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REVIEW ON LEIGH SYNDROME

Padmesh P. R.[1]*, E. Sam Jeevakumar[2], Anusree V. S.[3] and Gokul Krishna[4]

[1]5th Pharm D, Sree Krishna College of Pharmacy & Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[2]Associate Professor, Department of Pharmacy Practice. Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[3]Principal, Head of Department of Pharmacy Practice, Sree Krishna College of Pharmacy & Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

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***Corresponding Author**
Padmesh P. R.
5th Pharm D, Sree Krishna College of Pharmacy & Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

ABSTRACT

Leigh syndrome is defined as a severe neurological disorder characterized by a progressive loss of both mental and movement abilities. The symptoms will usually develop between the first three months to two years. Their common symptoms include problems with movement and balance, difficulty in talking, weak muscle tone and so on. Mainly it is seen in 1 in 40,000 newborns. Mutations of various genes cause Leigh syndrome which include mitochondrial DNA (mtDNA) mutations, and nuclear DNA (nDNA) mutations. Diagnosis of Leigh syndrome may be confirmed by using combined enzymatic and genetic analyses. There is no definitive treatment for cure and prevention for the affected patients, but have some tentative treatment which is administered to slow the progression of disease.

KEYWORDS: Neurological disorder, infants, Mitochondrial DNA mutations, Nuclear DNAmutations.

INTRODUCTION

Leigh syndrome is a neurodegenerative disease often occurring in infants and in infancy. It is also called Leigh necrotizing encephalopathy, Sub acute necrotizing encephalopathy. During a small number of people, they do not develop symptoms until their adulthood. For the primary time it's been introduced by a British neuropathologist, Denis Leigh in 1951, during a 7 month old baby. Genetically, alterations or mutations of the mitochondrial respiratory

enzyme complexor pyruvate dehydrogenase complex are believed to be liable for the event of Leigh syndrome. Diagnosis is predicted on findings of clinical manifestations, history, laboratory assessments, imaging, muscle biopsy with histochemical staining, activity of the mitochondrial respiratory chain enzyme, and identification of mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) mutations. Failure of the mitochondrial respiratory chain, leads to the regression of both mental and motor skills, resulting in disability and rapid progression to death. As the syndrome progresses, symptoms include generalized weakness, lack of muscular tone (hypotonia), and episodes of lactic acidosis, which can cause the impairment of kidney and respiratory function. Most of the people with Leigh syndrome have defects of mitochondrial energy production, like deficiency of an enzyme of the mitochondrial respiratory chain complex or the pyruvate dehydrogenase complex. Most of the cases Leigh syndrome is an inherited autosomal recessive trait. However, X-linked recessive and maternal inheritance, because of a mitochondrial DNAmutation, area dditional modes of transmission.

LEIGH SYNDROME

Other Names: Sub acute necrotizing encephalopathy.

Categories: Congenital and genetic diseases.

Subtypes: Leigh syndrome, Mitochondrial DNA-associated Leigh syndrome; Nuclear gene-encoded Leigh syndrome.

DEFINITION

Leigh syndrome could even be a rare, inherited neurodegenerative condition. It always becomes apparent in infancy, often after a viral infection. Rarely, it begins within the teenage or adult years.Signs and symptoms usually progress rapidly. Primary symptoms may include poor ability of sucking; loss of head control and motor skills; loss of appetite; vomiting; and seizures. Because the condition progresses, symptoms may include weakness and lack of muscle tone; spasticity; movement disorders; cerebellar ataxia; and peripheral neuropathy. Complications can causeimpairment of respiratory, heart and kidney function.

TYPES

- Mitochondrial DNA-associated Leigh syndrome follows a mitochondrial inheritance pattern (also called maternal inheritance).
- Nuclear gene-encoded Leigh syndrome could even be inherited in an autosomalrecessive

or X-linked manner.

EPIDEMIOLOGY

Leigh Syndrome is encountered in approximately 1 in 40,000 births, although some populations have much higher incidence. Mitochondrial DNA-associated Leigh syndrome, which is more rare than nuclear gene-encoded Leigh syndrome, is likely to occur in about1 in 100,000 to 1 in 140,000 births.

ETIOLOGY

Leigh syndrome is often caused by mutations in any of quite 75 different genes. Most of our genesare made up of DNA in the cell's nucleus (nuclear DNA). Some of our genes are made up of DNA in other cell structures called mitochondria (mitochondrial DNA, or mtDNA). Most people with Leigh syndrome have a mutation in nuclear DNA, and about 20% have a mutation in mtDNA. Most genes related to Leigh syndrome are involved in the process of energy production in mitochondria (oxidative phosphorylation). Five protein complexes, named complex I to complex IV, are involved in this process. The gene mutations related to Leigh Syndrome disrupt the function of proteins in these complexes.

Disruption of complex l also called NADH: Ubiquinone oxidoreductase, is the most common cause of Leigh syndrome. At least 25 genes involved in the formation of complex l which is foundeither nuclear or mitochondrial DNA, have been associated with Leigh syndrome.

Disruption of complex lV, also called cytochrome c oxidase or COX, is also a common cause of Leigh syndrome. One of the most frequently mutated genes in Leigh syndrome is SURF1 and thisgene, which is found in nuclear DNA, provides instructions for making a protein that helps assemble the COX protein complex. This complex involved in the last step of electron transfer inoxidative phosphorylation, provides the energy that will be used in the next step of the process to generate ATP. Mutations in the SURF1 gene typically lead to an abnormally short SURF1 protein that is broken down in the cells, resulting in the absence of functional SURF1 protein. The absences of this protein which reduces the formation of normal COX complexes, thus by impairs mitochondrial energy production.

The other most common mtDNA mutation in Leigh syndrome affects the MT - ATP6 gene, which provides instructions for making a piece of complex V, also known as the ATP synthase protein complex. Using the energy provided by the other protein complexes, the

ATP synthase complex generates ATP. MT- ATP6 gene mutations, which block the generation of ATP. Other mtDNA mutations associated with Leigh syndrome decreases the activity of other oxidative phosphorylation protein complexes or lead to reduced formation of mitochondrial proteins, all of which impair mitochondrial energy production.

Pathophysiology

The characteristic symptoms of Leigh syndrome are partially caused by bilateral, focal lesions within the brainstem, basal ganglia, cerebellum, and other regions of the brain. The lesions tackle different forms, including areas of demyelination, spongiosis, gliosis, necrosis, and capillary proliferation. Demyelination is the loss of the myelin sheath around the axons of neurons, inhibiting their ability to talk with other neurons. The brainstem is involved in maintaining basic life functions like breathing, swallowing, and circulation. The basal ganglia and cerebellum control movement and balance. Damage to those areas therefore results in the foremost symptoms of Leigh syndrome ie, loss of control over functions controlled by these areas. The lactic acidosis sometimesassociated with Leigh syndrome is caused by the buildup of pyruvate, which is unable to be processed in individuals with certain sorts of oxidative phosphorylation deficiencies. The pyruvate is either converted into alanine via alanine aminotransferase or converted into lactic acid by lactate dehydrogenase. Both of these substances can then build within the body.

Signs and Symptoms

The symptoms of classical Leigh syndrome (infantile necrotizing encephalopathy), usually begin between the ages of three months and a pair of years. In most children, the first noticeable sign (3 week) is the loss of previously acquired motor skills, loss of head control and poor sucking ability, loss of appetite, recurrent vomiting, irritability, continuous crying and possible seizure activity. Affectedinfants may fail to gain weight and grow. If the onset of Leigh syndrome is later in childhood (e.g., 24 months), a toddler may experience difficulty (dysarthria) and coordinating voluntary movements like walking or running. Progressive neurological deterioration associated with Leigh syndrome is marked by a variety of symptoms including generalized weakness, lack of tonicity (hypotonia), clumsiness, tremors, muscle spasms (spasticity) that end in slow, stiff movements of the legs, and absence of tendon reflexes. Episodes of lactic acidosis may occur and are characterized by abnormally high levels of lactic acid within the blood, brain and other tissues of the body. Periodically, levels of CO2 within the blood may be abnormally elevated (hypercapnia).Lactic acidosis and

hypercapnia, both may result in psychomotor regression and respiratory, heart, or kidney impairment.

Children with this syndrome usually develop respiratory problems like temporary cessation of spontaneous breathing (apnea), difficulty breathing (dyspnea), abnormally rapid breathing (hyperventilation), and abnormal breathing patterns (Cheyne-Stokes). Some infants may additionally experience difficulty swallowing (dysphagia).

Visual problems may include abnormally rapid eye movements (nystagmus), sluggish pupils, crossed eyes (strabismus), paralysis of certain eye muscles (ophthalmoplegia), deterioration of thenerves of the eyes (optic atrophy), visual impairment leading to blindness.

Leigh syndrome may affect the *Heart*. Some children with this disorder may have abnormal enlargement of the heart (hypertrophic cardiomyopathy) and overgrowth of the fibrous membranethat divides the numerous chambers of the heart (asymmetric septal hypertrophy). Disease affecting the nerves outside of the central nervous system (peripheral neuropathy) may eventuallyoccur, causing progressive weakness of the arms and legs. The symptoms of the X-linked infantilequiet Leigh syndrome are similar as those of classical Leigh syndrome.

The symptoms of the adult-onset sort of Leigh syndrome (subacute necrotizing encephalomyelopathy), a very rare sort of the disorder, generally begin during adolescence or early adulthood. Initial symptoms are generally related to vision and can include such abnormalities as blurred “filmy” central visual fields (central scotoma), colour blindness, and progressive visual loss due to degeneration of the nervus opticus (bilateral optic atrophy). At about 50 years old affected individuals may find it progressively difficult to coordinate voluntary movements (ataxia). Additional late symptoms may include partial paralysis and smooth muscle movements (spastic paresis), sudden muscle spasms (clonic jerks), grand mal seizures, and ranging degrees ofdementia.

DIAGNOSIS

Leigh syndrome can be diagnosed by using the following criteria,

- Progressive neurologic disorder with motor and intellectual developmental delay
- Signs and symptoms of brainstem and basal ganglia disease
- Raised lactate concentration in blood and cerebrospinal fluid (CSF)

Pathway to diagnosis Leigh syndrome

1. Medical History

- Parenteral consanguinity, similar cases in family, recurrent miscarriage.
- Disease onset / neurological deterioration after a period of metabolic stress (infection, prolonged fasting, surgery).
- 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 etc).

2. Physical Examination

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

3. Laboratory Parameters

- Lactic acidosis/ academia.
- Plasma amino acids (hyperalaninemia).
- Urinary organic acids (pyruvate, lactate, citric acid cycle intermediates, 3-methylglutanoicacid, ethylmalonic acid).
- Carnitine panel.
- General laboratory panel(liver, kidney, creatine kinase, amino acid level).
- Metabolic parameters suggestive of other metabolic disorder.

4. MRI/ Magnetic Resonance Spectroscopy (MRS)

- Symmetrical lesions suggestive of Leigh syndrome.
- Lactate peak in MRS.
- Other/ additional findings: indication for differential diagnosis.

5. Evaluation of findings and primary genetic analysis

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

6. Fibroblast culturing and muscle biopsy

- Critical evaluation of symptoms and findings. Evidence strong enough for invasive

procedure.

- Proceeding with skin biopsy alone: infant below 3 months, suspected pyruvate dehydrogenase complex deficiency, anaesthetic difficulties.
- Proceeding with skin biopsy and muscle biopsy.

7. Reevaluation of findings and genetic diagnostics

- Mitochondrial DNA screening if oxidative phosphorylation defect seems tissue specific.
- Screening of candidate nuclear genes if OXPHOS defect seems ubiquitous.
- Whole exome sequencing should be considered in unclear cases.

AFFECTED POPULATION

The classical sort of Leigh syndrome develops during infancy (infantile necrotizing encephalopathy) and usually begins between the ages of three months and a couple of years (2 years). This sort of the disease affects males and females in equal numbers. In some cases of Leigh syndrome which are inherited as an X-linked recessive trait, the symptoms typically develop during infancy. Almost twice as many males as females are affected by this form of the disease. In rare cases, Leigh syndrome may begin during late adolescence or early adulthood (adult-onset sub-acute necrotizing encephalomyelopathy). In these cases, which affect twice as many males as females, the progression of the disease is slower than the classical sort of the disease.

RELATED DISORDERS

Wernicke syndrome and *korsakoff syndrome* are related disorders that occur due to a deficiencyof thiamine (vitamin B1).

Wernicke's syndrome, also known as Wernicke encephalopathy, is a neurological disease characterized by the inability to coordinate voluntary movement (ataxia), and eye (ocular) abnormalities.

Korsakoff's syndrome is a neurological disorder which is characterized by a disproportionate memory loss in relation to other mental aspects.

Batten disease, a rare genetic disease, belongs to a group of progressive degenerative neurometabolic disorders referred to the neuronal ceroid lipofuscinoses.

The Neuronal Ceroid Lipofuscinoses (NCLs) are characterized by abnormal accumulation of

certain fatty, granular substances within nerve cells (neurons) of the brain and also on other tissuesof the body which will end in progressive deterioration (atrophy) of certain areas of the brain, neurological impairment, and other characteristic symptoms and physical findings. The symptoms of Batten disease are progressive loss of vision, seizures, and progressive neurological degeneration develop. In some cases, initial symptoms may be more vague and include clumsiness,balance problems and behavioral or personality changes.

Tay-Sachs disease is a rare, neurodegenerative disorder in which deficiency of an enzyme (hexosaminidase A) results in excessive accumulation of certain fats (lipids) known as gangliosides in the brain and nerve cells. This abnormal accumulation of gangliosides leads to progressive dysfunction of the central nervous system. This disorder is labelled as a lysosomal storage disease. Symptoms associated with Tay-Sachs disease may include an exaggerated startle response to sudden noises, listlessness, psychomotor regression and severely diminished muscle tone (hypotonia). With disease progression, affected infants and children may develop cherry-red spots within the central layer of the eyes, gradual loss of vision, and deafness, increasing muscle stiffness and restricted movements (spasticity), eventual paralysis, uncontrolled electrical disturbances in the brain (seizures), and deterioration of cognitive processes (dementia).

MOLECULAR BASIS OF LEIGH SYNDROME

Mitochondria are a very particular multitask organelle with their own functioning. Composed by two membranes and a circular DNA (mtDNA), they command cellular energy production throughtricarboxylic acid cycle (TCA) and electron transport chain (ETC), which is the main feature to generate ATP with in the aerobic metabolism through an oxidative phosphorylation (OXPHOS), depending mainly on their inner membrane integrity to accomplish the whole process. ETC occurs with electron transport in changing membrane potentials, ion flux associated with cofactors, as riboflavin and coenzyme Q10, and generate ATP to sustain cellular demands. Any damage in OXPHOS will diminish considerably energy supplies in high energy demand organs. Replicationand homeostasis are a dynamic bioprocess and may lead to accumulation of pathogenic variants.

TREATMENT

Till date there are no proven therapies for Leigh Syndrome of any type. Due to the fact that LS israre, and patients often die during early childhood, the treatment of Leigh syndrome is directed towards the specific symptoms that are apparent in each individual.

Drug Treatment

Substances like *'Nutraceuticals'* have been proposed for the treatment of either LS or other mitochondrial disorders. These drugs include – co-enzyme Q10, L-carnitine, α-lipoic acid, creatine-monohydrate, biotin, thiamine, riboflavin and others. Due to their antioxidant properties,or their functioning as *OXPHOS* complex cofactors.

However, in every patient with suspected LS, a high dose of biotin treatment (10 up to 20 mg/kg) and thiamine (100– 300 mg) should be given immediately, since *BBGD* (Biotin responsive basal ganglia disease) can clinically imitate LS and this treatment is potentially lifesaving.

In patients suffering from LS treatment with *coenzyme Q10* and its synthetic derivative idebenone and EPI-743 shows a promising effect since coenzyme Q10 deficiency is considered as a treatablemitochondrial disease.

In cases of decreased carnitine or creatine concentration, or increased creatine loss, supplementation of retinoic acid and vitamin E can be used, due to their antioxidant effect.

In an adult LS patient, *obstructive sleep apnoea* was successfully treated with high doses of thiamine, coenzyme Q10, L-carnitine and vitamins C and E combined with continuous positive airway pressure.

Dietary Treatment

Secondary deterioration of mitochondrial function has been reported in patients with anorexia and malnutrition. Inadequate nutrition, failure to thrive and feeding problems are very common symptoms in children with primary OXPHOS defects. An age/activity-appropriate *diet and energy intake* has been suggested in patients as an standard intervention protocol who arediagnosed with mitochondrial dysfunction.

For treatment of *PDHC* (Pyruvate Dehydrogenase Complex Deficiency), a possible underlyingcause of LS, ketogenic diets have often been.

Further Oral sodium bicarbonate or sodium citrate may also be prescribed to manage *lacticacidosis.*

In problems like *dysphagia and respiratory dysregulation* due to brain stem lesions, which

require the placement of a nasogastric tube/percutaneous endoscopic gastrostomy or a tracheostoma.

Respiratory dysrhythmias and central hypoventilation with apnoea requires home-care ventilatory support devices and should be monitored by polysomnography.

Genetic counseling is recommended for families of affected individuals with this disorder.

CONCLUSION

Leigh Syndrome is a rare devastating neurodegenerative disorder, typically manifest in infancy orearly childhood. However the exact mechanism is unclear. The main feature of this disease are symmetrical lesions in the basal ganglia or brain stem on MRI and a clinical course with rapid deterioration of cognitive and motor functions. The causatives can be described as mutations in mitochondrial and nuclear genes, encoding components of the oxidative phosphorylation system and dysfunction in the pyruvate dehydrogenase complex or coenzyme Q10 metabolism. There is no definitive treatment for cure and prevention for the affected patients, but have some tentative treatment which is administered to slow the progression of disease.

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