

Leigh syndrome - A Rare Genetic Disorder

Salwa Hareem
Department of Genetics
St Ann's College for Women,
Mehdipatnam
salwahareemgenetics@gmail.com

Dr. N Swapna
Department of Genetics
St Ann's College for Women,
Mehdipatnam

Dr. V. Venugopal Rao
Department of Genetics
St Ann's College for Women,
Mehdipatnam

Abstract— Leigh syndrome is a devastating neurodegenerative disease, typically manifesting in infancy or early childhood. Syndrome is characterized by seizures, developmental delay, muscle weakness, respiratory abnormalities, optic abnormalities, including atrophy and progressive cranial nerve degeneration with early onset in infants and children. Leigh syndrome is the most common pediatric presentation of mitochondrial disease and to date pathogenic mutation in >75 genes have been identified, encoded by 2 genomes. At the molecular level, a number of the point mutations have been located in mitochondrial DNA genes, including ATPase6 and tRNA genes, in nuclear genes encoding subunits of oxidative enzymes, such as pyruvate dehydrogenase. Biochemically these mutations are responsible for enzymatic defects in either respiratory complexes (I, IV, or V) or pyruvate dehydrogenase. To date, there is no cure for affected patients, and treatment options are unsatisfactory.

Keywords— Basal ganglia . brainstem . children . leigh syndrome . mitochondrial disease.

I. INTRODUCTION

Leigh syndrome also referred as subacute necrotising encephalopathy, was first described by the British psychiatrist and neuropathologist Denis Archibald Leigh in 1951.[1] Leigh syndrome is a rare inherited neurometabolic disorder that affects the central nervous system. This progressive disorder begins in infants between the ages of three months and two years. Rarely, it occurs in teenagers and adults. Leigh disease can be caused by mutations in mitochondrial DNA or by deficiency of an enzyme called pyruvate dehydrogenase.

In Leigh's disease, genetic mutations in mitochondrial DNA interfere with energy source that runs cells in area of brain that plays role in motor movement. The primary function of mitochondria is to convert the energy in glucose and fatty acids into a substance called adenosine triphosphate [ATP].[2]

The energy ATP derives virtually all of the cell's metabolic functions. Genetic mutation in mitochondrial DNA, therefore, results in a chronic lack of energy in these cells, [3] which in turn affects the central nervous system and causes progressive degeneration of motor functions.[4]

LS is clinically heterogeneous with significant variation between patients with respect to age of onset, age of death and symptomatology. Generally, onset occurs by 2 yrs of age.[5]

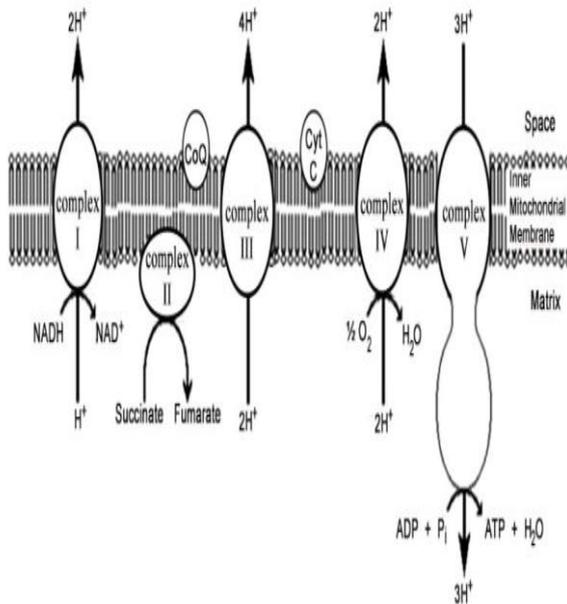
The first sign of Leigh syndrome seen in infancy are usually vomiting, diarrhea and difficulty swallowing (dysphagia), which disrupts eating. These problems often result in an inability to grow and gain weight at the expected rate (failure to thrive). Severe muscle and movement problems are common in Leigh syndrome. Affected individuals may develop weak muscle tone (hypotonia), involuntary muscle contraction (dystonia), and problems with movement and balance (ataxia). Loss of sensation and weakness in limbs (peripheral neuropathy), common in people with Leigh syndrome, may also make movement difficult.

Several other features may occur in people with Leigh syndrome. Many individuals with this condition develop weakness or paralysis of the muscles that move the eyes (ophthalmoparesis), rapid involuntary eye movement (nystagmus). Or degeneration of nerves that carry information from the eyes to the brain (optic atrophy). Severe breathing problems are common, and these problems can worsen until they cause acute respiratory failure. Some affected individuals develop hypertrophic cardiomyopathy, which is the thickening of heart muscle that LS is clinically heterogeneous with significant variation between patients with respect to age of onset, age of death and symptomatology. Generally, onset occurs by 2 yrs of age.[6]

BIOCHEMICAL PROFILE

The key function of mitochondria is to produce energy via the oxidative phosphorylation (OXPHOS)

pathway.



Electron transport chain.[5]

Leigh syndrome (LS) is caused by genetic impairment of the mitochondrial pathways of energy generation. Pyruvate is metabolized by pyruvate dehydrogenase (PDHc) to produce acetyl coenzyme A, which is utilized by the citric acid cycle (TCA) to produce electron donors for the pathway of oxidative phosphorylation (OXPHOS). OXPHOS is performed within in the mitochondrial inner membrane by 5 multiprotein complexes, known as complexes I to V. The respiratory chain utilizes the energy produced by this electron transfer to pump protons through complexes I, III, IV into the intermembrane space, generating a proton gradient that can be harnessed by adenosine triphosphate (ATP) synthase (complex V) to derive the synthesis of ATP. Deficiency of PDHx, complexes I to V, and coQ (10) can cause LS.[7]

DIAGNOSTIC

A pathway to diagnosis of Leigh syndrome:

1. Medical history

- ▶ Parental consanguinity, similar cases in the family, recurrent miscarriage
- ▶ Disease onset/neurological deterioration after a period of metabolic stress (eg, infection, prolonged fasting, surgery, etc.)
- ▶ Psychomotor regression/loss of acquired skills
- ▶ Exclusion of differential diagnoses (perinatal asphyxia, kernicterus, carbon monoxide or methanol intoxication, thiamine deficiency, Wilson's disease, biotin-responsive basal ganglia disease, encephalitis, etc.)

2. Physical examination:

- ▶ Symptoms suggestive of basal ganglia and/or brainstem dysfunction (dystonia, nystagmus, autonomic dysfunction, etc.)
- ▶ Specific findings (sensorineural deafness, hypertrichosis, etc.)

3. Laboratory parameters:

- ▶ Lactic acidosis/acidaemia
- ▶ Plasma amino acids (hyperalaninemia)
- ▶ Urinary organic acids (pyruvate, lactate, citric acid cycle intermediates, 3-methylglutaconic acid, ethylmalonic acid)
- ▶ Carnitine panel
- ▶ General laboratory panel (liver/kidney parameters, creatinine kinase, ammonia level, etc.)
- ▶ Metabolic parameters suggestive of other metabolic disorder?

4. MRI/magnetic resonance spectroscopy (MRS)

- ▶ Symmetrical lesions suggestive of Leigh syndrome (basal ganglia, brain stem)
- ▶ Lactate peak in MRS
- ▶ Other/additional findings; indications for differential diagnoses?

5. Evaluation of findings and primary genetic analysis

- ▶ If constellation of findings is suggestive of a specific genetic defect (ie, *SUCLA2*, *SERAC1*, *SURF1*)

6. Fibroblast culturing and/or muscle biopsy

- ▶ Critical evaluation of symptoms and findings. Evidence strong enough for invasive procedure?
- ▶ Proceeding with skin biopsy alone: infants below the age of 3 months; suspected pyruvate dehydrogenase complex deficiency, anaesthetic difficulties/critical clinical condition
- ▶ Proceeding with skin biopsy and muscle biopsy: in unclear cases of patients ideally above the age of 3 months; suspected mitochondrial DNA mutations

7. Re-evaluation of findings and genetic diagnostics

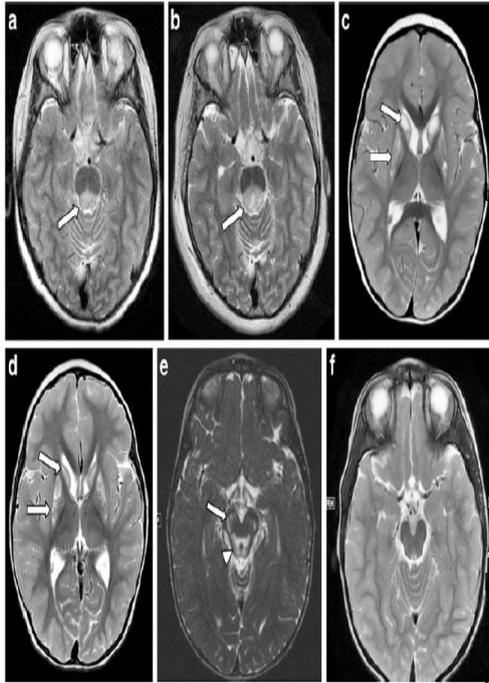
- ▶ Mitochondrial DNA screening if oxidative phosphorylation (OXPHOS) defect seems tissue specific; *POLG* gene mutations have to be taken into account
- ▶ Screening of candidate nuclear genes if OXPHOS defect seems ubiquitous
- ▶ Whole exome sequencing should be considered in unclear cases

Baertling F, et al. *J Neurol Neurosurg Psychiatry* 2014;85:257-265. doi:1136/jnnp-2012-304426

As MRI has become clinically available, to identified the leigh syndrome (LS). The term

leigh-like syndrome is used when this criteria are partially met, or when patients present atypical symptoms, laboratory findings or radiological features.[8]

Fig. 5 Evolution of lesions on MRI. Initial (a, c, e) and follow-up MRI studies (b, d, f) in three children illustrate the evolution of MRI lesions. a, b Axial T2-W images at the level of the pons in a boy at age 14 months (a) and at age 3 years (b) show progression of T2 signal abnormality and mass effect in the dorsal pons (arrows). c, d Axial T2-W images at the level of the basal ganglia in a girl at age 11 years (c) and at age 12 years (d) show evolution of the initially edematous lesions into encephalomalacia (arrows). e, f Axial T2-W images at the level of the midbrain in a boy at age 7 years (e) and at age 8 years (f) demonstrate complete resolution of signal abnormalities in the tegmentum (arrow in e) and periaqueductal region (arrowhead in e)



TREATMENT

The most common method used for the treatment of the leigh syndrome is thiamine or vitamin B1. oral sodium bicarbonate or sodium citrate may also be used to manage lactic acidosis. Researchers are currently using dichloroacetate to establish its effect on lactic acidosis.

In the patients who have X-linked form of leigh syndrome low carbohydrate, high fat diet can be recommended.

Rapamycin, a specific inhibitor of the mechanistic target of rapamycin (mTOR) signaling pathway, robustly enhances survival and attenuates disease.

But in actual no such accurate treatment is available for the complete cure of the disorder.[10]

CONCLUSION

Finding an underlying genetic cause of the LS patient can be challenging. MPS has transformed the approach for determining the genetic basis of LS. there is currently no effective treatment for LS. The availability of genetic testing has enabled recognition of the clinical and genetic heterogeneity in this disease.

REFERENCES

- [1] Leigh D. Subacute necrotizing encephalopathy in an infant. *J Neurol Neurosurg Psychiatry* 1951; 14:216-21.
- [2] Baertling F, et al. *Journal Neurosurg Psychiatry* 2014; 85:257-265. doi:10.1136/jnn-2012-304426.
- [3] *ANN NEUROL* 2016;79:190-203.
- [4] *Wileyonlinelibrary.com*. DOI: 10.1002/ana.24551.
- [5] *ANNALS of Neurology*, February 2016. DOI: 10.1002/ana.24551.
- [6] <https://ghr.nlm.nih.gov/>
- [7] skladal D, Halliday J, Thorburn DR, Minimum birth prevalence of mitochondrial respiratory chain disorders in children. *Brain* 2003;126:1905-1912.
- [8] A guide to diagnosis and treatment of leigh syndrome, Fabian Baertling, Richard J Rodenburg 2014:85:257-265.
- [9] Genetic Home Reference NIH.
- [10] James J. Filiano 2002, Elsevier Science. filiano et al: mitochondrial DNA depletion.