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ETHICALLY MANAGING LEIGH'S SYNDROME: A CLINICAL CASE STUDY

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ABSTRACT

Leigh syndrome, a rare inherited neurometabolic disorder described as subacute necrotizing encephalomyelopathy, affects the central nervous system and falls within a group of mitochondrial cytopathies involving disordered oxidative phosphorylation in the affected neural cells leading to disrupted enzyme of mitochondrial aberrations are attributed to variously inherited nDNA or mtDNA mutations The present study strives to demonstrate the efficacy, and therefore the need and ethical justification of therapeutic intervention at-least in the speech-language and swallowing realm; despite poor prognosis and the high risk of early death, in such infants through a representative case study. The case "x", a three years old girl suffered classical cognitive, neuromotor, and linguistic regression following suspected pneumonia at 18 months (probable trigger), before which she had 10-15 words vocabulary, able to recognize body parts, follow simple verbal command. The child presented severe dystonia, hypotonia, moderate dysphagia with persistent of sucking reflexes, oromotor inadequacies, absence of spoken words, absence of receptive language except to name-calling. Intensive physiotherapeutic and speech-language intervention were initiated. Orofacial exercises, dysphagia management protocols including the compensatory approaches and dietary modifications as well as direct language therapy for increase in vocabulary were taken up. After 2 months of therapy, there were significant improvements especially in swallowing rate and strength, integration of infantile reflexes and increase in linguistic receptivity, which clearly warrants continued therapy and consideration of AAC.

Keywords: Neurological disorder, Speech disorder, Leigh's syndrome, Speech therapy.

INTRODUCTION

Leigh's syndrome (L.S), a rare inherited neurometabolic disorder described as subacute necrotizing encephalomyelopathy affects the central nervous system and falls within a group of mitochondrial cytopathies involving disordered oxidative phosphorylation in the affected neural cells leading to disrupted enzyme balance (Ruhoy & Sanato,2014). These mitochondrial aberrations are attributed to variously inherited nDNA or mtDNA mutations. 75 different Genes such as SURF1 and MT-ATP6 are identified as major genetic factor which may cause Leigh's syndrome. Gene mutations may also cause Leigh's syndrome which leads to decrease the activity of oxidative phosphorylation protein complexes and affect energy production. Impaired oxidative phosphorylation leads to cell death because of decreased energy available in the cell. Within its variations, the most common symptoms include ataxia, myoclonia, psychomotor retardation or regression, dystonia, muscle weakness, intolerance to physical exercise, sensorineural hearing loss, movement in co-ordinations, seizures, learning disabilities, optic atrophy, pigmentary retinopathy, ophthalmoplegia, cardiomyopathy, diabetes, autism, growth atrophy, peripheral neuropathy, dementia, and multiple lipomas, and frequent episodes of respiratory issues due to lactic acidosis (Moggio, 2014). Speech language skills are also affected which include dysarthria. Leigh's syndrome is considered to be a disease of infancy and early childhood with disease onset before the age of 2 years (*Lee et al 2014).* If the onset of Leigh's syndrome is later in childhood a child may experience intellectual disability. Previously acquired intellectual skills may diminish with linguistic regression in all areas of language both in receptive and expressive domains. Classical form of the disease has an early onset, with the first signs being

motor regression, anorexia, vomiting, possible seizures and progress to muscle hypotonia, dystonia, ataxia as well as a plethora of cardiac, respiratory and optical disturbances. Prognosis is poor with very high mortality rate due to respiratory distress (Rahman et al 2015). Till now, there is no cure for affected patients, and treatment options are mostly unsatisfactory (Baertling et al. 2014). Typically, the age of onset of Leigh's syndrome develops between the ages of 3 months and 2 years (Leigh, 2008). The gender ratio is equal for both males and females. Leigh's syndrome are inherited an X-linked recessive trait, where Males are twice affected than females. It has been found by researchers that the prevalence of Leigh's syndrome has been estimated at 1 in 36,000-40,000 live births (National Organization for rare disorder, 2016). Speech-language and swallowing characteristics include regression in spoken language, learning disabilities and dysarthria, dysphagia, hearing loss related to oro-facial and auditory myopathies. It affects 1 in 40,000 newborns (U.S. National Library of Medicine, 2016). There is no evidence based assessment and intervention guideline to reduce the effect of rapid deterioration of cognitive, language and motor functions.

The study has been done by Sofou. K. et al. (2014) on diseases course and predictors of survival of Leigh's Syndrome where they administered this study on 130 patients (78 males and 52 females) with Leigh's syndrome in various countries of Europe. some common clinical features were abnormal motor findings, followed by abnormal ocular findings. Epileptic seizures were reported in 40% of patients. Infections are leading cause of acute exacerbations that requires hospitalization (44% patients). Increased lactate in the cerebrospinal fluid and as well as brainstem lesion were significantly correlated to a more severe disease course. The percentage of death is 39% mostly at the age of 21 years, at a median age of 2.4 years. If neuroimaging findings show brainstem lesion, the may be chance of poorer survival. The study showed the natural history of Leigh's syndrome and identifies novel predictors of disease severity and long-term prognosis.

Another study by Lee et al 2016, "on neurologic progression and functional outcome in Leigh's Syndrome, the goal of this study was to identify prognostic indicators of the disease progression and neurological outcome which reveals isolated complex I deficiency was the most frequently observed MRC defect. Mitochondrial DNA Mutation was identified in 11 patients, of which 81.8% were MTND Genes. Poor functional outcome and neurological deterioration were significantly associated with early onset and the presence of other lesion additional to baTsal ganglia involvement in the initial neuroimaging".

Need of study

Ethical dilemmas thus exist as to the extent and efficacy of speech-language intervention in L.S due to the reportedly poor prognosis and high mortality rate. An exemplary case with positive outcome may demonstrate the efficacy of intervention and change the conventional viewpoint of clinicians. Unfortunately till date there are no research on rehabilitation of disability of Leigh's syndrome and professional roles in its rehabilitation.

Aims & Objective

The present study strives to demonstrate the efficacy, and therefore the need and ethical justification of therapeutic intervention at-least in the speech-language and swallowing realm; despite poor prognosis and the high risk of early death, in such infants through a representative case study.

Methods

The case "x", a three years two months old girl suffered classical cognitive, neuromotor, and linguistic regression following suspected pneumonia at 18 months (probable trigger), before which she had approximately 10-15 words expressive vocabulary, able to recognize body parts and follow simple verbal command.

The child was brought to our clinic with the complaints of speaking, sitting and walking. She could speak single word before Pneumonia. Although the child was consanguineous, there is no history of similar illness in the family. Presently, the child is under medication of Nodosis (Sodium Bicarbonate), Biotin (Vitamin B7), Neurobion 40(thiamine hydrochloride, pyridoxine hydrochloride, cyanocobalamin), Nutrihale.

Motor development was reported to be normal till 18 months of age. Following the event of Pneumonia, there was sudden loss of most of key motor abilities. Similar pattern of regression was also observed in the cognitive-social developmental domain as well as language developmental domain. For example, in the cognitive-social domain, reflexive smile, social smile, focusing on faces, following movement, reaching for toys were present at 18 months of age, with sudden loss of all ability at 18 months of age. In the language domain, the child was reported to have acquired all the pre-linguistic skills like crying, differential crying, cooing, babbling age-appropriately. First word was acquired at 1 year (meaningfully |ma|) which suddenly disappeared at 18 months.

The child presented severe dystonia, hypotonia, moderate dysphagia with persistent of sucking reflexes, oromotor inadequacies, absence of spoken words, absence of receptive language except response to name-calling.

Medical records were reviewed where Neuroimaging Findings (MRI) revealed bilaterally symmetrical T2W/FLAIR hyperintensities involving posterior putamen, peritrigonal white matter, ventral midbrain in the region of substantia nigra, along central tegmental tract, inferior olivary nuclei, dorsolateral medulla at the base of restiform bodies & dentate nuclei. the finding suggested Mitochondrial Disorder Leigh's Syndrome/Subacute necrotizing encephalomylopathy (SNEM).

Audiological assessments including Auditory Brainstem Response (ABR) and otoacoustic emissions (OAE) both the test were administered and correlation of these two tests reveals bilateral hearing sensitivity within normal limits.

Neuromuscular and physiotherapeutic assessment was done by an experienced occupational therapist and the report showed flaccid quadriplegia with spastic rigidity at the extremities; hypotonia; DTR-not elicited; static balance was fair but on motion poor. Hand functions were poor. Lack of head control, widespread muscle wasting, ocular motility disorder, drooling were

present. The child was able to turn around from the supine to the left, but not to the right, could not roll, and was not able to sit up unaided.

In-depth speech and language evaluation was done for the child. Examination of the Oro-peripheral mechanism revealed hypotonic lip and tongue with affected function of all the articulators. Poor lip seal and drooling, restricted tongue movements and ageusia (loss of taste function of lip and tongue). Poor feeding skills and all the vegetative functions like chewing, sucking was affected. Appearance of teeth, hard palate and soft palate are normal. REELS puts both expressive and receptive language ages at 0-1 months. COMMDEALL reveals marked delay in Gross Motor, Fine Motor, Activity Daily Living, Receptive Language, Expressive Language, Cognitive Skills, Social Skills, Emotional Skills. Cognitive Prerequisites like vocal and body movement imitations, attention, object permanence etc. were virtually absent. Level of expression was at pre-intention level. Communication Function Classification System (CFCS) was at Level V. (Hidecker. M.J.C et al. 2012). Speech breathing assessment was done and it reveals her Breathing Rate was 39/min. Almost all primitive infantile reflexes such as sucking, rooting, mouth opening reflex were persistant, where as pathological reflexes were found present. Informal feeding skills assessment reveals mother was primary baby's feeder and frequent chocking, gulping, drooling, poor coordination in sucking and swallowing, poor bolus manipulation and not looking at feeder during feeding were significant observable characteristics.

Dysphagia assessment has been administered using the Dysphagia Severity Rating Scale (Waxman et al. 1990). It is consisted with 7 point rating scale which reveals the severity by Severe dysphagia-more than 10 % aspiration for all consistencies of food (Rating 6), Moderately severe dysphagia- aspiration is seen for one or more than one food consistencies (Rating 5), Moderate dysphagia-significantly aspiration is present for all food consistencies and patient can intake food of some consistencies by using specific technique (Rating 4), Mild-moderate dysphagia-aspiration exists and it can be controlled by modified diet and using specific swallow management techniques(Rate 3),Mild dysphagia-Oro pharyngeal dysphagia is present and slight modification of diet is done with some specific swallow management techniques (Rate 2), Minimal dysphagia-slight deviation from normal swallow has been seen by Videofluroscopy and patient can feel a slight change of sensation during feeding but no need of dietary modification (Rate 1), Normal swallowing process (Rate0). The severity of child was mild to moderate during pre-therapy assessment. At that time child has history of recurrent respiratory infections due to silent aspiration of saliva.

Intensive physiotherapeutic,c interventions were initiated. For physiotherapeutic intervention manual therapy involves holistic approach, Bobath's approach, Phelp's approach, significant increases in gross motor functions; neck control emergent; plantar reflexes suppressed; rolling over and sitting emergent; sensory perceptual responsiveness increased.

To improve Oro-motor strength:

Oro-facial exercises, dysphagia management protocols including the compensatory approaches and dietary modifications as well as direct Oro-motor exercises and oral sensory stimulation to increase Oro-motor strength were taken up.

To improve feeding skill:

The following protocol was followed during feeding, time given (100ml) 45 -60minutes, only thick liquid food was recommended by spoon feeding, in lying in lap with chin up position, amount of food is 2.5-4.5 ounces every 3-4 hours, 5ml/bolus. Gradually she was introduced puree diet.

To improve cognition:

Visual feedback technique was used which Heighten the child's awareness of receptor function and relate sensation to the source of stimulation: The infant's mouth is an important source of sensations and experience during the first year. With guidance the mother can be taught to employed techniques during feeding which will heighten the child's awareness of the stimuli aroused and help him identify this sensation with his environment.

To improve receptive language (age upto 8 months of language age):

Technique used incidental teaching:

Target: to recognize familiar objects.

Activities: Parents was asked to help the child learn the names of familiar objects as they turn the light in his darken room, they were demonstrated to say "light" as they hold him facing the light fixture. They made the room darken and repeat this procedure. This would be done until the child will look at the light source when the word light is spoken to him.

Target: to distinguish general meaning of facial expression.

Target: to improve understanding of "no" and "bye bye.

Activity: the child was shown various type of emoji like angry sad smile and simultaneously background sound related with the emoji was given. Ex: when the angry was present with that an angry voice also be present by the clinician.

To improve expressive language age (upto 8 months of language age):

Technique used consonantal modification:

To encourage and facilitate babbling when the child is crying to effect approximation of the lips by placing the hand beneath the mandible and gently elevating it.

Target: To stimulate encourage the vocalization:

Activities: To improve the laughing reflex gently stoking or tickling over the ribs has been given to the child.

To improve level of expression:

Target: Non-conventional pre symbolic communication

Activities: the child was encouraged and conditioned using some symbols like pointing, looking at object when she needs, opening mouth to express hunger and so on. Each purposeful attempt was positively reinforced by providing verbal praise, claps as well as token.

RESULTS AND DISCUSSION

After a period of 6 months of rigorous therapeutic intervention both at our centre and through parent-centred approaches, on post therapeutic assessment, significant improvements were demonstrated in the areas of cognitive prerequisites. (table:1). It was found that the child has begun to turn head on recognition of familiar voice which was previously absent.

Table 1: PROGRESS REPORT OF COGNITIVE PRE REQUISITES FOR LANGUAGE LEARNING

Area to be assessed	Behaviour in which the skills is demonstrated	Pre Therapy	Post Therapy
Attending	Turns head or makes an appropriate response to the noises in the environment	Present	Present
	Turns head and makes an appropriate response to sound of a familiar person's voice.	Absent	Emergent
	Looks at an object placed in front of her.	Absent	Present
Imitation of vocal behaviour (repeating sounds and words)	Holds on to objects when placed in hand.	Absent	Present
	Grasps an object when own hand and object are view.	Absent	Present
	Grasps an object when just the object is in view.	Absent	Emergent
Imitations of body movements	Repeat the gross body movement that the child has initiated after it is initiated by another persons.	Absent	Present
	Imitates gross body movements already familiar to the child and which the child can see him or her self making.	Absent	Present
	imitates gross body movement already familiar to the child that the child	Absent	Absent

	can not see him or her self making.		
Use of Object	Perform the same action on different objects.	Absent	Present
	Perform different action on the same objects.	Absent	Absent
	Make one objects act on another.	Absent	Absent
Means end relationship (the ability to achieve desire goal by some means)	Holds on to objects when placed in hand.	Absent	Present
	Grasps an object when own hand and object are view.	Absent	Emergent
	Grasps an object when just the object is in view.	Absent	Present
Object permanence (knowing that something still exists when it moves out of view).	Follows the movement of an object with his or her eyes	Absent	Present
	Looks at the place where a moving object disappeared	Absent	Present
	Looks at the place where an object should reappear after it has been hidden behind something else	Absent	Present
	Finds a partly hidden object	Absent	Present
	Finds an object that is completely hidden	Absent	Pressent
	Finds an object when it is hidden over and over again under one or two clothes.	Absent	Pressent
	Finds an object when it is hidden alternately under one or two clothes	Absent	Absent

After 6 months, Post therapeutic evaluation was done to evaluate the progress of the intervention which includes REELS, COMMDEALL, Cognitive Pre-requisites, Level of Expression.

Cognitive pre-requisites are the most crucial elements for speech and language development and here also found significant improvements in cognitive prerequisites including attending, vocal and body movement imitations, imitation of body movements, use of object, means -end relationship, object permanence were observed (as Table-1 shows).

Table 2: PROGRESS REPORT of RECEPTIVE EXPRESSIVE EMERGENT LANGUAGE SKILLS:

	Pre Therapy	Post Therapy
Receptive Language Age	0-1 month	4-5 months
Expressive Language Age	0-1 month	4-5 months

In comparison between pre and post therapeutic findings, (figure 2) shows significant improvement in REELS as both receptive language age and expressive language age was 4-5 months after the therapy. CommDEALL (figure 1) reveals all domains are significantly improved after therapy.

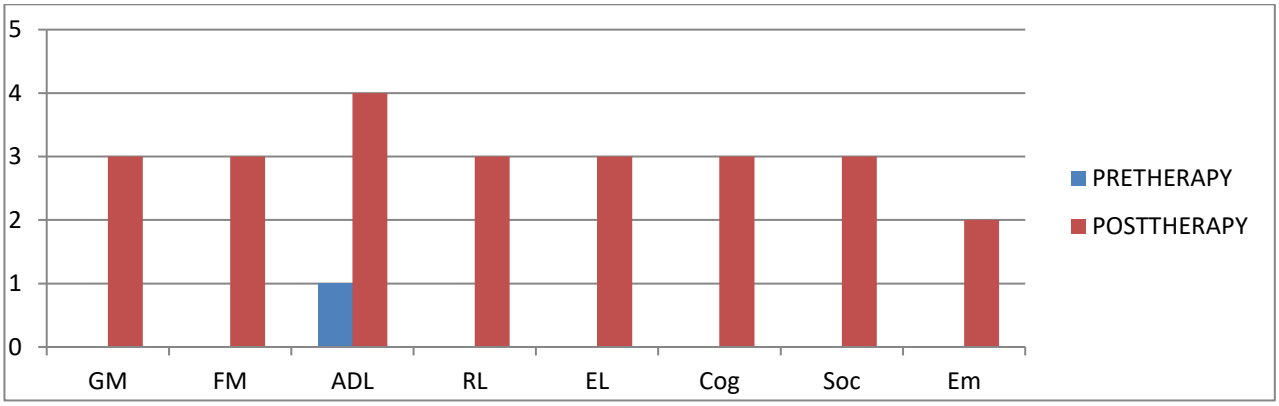


Figure 1: PROGRESS REPORT OF COMMDEALL DEVELOPMENTAL CHECKLIST

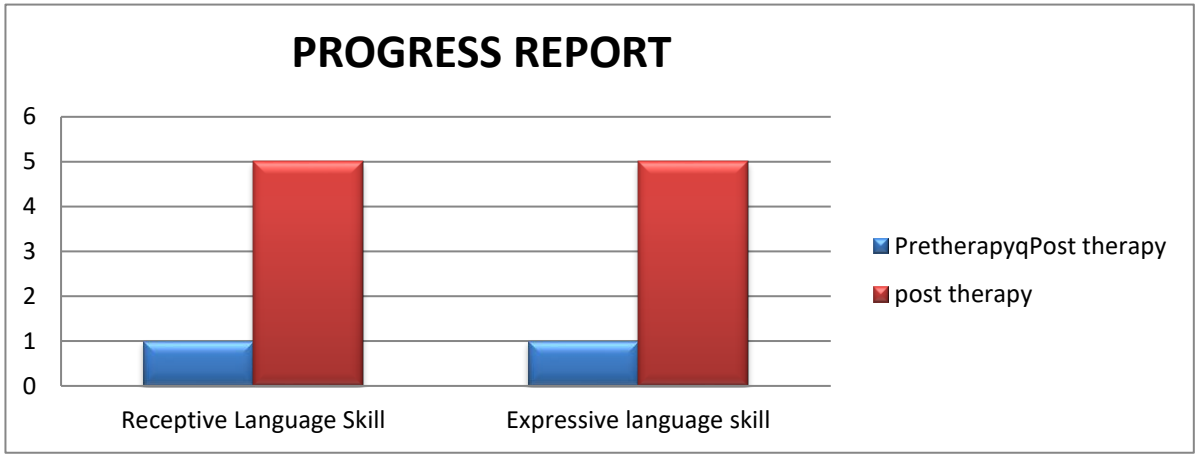
After 6 months of therapy, level of expression was improved. The child started showing intentional behaviour by reaching and pushing objects in motor gestural domain. Non-conventional pre symbolic communication like laugh and non speech sounds was observed in vocal domain (as Table-3shows).

Table 3: PROGRESS REPORT OF LEVEL OF EXPRESSION

	Levels	
	Pre Therapy	**Post Therapy**
Vocals	Pre intentional Behaviour	Non-conventional pre symbolic communication
Motor Gestural	Pre intentional Behaviour	Intentional Behaviour

For post therapy dysphagia assessment the child was sent to another clinic for Videofluroscopy assessment where the Dysphagia severity Rating Scale (Waxman etal,1990) shows Normal swallow mechanism (Rate 0) upto soft diet level. Along with this after the feeding management respiratory distress due to silent aspiration of saliva has been reduced.

Figure 2: PROGRESS REPORT of RECEPTIVE EXPRESSIVE EMERGENT LANGUAGE SKILLS.



There were also significant improvements especially in swallowing rate and strength, integration of infantile reflexes and increase in linguistic receptivity, which clearly warrants continued therapy and consideration of AAC, as demonstrated in post therapeutic assessment data.

Many studies on Leigh's syndrome in literature has highlighted a bleak picture: a strikingly high mortality rate (e.g Rahman et al 1996). There are other studies, which even though not emphasising on the mortality rate, highlights a severely poor functional outcome of the condition. Contradicting with such gloomy image of Leigh's syndrome, the present study strives to bring high hopes. Significantly good functional outcome is demonstrated in the present case and we may hope for independent daily living for our case in the future. There are but very few studies (e.g: Stacpoole Peter W,2016) which gives such positive outcomes. Another point needs a special mention. Previous study shows a high rate (14.1%) of feeding and sucking difficulties in Leigh's syndrome (Sofou k et al 2014), and the same study also shows respiratory complications to be the leading cause of death. In our case, there was a significant improvement in swallowing with a concomitant decrease in the chances of respiratory complications like aspiration. Thus, we may assume that a proper dysphagia management protocol

might decrease mortality in such cases. As there is no medical treatment to cure the affected patients and most of the treatment options are unsatisfactory, (Baertling et al 2014) so rehabilitation with proper goal management is shown effective according to this case study. Though this study shows significant improvement in the rehabilitation of Leigh's syndrome, there is an immense need of developing standardised protocol of speech language and swallow management for the child with Leigh's syndrome. As to the prognosis in L.S, Lee (2016) studied 39 individual with Leigh's syndrome with 85% has developmental delay, 31% has seizure, 26% has dystonia, 10% has ataxia, 13% has dysphagia and 13% has dysarthria and demonstrated poor prognosis during long-term follow-up, (Lee et al., 2009). On contrary, our study shows significant improvement after 6 months therapy. However, although there is statistically significant improvement in all domains of speech-language and swallowing still age appropriate skills were not reached after 6 months of therapeutic intervention. It is to see whether longer period of intervention will bring about further and faster improvements so that age appropriateness may be reached.

CONCLUSION

The present study clearly demonstrates significant benefit on therapeutic intervention. Thus, intensive multi-model therapeutic intervention seems to be ethically justifiable in-spite of the common notion of poor prognosis and early mortality. It warrants a positive and proactive view towards management of such congenital Neuro-developmental and Neuro-metabolic disorders. However, since literature posits prognosis to be highly individualized in Leigh's syndrome, to make a generalised prediction of the therapeutic outcome more longitudinal and cross sectional research works need to be conducted by considering different prognostic factors. This study opens up a new domain of service for speech-language pathologist in paediatric neuro-developmental disorders. Physiological evidence of improvement as a result of therapy may be studied using neuro imaging techniques like FMRI which would give evidence based prognostic indicator of speech language therapy as well as would give insight to the background neurophysiological mechanism, of Leigh's Syndrome. More clinical trials to validate the prognostic factors, therapeutic efficacy and develop treatment norms and protocols are needed in future.

Conflict of interest: Nil

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