Evaluation of neurodevelopmental outcome in Leigh's Syndrome/Leigh's like disorder– A hospital-based study.

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Abstract

Background: Leigh's syndrome is also called Leigh's disease or Subacute necrotising encephalomyelopathy. It is characterized by bilaterally symmetrical and subacute necrotic lesions in the basal ganglia, thalamus, the brainstem, and the posterior columns of the spinal cord. Genetically, it can be due to a defect in either mitochondrial or nuclear genes. The disease involves multiple organ systems, causing a heterogeneous presentation. There is a lack of literature enlightening on the pattern and severity of developmental retardation in Leigh syndrome; hence, this study was carried out.

Objective: To describe the neurodevelopmental profile in cases of Leigh syndrome / Leigh-like disorder.

Materials and methods: This was a hospital-based cross-sectional observational study of cases fulfilling Leigh's syndrome based on the Mitochondrial Disease Criteria (MDC) between 4 months and 42 months, who were followed up at the tertiary care center from March 2024 to August 2024. Children who were not hemodynamically stable were excluded. Their developmental assessment was done using the Bayley Scale of Infant and Toddler Development IV, and the level of impairment in all domains was noted.

Results: A total of 70 children were included. In our study, the developmental retardation in Leigh syndrome/Leigh-like disorder showed a global involvement, with major involvement being the fine motor domain, followed by gross motor domain, followed by expressive communication, followed by receptive communication, and the cognitive domain was the least affected.

Conclusion: There was significant involvement of global developmental delay in patients with Leigh syndrome/Leigh-like disorder, with predominant motor involvement and relative sparing of cognition. Early intervention focusing on improving motor coordination with improve the lifestyle of the child and family.

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- lissencephaly,
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- gene

Introduction

Leigh Syndrome (LS) was first described by Denis Archibald Leigh in 1951 as a Subacute Necrotising Encephalopathy (SNE) and is a complex and incurable early-onset neurodegenerative disease. Online Mendelian Inheritance in Man Database (OMIM 256000) has defined LS by these cardinal characteristics: "neurodegenerative disease with variable symptoms due to mitochondrial dysfunction caused by hereditary genetic defect accompanied by bilateral Central Nervous System (CNS) lesions that can be associated with further abnormalities in diagnostic imaging"[1]. It is the most common presentation of mitochondrial diseases in the pediatric population [2,3,4,5]. The incidence is known to be 1 in 40,000 births [2,6,7,8,9] but can also be as high as 1 in 2,000 in certain populations [10]. The incidence in our country is still unknown.

The clinical spectrum is known to be widely heterogeneous, though the characteristic neuropathology features are typically consistent [2]. The most common clinical features are ataxia, hypotonia, developmental delay, seizures, poor feeding or feeding difficulties associated with dysphagia, persistent vomiting, failure to thrive, abnormal ocular disturbances [1]. There can be respiratory dysfunction, which often leads to death [11]. In older infants or young children, LS may present with ataxia, dystonia, or intellectual decline. Later, the children present with episodic regression within periods of clinical stability [11].

Literature shows similarity of Leigh syndrome with Thiamine deficiency, causing Wernicke's encephalopathy, leading to Leigh-like disease [12]. Large community-based studies are needed to differentiate thiamine deficiency leading to Leigh-like disease or genetic defects causing Leigh syndrome [13]. Though developmental delay is a known condition of Leigh syndrome/Leigh-like disorder, the exact severity and the pattern of developmental delay remain unknown. Hence, the study was chosen to shed light on the pattern of involvement of various developmental domains in children with Leigh syndrome/Leigh-like disorder.

Materials and methods

The objective is to describe the neurodevelopmental profile in cases of Leigh syndrome / Leigh-like disorder. Cases fulfilling Leigh-like disorder based on Mitochondrial Disease Criteria (MDC)[14], being followed up in a tertiary care center in Bangalore, were included from March 2024 to August 2024. In this hospital-based cross-sectional observational study, all cases between 4 months to 42 months of age diagnosed with Leigh sy like disorder with a disease durati 3 months. Hemodynamically unst within 2 weeks of hospital admiss consent from the parents and ethical obtained from the institutional ethical committee.

Demographic details and history of the study participants were taken. Age was corrected for prematurity. Their physical examination with neurological examination findings was noted. Other investigation reports like CBP (Complete Blood Picture), TMS (Tandem Mass Spectrometry), GC-MS (Gas Chromatography Mass Spectrometry), WES (Whole Exome Sequencing), MGS (Mitochondrial Genome Sequencing), MRI brain, lactate levels, Vitamin B_{12} levels, etc., were noted, if available. The neurodevelopment of the study participants was assessed using the Bayley scale of Infant and Toddler Development IV (BSID IV) [15], and the score was recorded. The same score was used to assess the level of impairment and was recorded as: Developmental age and Percentage delay.

Results :

A total of 70 children, who were previously diagnosed with Leigh syndrome/Leigh-like disorder, between the ages of 4 months and 42 months, were taken for the study. Table 1 shows details of history with Mean with Standard Deviation, Median with IQR, and range. Table 2 shows details of examination findings with Mean with Standard Deviation, Median with IQR, and range. Table 3 shows details of Investigation findings with Mean with Standard Deviation, Median with IQR, and range. Table 4 shows details of developmental assessment with Mean with Standard Deviation, Median with IQR, and range. Figure 1 shows clinical and MRI images of a child during acute presentation. Figure 2 shows clinical and MRI images of the child during the follow-up period.

Table 1: Table showing the details of history

History	Mean ± SD || Median (IQR) || Min-Max
Age (Months)	18.57 ± 8.49 || 17.27 (12.20-22.57) || 3.83 - 41.17
Gender	
Male	38 (54.3%)
Female	32 (45.7%)
Place Of Origin: State	
Karnataka	50 (71.4%)
Andhra Pradesh	8 (11.4%)
West Bengal	4 (5.7%)
Bihar	2 (2.9%)
Maharashtra	2 (2.9%)
Tamil Nadu	2 (2.9%)
Rajasthan	1 (1.4%)
Uttar Pradesh	1 (1.4%)
Place Of Living: District	
Ananthapur	4 (6.7%)
Bellary	2 (3.3%)
Bengaluru	7 (11.7%)
Chikkaballapur	5 (8.3%)
Chikkamagaluru	1 (1.7%)
Chittor	2 (3.3%)
Dabbaguli	1 (1.7%)
Hassan	1 (1.7%)
Kolar	7 (11.7%)
Mandya	6 (10.0%)
Raichur	1 (1.7%)
Ramnagar	6 (10.0%)
Satyasai	2 (3.3%)
Tumkur	15 (25.0%)
Age Of Detection (Months)	3.80 ± 3.72 || 3.00 (2.00-3.38) || 1.00 - 24.00
Consanguinity	
None	58 (82.9%)
2nd Degree	3 (4.3%)
3rd Degree	9 (12.9%)
Family history	
No	60 (85.7%)
Similar Complaints in Siblings	3 (4.3%)
Seizure Disorder In 1st Cousin	2 (2.9%)
Seizure Disorder in Uncle	2 (2.9%)
Seizure Disorder in Siblings	1 (1.4%)
Sibling Death	1 (1.4%)

Similar Complaints In 1st Cousin	1 (1.4%)
Developmental Retardation Timing: Before Acute Onset (Yes)	20 (28.6%)
Weakness (Yes)	70 (100.0%)
Motor regression (Yes)	22 (31.4%)
Seizures (Yes)	55 (78.6%)
Lethargy (Yes)	64 (91.4%)
Poor sucking (Yes)	64 (91.4%)
Tremors (Yes)	10 (14.3%)
GI symptoms (Yes)	11 (15.7%)
Failure to thrive (Yes)	14 (20.0%)
Respiratory symptoms (Yes)	4 (5.7%)

Table 2: Table showing details of examination findings

Examination	**Mean ± SD || Median (IQR) || Min-Max**
weight for age percentile	
<3rd	14 (20.0%)
3rd to 15th	52 (74.3%)
15th to 50th	3 (4.3%)
50th to 85th	1 (1.4%)
height for age percentile	
<3rd	22 (31.4%)
3rd to 15th	47 (67.1%)
15th to 50th	1 (1.4%)
Head Circumference Standard Deviation	
<-3	8 (11.4%)
- 3 To - 2	60 (85.7%)
- 2 To 1	2 (2.9%)
Neurocutaneous Markers	
None	61 (87.1%)
Café-au-Lait Spot	4 (5.7%)
Mongolian Spot	4 (5.7%)
Hypopigmented Macule	1 (1.4%)
CNS examination: HMF and speech (Speech Delay)	70 (100.0%)
CNS examination: Bulk	
Normal	50 (71.4%)
Wasting	20 (28.6%)
CNS examination: Tone	
Normal	27 (38.6%)

Hypertonia	27 (38.6%)
Hypotonia	11 (15.7%)
Variable	5 (7.1%)
CNS examination: Reflexes	
Normal	16 (22.9%)
Exaggerated	54 (77.1%)
CNS examination: Sensory	
Normal	70 (100.0%)
Abnormal	0 (0.0%)
CNS examination: Extrapyramidal	
Normal	25 (35.7%)
Dystonia	41 (58.6%)
Choreoathetosis	4 (5.7%)
Ataxia	13 (18.6%)
CNS Examination: Skull And Spine	
Normal	70 (100.0%)
Abnormal	0 (0.0%)

Table 3: Table showing details of investigation findings

Investigations	**Mean ± SD || Median (IQR) || Min-Max**
Hemoglobin (g/dL)	9.89 ± 1.26 || 10.00 (9.00-11.00) || 7.00 - 12.00
Homocystine (micmol/lit)	19.52 ± 16.71 || 13.00 (9.25-24.75) || 3.00 - 70.00
B12 (pg/mL)	469.53 ± 371.19 || 350.00 (219.00-589.15) || 139.60 - 2000.00
pH	7.26 ± 0.10 || 7.27 (7.20-7.33) || 7.00 - 7.47
pCO2	57.10 ± 41.35 || 44.00 (37.00-49.40) || 27.60 - 158.00
Base excess	-4.49 ± 2.52 || -3.90 (-6.65--2.22) || -8.70 - -1.50
NH3	71.53 ± 52.95 || 53.50 (35.25-101.40) || 10.00 - 169.00
Lactate (mg/dL)	34.33 ± 18.71 || 31.00 (23.00-42.20) || 11.00 - 109.20
Whole-Exome Sequencing	
ARFGEF1 gene, likely pathogenic	1
MT-CYB gene, uncertain significance	1
Thiamine metabolism dysfunction syndrome, likely pathogenic	1
Tandem Mass Spectrometry	
Normal	70 (100.0%)
Abnormal	0 (0.0%)
2D ECHO	

Normal	9
HOCM	1
Mild Left Ventricular Hyperintensities	1
Mild TR	1
Mild TR + Severe PAH	1
Severe PAH	1
Mother's Hb (g/dL)	10.50 ± 0.93 || 10.50 (10.00-11.00) || 9.00 - 12.00
Mother's B12 (pg/mL)	224.50 ± 69.80 || 215.50 (195.00-282.50) || 120.00 - 303.00
Mother's Homocystine (mmol/L)	37.00 ± 31.86 || 30.00 (12.50-48.50) || 11.00 - 96.00

Table 4: Table showing details of developmental assessment

Development	Mean ± SD	Median (IQR)	Min - Max
Cognitive age equivalent (Months)	14.23 ± 8.39	12.50 (8.00-19.00)	0.7 - 36.0
Cognitive Percentage delay	28.10 ± 20.45	22.90 (14.50-38.54)	0.8 - 100.0
Receptive Communication age equivalent (Months)	12.27 ± 8.02	11.00 (6.00-16.75)	0.7 - 33.0
Receptive communication Percentage delay	39.31 ± 23.05	35.60 (21.14-52.57)	4.3 - 100.0
Expressive Communication age equivalent (Months)	11.82 ± 7.79	11.00 (5.50-16.00)	0.7 - 32.0
Expressive communication Percentage delay	41.36 ± 23.35	37.10 (21.18-62.09)	0.8 - 100.0
Fine motor age equivalent (Months)	11.05 ± 7.30	10.00 (5.00-14.75)	0.7 - 32.0
Fine motor Percentage delay	44.00 ± 23.67	37.33 (25.45-61.76)	2.4 - 100.0
Gross motor age equivalent (Months)	11.16 ± 7.39	10.00 (5.25-16.50)	0.7 - 32.0
Gross motor Percentage delay	42.26 ± 30.46	40.28 (22.70-63.03)	-95.5 - 100.0

Discussion

Leigh syndrome is a progressive neurodegenerative disorder with onset usually in infancy or early childhood and a characteristic neuropathology [12]. It is one of the common disorders of mitochondrial etiology [1]. This study aimed to describe the developmental profile in cases of Leigh syndrome/ Leigh-like disorder. Understanding the pattern of involvement of developmental retardation will help us in initiating early intervention in these children, and to counsel on the prognosis.

The Bayley Scale of Infant and Toddler Development IV (BSID IV) can be done from age 16 days to 42 months [14]. The inclusion criteria of this study involved children diagnosed with Leigh syndrome/ Leigh-like disorder, with a disease duration of at least 3 months. Hence, in our study, we involved children aged between 4 months to 42 months of age. Among them, the mean age in months was 18.57 ± 8.49. Since this study was done when the child was brought for follow-up, the age distribution does not give any significant information.

In our study, 54.3% of the participants were male and 45.7% were female children. In a study done by Chan-Mi Hong in South Korea, to see the clinical characteristics of early onset and late onset Leigh syndrome, 46.4% were male and 53.6% were female [2]. In another study done by Xueli Chang in China, which is a meta-analysis on Leigh syndrome, there were a total of 279 patients, out of which 162 (58%)

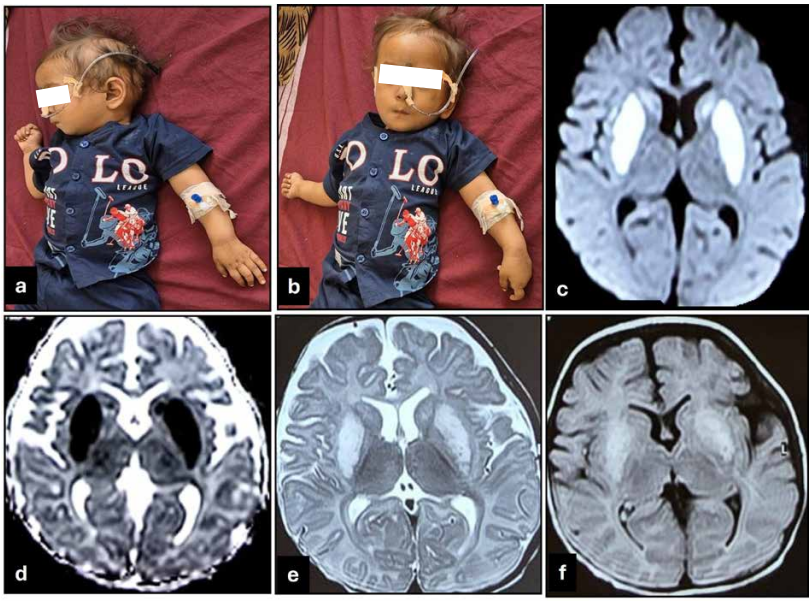

Figure 1. An 8-month-old infant with recurrent vomiting, regurgitation of feeds, and encephalopathy of subacute onset. Irritability reduced on day 3 of treatment; however, persistent oral dyskinesia compelled the need for naso-gastric feeds. Typical cortical fisting, limb dystonia with intermittent neck extension and arching were noted along with hypopigmented sparse hairline representing micronutrient deficiency (a and b). On neuroimaging, axial DWI (c) showed bilateral symmetric areas of diffusion restriction in the Putamen and caudate with signal drop in corresponding areas in ADC (d), suggestive of acute cytotoxic striatal injury. Axial T2WI and T2-FLAIR (e and f) depict diffuse frontotemporal cerebral atrophy with bilateral symmetric homogenous hyperintense signal changes in the putamen in T2-FLAIR(f).

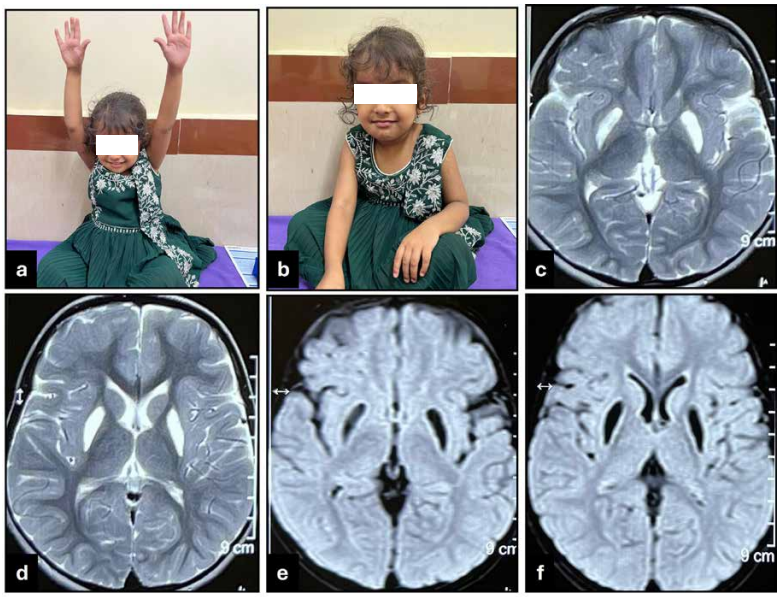

Figure 2. A three-year-old girl, seen during a follow-up visit at the child neurology clinic, with a significant sentinel event of acute encephalopathy, metabolic acidosis, and hyperlactatemia requiring a prolonged stay at the critical care unit at 3 months of age. Subsequently, she had lost all her milestones, only to regain them over the next 3 years with a metabolic cocktail and physiotherapy. Currently, she is ambulatory without support, albeit with an abnormally wide gait. She faces minor difficulty in performing activities of daily living due to dystonia (a and b). MRI Brain obtained 3 years after recovering from the encephalopathic crisis. Axial T2WI (c and d) shows bilateral symmetric, homogenous hyperintense signal changes involving the putamen. T2-FLAIR (e and f) shows symmetric hypointensity in the corresponding areas of T2 hyperintensities (c and d) involving bilateral putamen, suggestive of gliosis.

were male and 117 (41.9%) were female [16]. The difference in gender distribution in different studies could be due to the difference in the overall gender distribution of the population.

In the current study, the majority (71.4%) of the participants were from Karnataka state, followed by 11.4% from Andhra Pradesh. Among those from Karnataka, 25% of the patients are from the Tumkur district of Karnataka. The study was conducted in Karnataka and Andhra Pradesh, which are close to the state, explains the state-wise distribution. Tumkur district could be involved more, which might be secondary to any genetic involvement from the region or a nutritional cause. Further studies are required to know whether the major involvement of the Tumkur region is due to any causative factor prevalent in that area or is incidental.

Data retrieved from parents retrospectively during follow-up showed that, in the present study, the mean age of detection of the condition, in months, was 3.72 months, with a range of 1-24 months. In a study done by Xueli Chang in China, 77.5% of the children were diagnosed before age 2 years [16]. Another study done by Chan-Mi Hong showed that the median age of first clinical presentation was 9 months [2]. Since Leigh is a mitochondrial disorder [1], the initial presentation is usually in infancy, as they fall into metabolic crisis early.

In our study, 82.9% of the study population did not have a history of consanguinity, 4.3% had second-degree consanguinity, and 12.9% had third-degree consanguinity. There is not much available data on the impact of consanguinity on Leigh syndrome. Since consanguinity is more common in South India, further studies may be required to assess this association [17]. In the present study, 85.7% of the participants did not have a significant family history. In a study done by Chan-Mi Hong in South Korea, among the total participants of 110, only 16 had a significant family history [2]. This low percentage of involvement of other family members can be attributed to the fact that the heritability of Leigh syndrome is varied, as there is involvement of both mitochondrial and nuclear genes, with varying heritability. Further, nutritional causes like Thiamine deficiency also contribute to this disorder[1].

The onset of developmental retardation in our study was seen before the child had a metabolic crisis in 28.5% of the participants. This information was extracted by the recall method from parents, and there could be a good chance of recall bias. More information on other causes of developmental disorders could have given a better analysis.

In our study, the predominant clinical manifestations are, history of motor weakness in 100%, followed by lethargy and poor sucking in 91.4% and seizures in 78.6% of the study participants. In a study done by Chan-Mi Hong, assessing the clinical characteristics of early and late onset Leigh syndrome, seizures were seen in 24% and weakness was seen in 11% of the study population [2]. In another study done by Xueli Chang, weakness was found in 29.3% and seizures were found in 23% of the study population [16]. Leigh syndrome is a heterogeneous disorder with varied clinical presentation [1]. More studies are required among the Indian population in order to understand the difference in the frequency of the major clinical manifestations.

In our study, 20% of the participants weighted age <3rd percentile, and 74.3% fell between the 3rd to 15th percentile. In a meta-analysis conducted by Xueli Chang, out of 204 patients, there were 42 events of failure to thrive, which approximates to 20%, which also correlates with the findings in our study [16]. Our study also showed that 31.4% of the study population had height less than the 3rd percentile for age, and 11.4% had head circumference <-3 Standard deviations for age. Short stature can be expected in this condition, owing to the chronicity, and because of seizure episodes, microcephaly can be a common presentation. There is not much data available to compare these parameters to other studies.

Among our study participants, neurocutaneous markers were seen in 13%, among which the most commonly seen were café au lait spots and Mongolian spots, in 5.7% each. One child (1.4%) had seventh nerve palsy, wasting was seen in 20 children (28.6%), abnormal tone in approximately 62%, which could be hypertonia or hypotonia or variable tone, exaggerated deep tendon reflexes in 77.1%, ataxia in 18.6% and basal ganglia features in about 65%. Since the study was done in any acute crisis, all the children were hemodynamically stable with normal higher mental functions. Leigh syndrome has a heterogeneous clinical presentation, with the commonly involved system being the central nervous system [1].

In this study, GI symptoms were seen in 15.7% and respiratory symptoms were seen in 5.7%. The cardiovascular system was affected in 5 patients, with the available echocardiography. Another study showed that the GI system was affected in 37.3% and the cardiovascular system was involved in 8.2%. These findings confirm a clinically significant involvement of other systems in Leigh disease, with a heterogeneous presentation [1].

In our current study, investigations were done at the time of acute presentation, and they were not available in all the patients, due to multiple reasons. There was elevated lactate, above 30mg/dL, in 30 patients, among the available data. The mean lactate levels were 34.3mg/dL. The mean base excess was -4.49; base excess more than -2 was found in 9 patients, among the available data. This shows metabolic acidosis at acute presentation. A study done by Albert Z. Lim in the United Kingdom showed elevated lactate in 68% of patients [10]. Another study done by Chan-Mi Hong in South Korea also showed lactic acidosis in approximately 60% of the study population [2]. This signifies the anaerobic metabolism that takes place, leading to metabolic acidosis in mitochondrial disorders [1].

Multiple studies have confirmed that developmental delay or regression is seen in Leigh syndrome. Studies investigating the pattern and severity of involvement are lacking. Hence, this study aims to throw light on the developmental profile of children with Leigh syndrome/Leigh-like disorder, by using the Bayley Scale of Infant and Toddler IV. In our study, the mean cognitive age equivalent was 14 months, the mean receptive communication age equivalent was 12 months, the mean expressive communication age equivalent was 11 months, the mean fine motor age equivalent was 11 months, and the mean gross motor age equivalent was 11 months. This is opposed to the mean population age of 18 months. The mean percentage delay in the cognitive domain was 28%, the mean percentage delay in receptive communication was 39%, the mean percentage delay in expressive communication was 41%, the mean percentage delay in the fine motor domain was 44% and the mean percentage delay in the gross motor domain was 42%. This implies that cognition is relatively preserved, and fine motor skills are the most severely affected domain in this study population. There is not much literature on the severity and pattern of developmental delay currently. Further studies are needed to see the validity of our study results.

Conclusions

There was significant involvement of global developmental delay in patients with Leigh syndrome/Leigh-like disorder, with predominant motor involvement and relative sparing of cognition. Early intervention focusing on improving motor coordination with improve the lifestyle of the child and family.

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