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GENETIC AND CLINICAL INSIGHTS INTO LEIGH SYNDROME: MECHANISMS AND DIAGNOSIS

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Abstract. *Leigh syndrome is one of the illnesses that is caused by genetic mutation that leads to a defect in mitochondrial energy production and it affects the central nervous system, typically appearing in infancy. It is a heterogeneous disorder and encoded by two genomes: mitochondrial and nuclear. Leigh Syndrome is a rare and serious disease that mostly affects young children. It happens when problems in the mitochondria, the parts of cells that make energy, stop the body from working properly. This article covers information about the history of this disorder and explains what the mitochondria is. Types, features and diagnosis of the leigh syndrome are explained after that.*

Key words: *leigh syndrome, disorder, mitochondria, energy production, DNA, metabolism, gene, genome*

Аннотация. *Синдром Ли — одно из заболеваний, вызванных генетической мутацией, приводящей к дефекту в митохондриальном производстве энергии, и оно поражает центральную нервную систему, обычно проявляясь в младенческом возрасте.*

Это гетерогенное расстройство, кодируемое двумя геномами: митохондриальным и ядерным. Синдром Ли — редкое и серьезное заболевание, которое чаще всего поражает маленьких детей. Оно возникает, когда проблемы в митохондриях — частях клеток, вырабатывающих энергию, — нарушают нормальную работу организма. В данной статье представлена информация об истории этого расстройства и объясняется, что такое митохондрии. Далее рассматриваются типы, особенности и диагностика синдрома Ли.

Ключевые слова: *синдром Ли, расстройство, митохондрии, производство энергии, ДНК, метаболизм, ген, геном.*

INTRODUCTION

Leigh syndrome is named after Archibald Denis Leigh, a British neuropsychiatrist who first described the condition in 1951.

Leigh syndrome is a severe neurological disorder that usually becomes apparent in the first year of life. This condition is characterized by progressive loss of mental and movement abilities (psychomotor regression) and typically results in death within two to three years, usually due to respiratory failure. A small number of individuals do not develop symptoms until adulthood or have symptoms that worsen more slowly.

The first signs 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 contractions (dystonia), and problems with movement and balance (ataxia).

Loss of sensation and weakness in the limbs (peripheral neuropathy), common in people with Leigh syndrome, may also make movement difficult.

Leigh syndrome affects an estimated 1 in 40,000 individuals. In the Faroe Islands, the incidence is higher (1 in 1,700 individuals)

MITOCHONDRIA

Mitochondria are the “powerhouses” of our cells, responsible for producing about 90% of the energy needed to sustain life. These tiny organelles are found in nearly all the cells of the body, except red blood cells, and play a crucial role in converting the food we eat and the oxygen we breathe into energy that powers cellular functions.

When mitochondria don’t work properly, it leads to mitochondrial diseases, where the body’s cells cannot generate enough energy to function effectively, often resulting in severe health issues

TYPES OF LEIGH SYNDROME

The types of Leigh syndrome include:

- **Early-onset (infantile):** The most common form of Leigh syndrome appears before age 2. Providers also call it classical Leigh syndrome or infantile necrotizing encephalopathy. The condition affects boys and girls equally.
- **Late-onset (adult-onset):** Symptoms appear after age 2 and may not occur until adolescence or early adulthood. Adult-onset Leigh syndrome is rare. The condition affects more males than females. The disease progresses slower than the infantile type.
- **Leigh-like syndrome:** A person has some symptoms of Leigh syndrome but imaging scans don’t detect signs of the disease.

Pathophysiological aspects of OXPHOS disorders

A key function of mitochondria is to produce energy via the oxidative phosphorylation (OXPHOS) pathway. This process takes place at the inner mitochondrial membrane and is executed by four respiratory chain complexes (reduced nicotinamide adenine dinucleotide (NADH) ubiquinone reductase=complex I, succinate ubiquinone reductase=complex II, ubiquinol cytochrome c oxidoreductase=complex III and cytochrome c oxidase=complex IV).

Within the respiratory chain, coenzyme Q10 (ubiquinone) functions as an electron carrier from complex I and II to complex III. The energy released by electrons flowing through the respiratory chain is used to transport protons across the inner mitochondrial membrane.

The proton gradient, generated by this translocation, and the ensuing inward-negative mitochondrial membrane potential across the inner mitochondrial membrane provide the driving force for ATP synthesis by complex V (adenosine triphosphate (ATP) synthase).

Of note, cells which require high amounts of OXPHOS-derived energy, such as muscle cells and neurons, are specifically vulnerable to mitochondrial dysfunction.

LS may be associated with deficiencies of any OXPHOS enzyme (isolated or in combinations). Underlying mutations may be found in the nuclear DNA or mitochondrial DNA (mtDNA). Coenzyme Q10 deficiency and disturbed pyruvate metabolism are also known causes of LS. OXPHOS deficiency may lead to lactic acidosis/academia.

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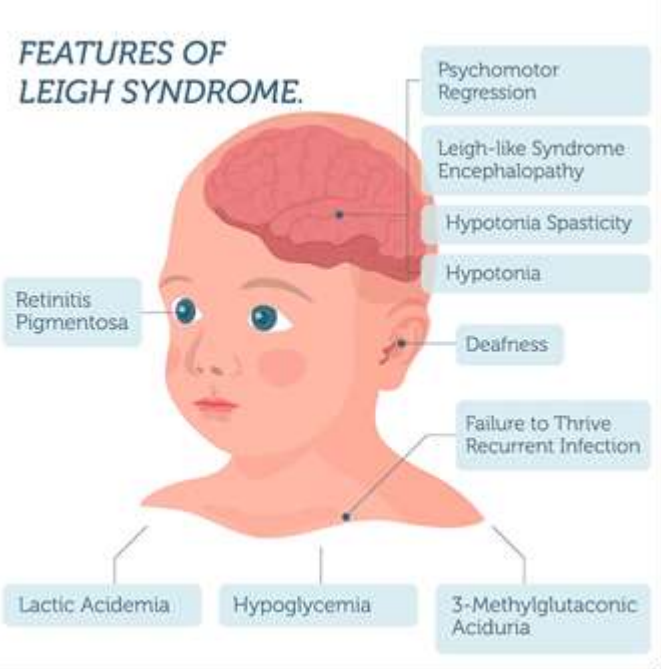
Pyruvate accumulates, and is eventually metabolised to lactate by the lactate dehydrogenase, or transaminated to alanine by the alanine aminotransferase which leads to an increase of these two substances in blood, urine and cerebrospinal fluid (CSF).

Further effects of respiratory chain deficiency include increased generation of reactive oxygen species, disturbed intracellular calcium homoeostasis and altered mitochondrial morphology.

FEATURES OF LEIGH SYNDROME



CAUSES OF LEIGH SYNDROME

Our DNA is made up of DNA in the nucleus of our cells (nuclear DNA, half of which is inherited from the father and half of which is inherited from the mother, and mitochondrial DNA (which is in the mitochondria, inherited from the mother).

Leigh syndrome can be caused by nearly 100 nuclear DNA genes and 16 mitochondrial DNA genes, with more genes continuing to be discovered. Your doctor may order some genetic tests in blood (or a cheek swab, or a urine sample) in order to arrive at the exact genetic diagnosis.

Experts have identified mutations in more than 75 different genes that can cause Leigh syndrome. The gene mutations affect your body's ability to make ATP.

An estimated 8 in 10 children with Leigh syndrome inherit the gene change that causes the condition through one of two ways:

- **Autosomal recessive disorder:** A child inherits the same gene mutation from each parent. The parents are carriers of the changed gene, but they don't have the disease.
- **X-linked recessive genetic disorder:** A gene change on an X chromosome causes the condition. It can come from the biological mother or father. If one of the mother's two X chromosomes has the gene change, there's a 1 in 4 chance that her son or daughter will inherit the mutated gene. If a boy inherits the gene change, they'll develop Leigh syndrome; a girl will not.

However, a daughter can pass the defective gene to her future children. A father can pass a changed X chromosome to his daughter, but not to his son.

GENETIC DIAGNOSIS

Mitochondrial disorders show a very broad spectrum of clinical and biochemical features and involve hundreds of genes encoded both by the mtDNA and by the nuclear DNA.

Therefore, finding the causal genetic defect in individual patients with suspected mitochondrial disease can be a challenge. A minority of mitochondrial patients displays a recognisable combination of features that are characteristic of specific mitochondrial syndromes.

In those patients, direct sequence analysis of the appropriate gene is indicated. These include the 'classical' mitochondrial diseases caused by specific mutations in the mtDNA, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes) syndrome, or NARP (neuropathy, ataxia and retinitis pigmentosa) syndrome, but also more recently, genetically characterised mitochondrial diseases caused by nuclear DNA mutations, such as Sengers syndrome or MEGDEL syndrome. In the majority of suspected cases of mitochondrial disease, this strategy is not an option, because the clinical features are not very specific, or the number of candidate genes is too large. For example, there are currently 64 entries in OMIM, which include the term 'LS' (http://www.omim.org).

As a starting point, full sequence analysis of the mtDNA often is the first step in the genetic diagnosis of suspected mitochondrial patients, including Leigh(-like) syndrome patients.

The mtDNA is preferably isolated from clinically and/or biochemically affected tissue, usually muscle, as it can be expected that the percentage of heteroplasmy of a presumed mtDNA mutation is sufficiently high to be detectable in those tissues. If there is evidence for mtDNA depletion, but mtDNA mutations are not detectable, *POLG* gene mutations have to be taken into account. This nuclear gene encodes polymerase gamma, a mtDNA polymerase responsible for mtDNA replication and repair. Its deficiency can cause phenotypes like Alper's syndrome and LS.

In case mtDNA mutations have been excluded, the next step is to select candidate nuclear genes for sequence analysis. The selection of genes is based on the clinical and biochemical features of the patient. Usually, there are multiple candidate genes, the number can even be as high as 60 or 70 genes in certain cases, for example, in a complex I deficient patient. The conventional strategy is to sequence the most frequently mutated genes from the selected candidate genes. For complex I deficiency, this usually includes *NDUFV1*, *NDUFS1*, *NDUFS2*, *NDUFS4* and *NDUFS7*. If negative, patients enroll research cohorts for further genetic testing of other candidate genes on a research base. At present, this strategy is rapidly evolving as next-generation sequencing (NGS) technologies, that allow parallel sequencing of multiple candidate genes or even entire exomes, are increasingly being applied. In recent years, NGS has been successfully applied to identify novel mitochondrial disease genes (examples: *ACAD9*, acyl glycerol kinase, *MTFMT* and *SERAC1*). Although NGS technology is still considered a research tool by many laboratories, diagnostic application of, for example, whole exome sequencing is also becoming available. This will dramatically change the genetic diagnosis of mitochondrial disorders, as it will make screening of all candidate genes by a single diagnostic test possible

CONCLUSION

Leigh syndrome is a rare but severe neurodegenerative disorder primarily affecting infants and young children, characterized by progressive neurological decline due to impaired mitochondrial energy production.

As a genetically heterogeneous condition, it involves mutations in both nuclear and mitochondrial DNA, reflecting the complexity of its inheritance patterns and clinical presentation.

The central role of mitochondria in ATP synthesis highlights why tissues with high energy demands, such as the brain and muscles, are particularly vulnerable.

Advances in understanding the pathophysiology of oxidative phosphorylation (OXPHOS) defects have provided deeper insight into the mechanisms underlying the disease, including lactic acidosis, oxidative stress, and cellular dysfunction. Despite its rarity, Leigh syndrome poses significant diagnostic challenges due to its broad spectrum of symptoms and the large number of genes involved. However, modern genetic approaches, especially next-generation sequencing technologies, have greatly improved the ability to identify causative mutations and enhance diagnostic accuracy.

In conclusion, continued research into mitochondrial function, genetic mutations, and innovative diagnostic techniques is essential for earlier detection, better management, and the future development of targeted therapies for Leigh syndrome.

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