researchers have discovered more than 60 distinct mutations in either the mitochondrial DNA or the nuclear DNA, which are both found in the cell's nucleus. Mitochondrial DNA mutations are responsible for about 10 to 30% of the cases of Leigh Syndrome. The development of the illness is significantly influenced by these genetic anomalies (2).

We propose a three-part classification of Leigh Syndrome based on the definition provided in the Online Mendelian Inheritance in Man Database (OMIM 256000):

1. A neurodegenerative condition with a range of symptoms: Leigh Syndrome is a condition that causes the progressive degeneration of the nervous system, leading to a range of different symptoms in affected individuals.
2. Mitochondrial dysfunction due to a hereditary genetic defect: The underlying cause of Leigh Syndrome is a problem with the mitochondria, which are responsible for producing energy in our cells. This dysfunction is caused by an inherited genetic mutation.
3. Bilateral central nervous system (CNS) lesions and potential abnormalities in diagnostic imaging: Leigh Syndrome is associated with specific brain lesions on both sides of the central nervous system (3).

Pathophysiology

Mitochondria produce energy through the oxidative phosphorylation (OXPHOS) pathway. The oxidative phosphorylation (OXPHOS) pathway involves four respiratory chain complexes:

Transfers electrons from NADH to ubiquinone in Complex I (NADH ubiquinone reductase).

Transfers electrons from succinate to ubiquinone through Complex II (Succinate Ubiquinone Reductase).

Transfers electrons from ubiquinol to cytochrome c in Complex III (Ubiquinol Cytochrome C Oxidoreductase).

Cytochrome c oxidase, also known as Complex IV, transfers electrons from cytochrome c to molecular oxygen to produce water.

Together, these complexes transmit electrons, resulting in the formation of a proton gradient and the synthesis of ATP, which supplies the cell with energy. Coenzyme Q10, also known as ubiquinone, functions as an electron transporter within the respiratory chain, facilitating the transfer of electrons from Complexes I and II to Complex III. It is essential for enabling the flow of electrons during the process of oxidative phosphorylation, which uses energy to create ATP, the main energy unit of the cell. Leigh syndrome (LS) can result from problems with any of the OXPHOS enzymes, either individually or in combination. Nuclear or mitochondrial DNA (mtDNA) mutations may be the root of many problems. Additionally, LS can also be caused by deficiencies in coenzyme Q10 or disruptions in pyruvate metabolism (**Figure 1**) (3).

Clinical features

Gastrointestinal abnormalities	constipation, diarrhea, dysogagia, vomiting, gastritis, hepatomegaly
Cardiac abnormalities	hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmia
Neuromuscular abnormalities	ataxia, hypotonic, seizures, dystonia, motor weakness
Ocular abnormalities	nystagmus, optic atrophy, ptosis, visual impairments
Relating to the skin	Unusual skin odor, darkened skin eruptions, and excessive hair growth
Endocrine	Diabetes, Thyroid dysfunction

(3–5)

Laboratory tests are crucial in diagnosing metabolic disorders like Leigh syndrome. Look for lactic acidosis or acidemia. Elevated plasma amino acids, particularly hyperalaninemia, may be present. Analysis of the organic acids in the urine can reveal aberrant concentrations of pyruvate, lactate, intermediates of the citric acid cycle, 3-methylglutaconic acid, and ethylmalonic acid. Carnitine panel aids in evaluating problems connected to carnitine. A standard laboratory panel measures ammonia level, creatinine kinase, and liver/kidney parameters. These tests aid in the precise diagnosis of Leigh syndrome and help rule out other metabolic illnesses with comparable symptoms. Thiamine (100-300 mg) and high-dose biotin therapy (10 to 20 mg/kg) must be given right away in suspected instances of Leigh syndrome (LS). Patients with mitochondrial dysfunction may experience worsened

mitochondrial function due to anorexia and malnutrition. It is advised to follow a diet that is suitable for your age and level of activity. Dietary intervention can improve mitochondrial function in malnourished patients. Avoid overfeeding in those with primary OXPHOS defects. (4)

Doctors use the following criteria to diagnose Leigh syndrome

(1) Neurological conditions that worsen over time and cause delayed intellectual and motor development.

(2) Indicators of problems with the brainstem or basal ganglia.

(3) Significant blood or cerebrospinal fluid lactate concentrations.

(4) Particular, to Leigh syndrome-only necrotic (dead tissue) lesions found in the brainstem and/or basal ganglia (6). Children with mitochondrial abnormalities don't have a specific treatment option. Each person has a different prognosis and set of results. The goal of symptomatic therapy is to increase ATP synthesis and decrease lactate levels. Thiamine, which supports the pyruvate dehydrogenase complex, has been observed to assist some patients' neurological disorders (7). Riboflavin treatment resulted in a significant improvement since it almost restored normal adenosine triphosphate (ATP) generation. ATP is a critical energy molecule in the body, and riboflavin helped enhance its production, leading to positive outcomes for patients with mitochondrial disorders (8, 9). Patients with acute central respiratory failure showed quick improvement in both clinical symptoms and biochemical markers when treated with intravenous soya bean oil, which is a ketogenic emulsion. This treatment had positive effects on their condition, aiding their recovery (10). Pyruvate dehydrogenase-deficient people have been proved to benefit from the ketogenic diet. This diet can improve their overall outcome and help manage the condition more effectively (11). It has been discovered that the treatments coenzyme Q and carnitine (12) are successful. Injections of intramuscular botulinum toxin significantly reduced dystonia, a syndrome marked by uncontrollable muscle contractions and spasms, according to Leung et al. (13). Nucleus transfer into an enucleated oocyte is a developing novel strategy for preventing mitochondrial diseases. This technique involves transferring the nucleus of a cell into an egg cell with its nucleus removed, which may help prevent certain mitochondrial-related conditions (14). In cases of Leigh Syndrome, the cerebrospinal fluid (CSF) lactate levels are significantly elevated, but the lactate levels in the blood (arterial lactate) may appear normal. Traditionally, Leigh Syndrome was linked to high levels of lactate in the blood, but previous research has shown that even with clear signs of the condition in brain imaging and spectroscopic tests, the lactate levels in the blood can still be within normal ranges (15).

Case report

A 10-month-old female child was admitted with symptoms of vomiting after receiving a complementary meal, not gaining weight and with a reduction in activity after 6 months of age . She also complained of the right upper and left lower limbs of her body vibrating over the previous 7 days.

Physical examination

General condition	Fair	Height	66 cm
CNS	conscious, alert	Head circumference	40.5 cm
CVS	S1, S2 + , No Murmurs	MUAS	12.5 cm
RS	AEBE B/L Crepts +	WT/HT	b/w 250 to 350
GIT	soft, non-distended	Malnutrition	Moderate acute malnutrition
Weight	5.95 kg		

Development history

Gross motor: Neck holding absent
Fine motor: Palmar grasp present
Social: Stranger anxiety present
Language: Cooing present
Hence global delayed development present.

Vitals

The patient's vital signs were assessed, revealing a respiratory rate (RR) of 38 breaths per minute and a pulse rate (PR) of 124 beats per minute, both slightly elevated. However, their temperature was within the normal range at 98.60 F. Oxygen saturation (SpO2) was measured at 98% on room air, indicating adequate oxygenation, while the random blood sugar (RBS) level was 96 mg/dL, suggesting normoglycemia.

Past history

The child was started on top feed (Buffalo's Milk) at the age of 4 months as mother was suffering from

pneumonia. On introduction to the feeding, the baby was not gaining weight adequately and having repeated episodes of stool and vomiting.

Immunization history: the child is given vaccines up to Pentavac III vaccine.

Birth history: Full Term/38 week/2.7 kg/Female/Cried immediately after Birth/Hospital Delivery/No NICU stay/No maternal morbidity.

Laboratory findings

PARAMETERS	DAY 1	NORMAL RANGE
Hemoglobin	10.60 gm/dL	11.5–15.5 gm/dL
RBC	5.56 × 10^6/cmm	3.9–5.1 × 10^6/cmm
PCV	39.50%	35–45%
MCV	71 fL	77–95fL
MCHC	26.90 gm/dL	29–37gm/dL
RDW	17.30%	11.6–14%
WBC	11300/cmm	5000–13000/cmm
Platelets	443000/cmm	170000–450000/cmm
Differential count	48/50/01/01	40–70%/30–50%/1–6%/2–12%
S. Sodium	135 mEq/L	135–145 mEq/L
S. Potassium	4.70 mEq/L	3.5–5.1 mEq/L
Ionized Calcium	1.28 mmol/dL	1.12–1.32mmol/dL
S. Urea	39 mg/dL	14–40mg/dL
S. Creatinine	0.57 mg/dL	0.6–1.2 mg/dL
S. ALT (SGPT)	28 IU/L	0–40IU/L
S. AST (SGOT)	41 IU/L	0–37IU/L
S. Inorganic Phosphorus	6.30 mg/dL	2.5–4.5 mg/dL
S. Magnesium	1.50 mg/dL	1.8—2.8 mg/dL
Blood Ammonia	156 mmol/L	9–35
S. Chloride	106 mmol/L	98–110mmol/L

Diagnostic tests

Multislice CT scan of brain-plain

1. Bilateral symmetrical hypodensities in bilateral cerebellar white matter and globus pallidi- Leucodystrophy ADV: MRI OF BRAIN.
2. Prominent ventricles, cerebral sulci and cisterns.

MRI of brain-plain

1. Bilateral symmetrical abnormal signals of cytotoxic edema in globus pallid.
2. Bilateral symmetrical abnormal signal intensity lesions in cortical-subcortical location bilateral cerebellar hemispheres.
3. Possibility of inborn error of metabolism- Leigh Syndrome.

Final diagnosis

Failure to thrive with quadriparesis with dystonia with intermittent stridor (laryngeal dystonia) with bulbar weakness secondary to Leigh syndrome proved from MRI report.

Treatment given

KS feed @ 130cc/kg/day @ 100cc/3-hour Complementary feed.

Drug Name	Dose	Frequency
INJ AUGMENTIN	30mg/kg/dose @ 180mg	TDS
INJ AMIKACIN	15mg/kg/day @ 90mg	OD
INJ CEFIXIME	3 ml	OD
T. PACITANE	2 mg @ 1/4 tab	BD
T. THIAMINE	100 mg	BD
T. BIOTIN	5 MG 2- tab	BD
SYP NEUTROLIN	2.5 ml	BD
SYP L-CARNITINE	3 ml	BD
SYP CALCIUM + VITAMIN D3	2.5 ml	BD
SYP SODIUM BENZOATE	250mg/kg/dose @ 2.5ml	QDS

Discharge medications

Drug Name	Dose	Frequency
T. PACITANE	1/4 tab	BD
T THIAMINE	100 mg	1-1-1
T. BIOTIN	5mg	2-0-2
SYP L-CARNITINE	3 ml	BD
SYP CALCIUM + VITAMIN D3	2.5 ml	BD
SYP SODIUM BENZOATE	2.5 ml	QDS

The patient was advised to collect E.E.G and dasii report along with disability certificate.

Discussion

A rare childhood neurological illness called Leigh's disease is thought to affect 2.05 cases out of every 100,000 people.

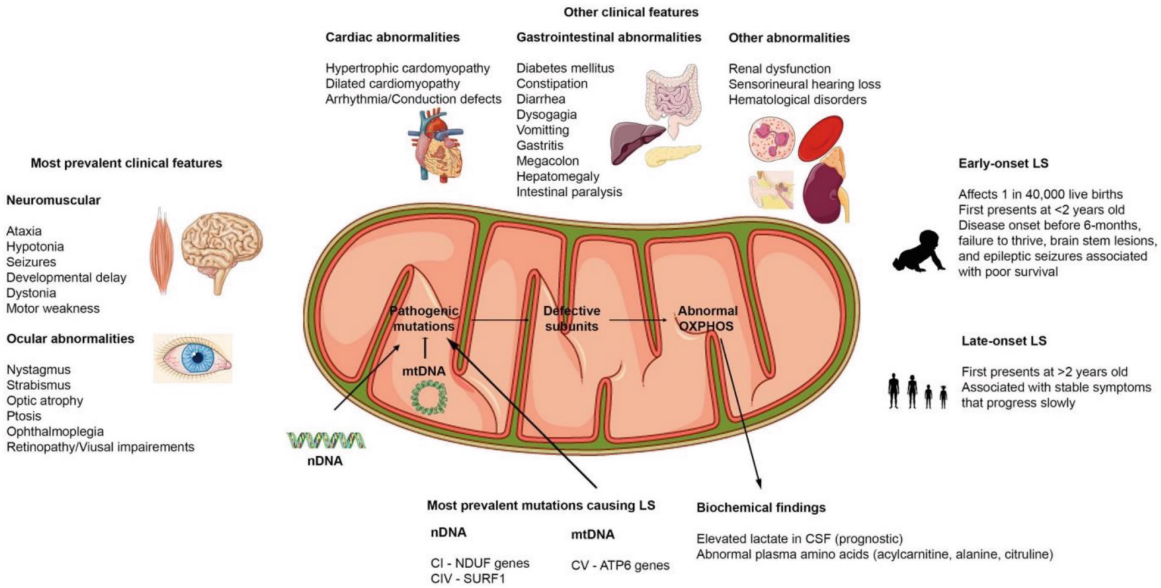

FIGURE 1 | Pathophysiology of Leigh syndrome (24).

It causes respiratory and mobility problems due to gradual brain aging (16). Among preschool-aged children, Leigh syndrome affected approximately one in every 32,000 kids (17).When it manifests in its infancy or juvenile forms, or in extremely rare circumstances, even in adults, Leigh syndrome signs might appear before the age of 2 years. The symptoms include problems with movement and muscle tone, weakness, coordination issues (ataxia), visual problems, developmental delays, rapid breathing (tachypnea), and seizures (18, 19) children with Leigh syndrome typically start showing symptoms during their first year of life. These symptoms may include difficulties with feeding, frequent vomiting, and failure to gain weight and grow properly (failure to thrive) (20). Children with Leigh syndrome often do not survive for long after symptoms appear, usually due to breathing problems getting worse over time. Laboratory tests show certain chemical imbalances in the body. It is inherited in a way that both parents must pass on the gene. The problem can occur in different parts of the body's enzyme pathway for energy production. Pyruvate carboxylase, pyruvate dehydrogenase, cytochrome C oxidase, and Complex 1 (NAD-Coenzyme Q Reductase) deficits are further related enzyme deficiencies. (18–22) Sirtuin 1 is important to mitochondrial function and biogenesis. Sirtuin 1 is critical to heart, lung, muscle, and brain function. The role of Sirtuin 1 activators versus Sirtuin 1 inhibitors is important as dietary interventions to improve outcomes in affected individuals (23).

Conclusion

Leigh syndrome, a devastating ailment, stands as a rare entity characterized by relentless neurological deterioration, predominantly commencing in infancy or early childhood. The clinical repertoire comprises an array of symptoms, including feeding difficulties, emesis, developmental setbacks, and neurological deficits. Regrettably, the prognosis for individuals grappling with Leigh syndrome often remains grim due to the inexorable progression of the disease. This case has reported a female child with leigh syndrome characterized by a vibratory movement of upper limb and left lower limb, decreased activity, and vomiting after taking complementary feed that was treated after the administration of T. PACITANE 1/4 tab BD, T THIAMINE 1-1-1 TDS, T BIOTIN 2-0-2, SYP L-CARNITINE 3ML BD, SYP CALCIUM + VITAMIN D3 2.5ML QDS, SYP SODIUM BENZOATE 2.5ML QDS. This case report underscores the vital imperative of prompt diagnosis and the implementation of a multidisciplinary therapeutic approach in the context of Leigh syndrome. Furthermore, the patient has been advised to undergo further evaluations, encompassing EEG assessments and disability appraisals. An enhanced comprehension of the clinical presentation and therapeutic management of Leigh syndrome is imperative for healthcare providers, with the ultimate aim of delivering judicious care and support for afflicted individuals and their families. In conclusion, this case illustrates the upsetting Leigh syndrome symptoms in a 10-month-old female infant. The clinical presentation, supported by diagnostic findings, confirmed Leigh syndrome, characterized by quadriparesis, dystonia, and bulbar weakness. Treatment comprised a multifaceted regimen. Leigh syndrome, although rare, bears grave consequences, emphasizing the need for early recognition and multidisciplinary management to improve outcomes in affected individuals.

Conflict of Interest

The authors declare that there are no conflicts of interest to disclose in relation to this case report. The research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Author contributions

SN provided guidance and editorial oversight for the entire document, ensuring the accuracy and quality of the content. H P collected and compiled the data presented in the case report, contributing to the essential information and clinical details. K H played a crucial role in reviewing the document for plagiarism and paraphrasing as needed to maintain the integrity of the content. These contributions were instrumental in the creation of the case report, and each author played a distinct role in its development. All authors contributed to the article and approved the submitted version.

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