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MITOCHONDRIAL DYSFUNCTION IN LEIGH SYNDROME: FROM GENETIC BASIS TO THERAPEUTIC APPROACHES

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Abstract. Leigh syndrome (LS), also known as subacute necrotizing encephalomyelopathy, is a rare, genetically determined metabolic disorder caused by primary or secondary dysfunction of the mitochondrial electron transport chain. It typically manifests in early childhood, before the age of two, primarily affecting the nervous system and often resulting in premature death. Mouse models with silenced *NDUFS4* genes demonstrate symptoms similar to human LS, including ataxia, growth retardation, respiratory dysfunction, and elevated lactate levels in the blood and cerebrospinal fluid, with mortality rates reaching 90%. LS inheritance patterns include autosomal recessive, mitochondrial, or X-linked recessive mechanisms. Most cases involve mutations in nuclear DNA, with fewer linked to mitochondrial DNA (mtDNA). Over 75 causative genes have been identified, with *MT-ATP6* mutations being the most common, responsible for maternally inherited Leigh syndrome (MILS). Diagnostic approaches include prenatal testing, brain imaging (e.g., magnetic resonance imaging), and biochemical tests measuring lactate in blood and cerebrospinal fluid. There is currently no effective treatment; available therapies focus on vitamin supplementation and symptom management to improve patients' quality of life. This study aims to review current knowledge on Leigh syndrome, including its etiology, clinical presentation, diagnostic methods, and available therapies. Emphasis is placed on the disorder's genetic basis and the diversity of mutations involved, providing insights into the underlying mechanisms and potential research directions.

Key words: Leigh syndrome, mitochondrial disease, gene mutations, mtDNA, electron transport chain.

INTRODUCTION

Mitochondria play a critical role in various cellular processes, such as regulating cellular metabolism, apoptosis, energy production, lipid biosynthesis, and generating reactive oxygen species. They are present in every cell of the body, and their dysfunctions can lead to severe disruptions in homeostasis. Mitochondrial dysfunction results in reduced energy supply to cells, particularly affecting tissues, and organs with high energy demands, such as the brain, heart, and muscles (Protasoni et al. 2021). Mitochondrial diseases are most often genetically determined metabolic disorders caused by mutations in mitochondrial DNA or nuclear genes and occur in humans and animals. Their prevalence is estimated to be approximately 1 in

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5000. Mitochondrial DNA encodes 13 proteins that are components of the oxidative phosphorylation system. A mutation in even a single gene encoding a mitochondrial protein will most commonly result in dysfunction of the mitochondrial respiratory chain's function and structure (Parikh et al. 2015; Ng and Turnbull 2016; Russell et al. 2020; Hong et al. 2023).

Patients affected by mitochondrial disease present a diverse range of multisystemic symptoms that can involve virtually any organ in the body, making diagnosis and treatment particularly challenging (Rahman 2020; Russell et al. 2020). Effective therapies for mitochondrial diseases are still lacking, and treatment is primarily symptomatic and supportive, often involving supplementation with vitamins and cofactors (Ng and Turnbull 2016; Hirano et al. 2018).

This review article describes the genetics of Leigh syndrome, along with its allelic variants, and disease characteristics including an animal model.

GENETICS OF LEIGH SYNDROME

Leigh syndrome (LS) can be inherited in an autosomal recessive manner, maternally (mitochondrially), or as an X-linked recessive trait. It may result from mutations in over 75 different genes (Liang et al. 2021). These mutations can affect both nuclear and mitochondrial genomes, involving all complexes of the respiratory chain. The majority of patients with Leigh syndrome have mutations in nuclear DNA, while approximately 25% have mutations in mtDNA (Ruhoy and Saneto 2014). These mutations most commonly affect subunits of the mitochondrial respiratory chain, but can also involve genes related to the replication, transcription, and translation of mtDNA.

The most common cause of LS is a mutation in the *MT-ATP6* gene (~40%), followed by mutations in the *MT-ND3* (~20%), *MT-ND5* (~15%), *MT-ND6* (~10%), *MT-ND4* (~5%), *MT-ND1* (<5%) and *MT-TL1* (<5%) genes (Bonfante et al. 2016; Sofou et al. 2018; Ganetzky et al. 2019; Liang et al. 2021). All mutations related to Leigh syndrome in mtDNA have been compiled and presented below (Table 1).

Table 1. Mutations in mitochondrial genes in Leigh syndrome

Gene	Allelic variants	Gene	Allelic variants
MT-ATP6	m.8993T>G	*MT-ND5*	m.13513G>A
	m.8993T>C		m.13042G>A
	m.9176T>C		m.13084A>T
	m.9176T>G		m.13045A>C
	m.9185T>C		m.12706T>C
MT-ND1	m.3460G>A		m.13514A>G
MT-ND2	m.4681T>C	*MT-ND6*	m.14459G>A
MT-ND3	m.10191T>C		m.14484T>C
	m.10197G>A		m.14487T>C
	m.10158T>C		m.14600G>A
MT-ND4	m.11984T>C	*MT-TL1*	m.3243A>G
	m.11777C>A		

MUTATION IN THE *MT-ATP6* GENE

The *MT-ATP6* gene is located on mitochondrial DNA and encodes subunit 6 of ATP synthase, which is part of complex V of the respiratory chain. It is situated between nucleotide pairs 8527 and 9207 of the mitochondrial genome and has a length of 0.68 kb (Anderson et al. 1981; Wallace 1989).

The most common mutation leading to the disease is m.8993T>G, which results in a strictly conserved change from leucine 156 to arginine (Leu156Arg) in the ATP6 protein, as noted in 56 pedigrees (Finsterer 2008; Su et al. 2021). Less common mutations include m.8993T>C, which substitutes leucine 156 with proline (Leu156Pro), m.9176T>C (Leu217Pro), m.9176T>G (Leu217Arg), and m.9185T>C (Leu220Pro) (Finsterer 2008).

MUTATION IN THE *MT-ND* GENE

It has been indicated that nearly all subunits of complex I encoded by mtDNA (ND1, ND2, ND3, ND4, ND5, and ND6) are associated with the occurrence of Leigh syndrome. Most of these subunits are encoded by the guanine-rich heavy strand of mtDNA and do not contain introns (Anderson et al. 1981).

MT-ND1

The *MT-ND1* gene encodes one subunit of the NADH dehydrogenase complex. The gene has a length of 0.96 kb of continuous coding sequence, does not contain introns, and is located between nucleotide positions 3306 and 4262. It features a 5' untranslated region of two bases (AC), with the start codon being methionine ATA and the stop codon being UAA (Anderson et al. 1981; Wallace 1989).

In the ND1 subunit, there is only one mutation associated with the occurrence of Leigh syndrome – m.3460G>A (Ala52Thr), which has thus far been detected in a single patient (Finsterer 2008).

MT-ND2

Subunit 2 of the mitochondrial NADH: oxidoreductase complex is encoded by a gene located between nucleotides 4470 and 5511. The gene has a length of 1.04 kb of continuous coding sequence. It begins with the start codon ATT and ends with the stop codon UAA (Anderson et al. 1981; Wallace 1989).

The mutation in the *MT-ND2* gene results in the substitution m.4681T>C (Leu71Pro), which has so far been detected in only one patient (Finsterer 2008).

MT-ND3

The *MT-ND3* gene encodes one of the seven subunits of NADH dehydrogenase. It is located between nucleotide positions 10059 and 10404 and has a length of 0.35 kb of continuous coding sequence. It begins with the start codon AUG and ends with the terminating codon UAA (Anderson et al. 1981; Wallace 1989).

Point mutations in the *MT-ND3* gene, specifically m.10191T>C (Ser45Pro), are associated with Leigh syndrome due to a deficiency in complex I of the respiratory chain (Nesbitt et al. 2012). Within this subunit, substitutions such as m.10197G>A (Ala47Thr), which have been

documented in three pedigrees, and m.10158T>C (Ser34Pro) have also been observed (Finsterer 2008; Leng et al. 2015).

MT-ND4

The mitochondrial-encoded ND4 subunit of the NADH oxidoreductase complex spans 1377 nucleotide pairs and is located between nucleotide positions 10760 and 12137. The *MT-ND4* reading frame is continuous, without introns, and ends with the stop codon UAA. It has an associated gene *MT-ND4L* (Anderson et al. 1981; Wallace 1989).

Two mutations have been observed in the ND4 subunit: m.11984T>C (Tyr409His) and m.11777C>A (Arg340Ser) (Finsterer 2008; Schubert and Vilarinho 2020).

MT-ND5

The *MT-ND5* gene encodes one of the seven subunits of complex I of the respiratory chain. It has a length of 1.81 kb of continuous coding sequence and is located between nucleotide positions 12337 and 14148. It begins with the start codon AUA for methionine and ends with the stop codon UAA. An additional 521 nucleotide pairs extend as a 3' untranslated region, which is an antisense sequence of the *MT-ND6* gene (Anderson et al. 1981; Wallace 1989).

The ND5 subunit is characterized by the highest number of allelic variants, with the most common being m.13513G>A (Asp393Asn). Less frequently observed variants include m.13042G>A (Ala236Thr), m.13084A>T (Ser250Cys), m.13045A>C (Met237Leu), m.12706T>C (Phe124Leu), and m.13514A>G (Asp393Gly) (Finsterer 2008; Liang et al. 2021).

MT-ND6

Another subunit of complex I of the respiratory chain is ND6, encoded by the guanine-rich light strand of mtDNA and is located between nucleotide positions 14149 and 14673. It has a length of 0.52 kb of continuous coding sequence, beginning with the start codon AUG for methionine and ending with the stop codon UCG (Anderson et al. 1981; Wallace 1989).

The ND6 subunit exhibits four allelic variants: m.14459G>A (Ala72Val), m.14484T>C (Met64Val), m.14487T>C (Met63Val), which has been detected in four patients, and m.14600G>A (Ser467Asn) (Finsterer 2008).

MUTATION IN THE *MT-TL1* GENE

The *MT-TL1* gene encodes tRNA leucine (UUR), with a length of 0,07 kb, located between nucleotide positions 3230 and 3304.

The only variant mutation within this gene is m.3243A>G, which leads to impaired protein synthesis and negatively affects the function of the entire respiratory chain and ATP production (Janssen et al. 2007).

GENE FUNCTION

The *MT-ATP6* gene provides the information necessary for the production of subunit 6 of ATP synthase, a protein essential for proper mitochondrial function. Specifically, this subunit is a key component of the proton channel and plays a direct role in proton transport across

the membrane. It is part of complex V of the mitochondrial respiratory chain. The function of ATP synthase is to catalyze the final stage of oxidative phosphorylation, where energy from the proton gradient is used to synthesize adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate (Pi) (Jonckheere et al. 2012). Mutations in this gene cause the most common maternally inherited form of Leigh syndrome (MILS), which is the most frequent mtDNA mutation A diagnosis of MILS is made when an individual exhibits more than 90% mtDNA heteroplasmy in their cells (Ruhoy and Saneto 2014).

The *MT-ND* genes (*MT-ND1*, *MT-ND2*, *MT-ND3*, *MT-ND4*, *MT-ND4L*, *MT-ND5*, *MT-ND6*) encode the subunits of complex I of the respiratory chain. Complex I is the initial step in the electron transport chain of the mitochondrial oxidative phosphorylation system (OXPHOS) and is responsible for transferring electrons from NADH to ubiquinone (coenzyme Q) through a series of carriers (Okoye et al. 2023). Mutations in complex I can lead to severe dysfunction of the respiratory chain and have been identified as the cause of most cases of Leigh syndrome. It has been observed that three mtDNA genes (*MT-ND2*, *MT-ND3*, *MT-ND5*) are significantly implicated in Leigh syndrome, with mutations in *MT-ND3* and *MT-ND5* being the most common in the disease (Bakare et al. 2021).

The *MT-TL1* gene provides the information necessary for the synthesis of a specific form of tRNA, designated as mt-tRNA$^{Leu(UUR)}$. This tRNA function is to deliver leucine to mitochondrial ribosomes, where leucine is incorporated into the growing polypeptide chain during translation (Maniura-Weber et al. 2006). Mutations in this gene result in a deficiency in the electron transport chain. Both normal (3243A) and mutated (3243G) mtDNA can coexist within a single cell in a state of heteroplasmy. A high level of heteroplasmy (approximately 90%) leads to the development of Leigh syndrome and can result in early infantile death (Kandel et al. 2017).

ANIMAL MODEL FOR LEIGH SYNDROME

Deficiency of mitochondrial complex I, associated with Leigh syndrome, is induced by pathogenic mutations in the *NDUFS4* gene, which is encoded by nuclear DNA. This mutation results in the absence of the NDUFS4 protein in humans. It is inherited in an autosomal recessive manner, leading to its presence in every cell. Mouse models of Leigh syndrome have been created with the *NDUFS4* gene knocked down by the deletion of exon 2, causing a frameshift and preventing the production of the NDUFS4 protein. Mice with induced Leigh syndrome exhibit hair loss after 21 days of birth, attributed to elevated levels of inflammatory marker mRNA in the skin (Van De Wal et al. 2022). By 30 days, these mice become lethargic, exhibit developmental stagnation, show inhibition of growth, begin to lose vision, and develop severe ataxia, leading to loss of balance and uncoordinated gait. Additionally, there was an increase in lactate levels in the cerebrospinal fluid and blood, respiratory problems, and hypothermia (Kruse et al. 2008; Quintana et al. 2012; Van De Wal et al. 2022). Mice with induced Leigh syndrome typically die between 35 and 50 days of age. Tests reveal bilateral spongiform lesions in the vestibular nuclei and neurodegeneration in other brain regions. This encephalopathy leads to a drastic reduction in lifespan, with mortality exceeding 90% in model mice by 50 days of age (Quintana et al. 2012; Van De Wal et al. 2022).

LEIGH SYNDROME

Leigh syndrome, also known as subacute necrotizing encephalomyelopathy, is a rare, incurable, and genetically determined metabolic disorder. It primarily affects the central nervous system and

manifests between 3 and 12 months of age (Ruhoy and Saneto 2014; Chang et al. 2020). The disease was first described by Denis Leigh in 1951 and was characterized by focal, bilaterally symmetric, and subacute necrotic lesions in the thalamus, brainstem, and posterior columns of the spinal cord (Leigh 1951). The condition is caused by primary or secondary dysfunction of the mitochondrial electron transport chain (Finsterer 2008; Sofou et al. 2014). In 79.7% of patients, deficiencies in respiratory chain enzyme complexes have been observed, with complex I deficiency accounting for 35% and complex IV deficiency for 16% (Chang et al. 2020). Excessive burden on the mitochondrial respiratory chain triggers pathogenic processes. Disruptions in proton and electron flow lead to the production of reactive oxygen species (ROS), resulting in oxidative stress and inflammatory processes. Persistent stress and inflammation ultimately cause cell death, mutations in mtDNA, and the development of symptoms associated with Leigh syndrome (Bakare et al. 2021).

SIGNS AND SYMPTOMS

Symptoms of LS can be diverse, but they most commonly affect the nervous system. These include developmental delay (57%), hypotonia (42%), movement disorders such as ataxia, respiratory dysfunction (34%), seizures (33%), feeding difficulties (29%), and general weakness (27%) (Finsterer 2008; Baertling et al. 2014; Chang et al. 2020). Feeding difficulties result in poor weight gain, observed in approximately 40% of patients. In addition to neurological symptoms, ocular manifestations such as ophthalmoplegia (25%), optic atrophy (15%), and retinopathy (10%) may also occur (Wei et al. 2018; Ardissone et al. 2023). The most frequently observed symptom is elevated lactate levels in blood or cerebrospinal fluid (72%). Cardiological manifestations, such as hypertrophic cardiomyopathy or dilated cardiomyopathy, are also reported (Sofou et al. 2014; Schubert et al. 2020). Pathological changes associated with the disease include demyelination, spongiosis, gliosis, and necrosis of capillaries. Consequently, the brainstem, which regulates and maintains basic life functions (breathing, circulation, and swallowing), and the cerebellum, which is responsible for movement and balance, become damaged (Chang et al. 2020).

HETEROPLASMY

The heterogeneous nature of Leigh syndrome can be partially attributed to the complex nature of the mitochondrial electron transport chain, which consists of subunits encoded by both nuclear DNA and mitochondrial DNA. Given that mitochondria do not follow Mendelian inheritance patterns, both normal and mutated mtDNA can coexist within a cell, creating a phenomenon known as heteroplasmy. Heteroplasmy contributes to the complexity and varied phenotype characteristic of Leigh syndrome, with the disease most commonly manifesting when heteroplasmy reaches approximately 90% (Kandel et al. 2017; Bakare et al. 2021).

DIAGNOSIS

Diagnosis of Leigh syndrome can occur as early as the fetal stage through prenatal testing. These tests aim to assess the risk of developing the disease in the perinatal period and during infancy. If the disease is inherited maternally, the percentage of heteroplasmy in the mother should be determined through blood, urine tests, and chorionic villus sampling (Schubert et al. 2020). The diagnosis of LS involves imaging studies such as MRI (magnetic

resonance imaging of the brain), which is a crucial diagnostic tool, as well as genetic testing and autopsy. MRI visualizes bilateral symmetric damage in the brainstem and cerebellum. Additionally, biochemical tests to measure lactate levels are useful, as the disease often leads to increased lactate concentrations in the blood and/or cerebrospinal fluid (Ruhoy and Saneto 2014; Lee ang Chiang 2021).

FORMS OF THERAPY

Treatment for Leigh syndrome is primarily symptomatic, as there is no effective cure for the disease. Antiepileptic medications are used to prevent further epileptic seizures. Supplementation with coenzyme Q10, thiamine, and biotin is also employed to support mitochondrial function (Ruhoy and Saneto 2014). One therapeutic approach is the ketogenic diet, which provides an alternative source of energy in the form of ketone bodies. These ketones can be more efficiently utilized by mitochondria, reducing oxidative stress, enhancing antioxidant activity, and improving the scavenging of free radicals (Lee ang Chiang 2021).

Gene therapy holds promise for editing genes and treating mitochondrial diseases. Currently, tools such as restriction endonucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR/Cas9 technology are being used for this purpose. The restriction endonuclease SmaI can recognize a specific DNA sequence associated with a mutation and modify it to eliminate the mutated mtDNA (Tanaka et al. 2002; Bakare et al. 2021).

PROGNOSIS

The disease is highly fatal and rapidly progressive, with most patients dying within a few years of diagnosis. Patients who present with the disease before 6 months of age, who exhibit developmental delays and epilepsy, have a lower chance of survival. The primary causes of death are complications related to the respiratory system and progression of Leigh syndrome (Ruhoy and Saneto 2014; Sofou et al. 2014). Even with accurate diagnosis and treatment, survival rates remain low (Schubert et al. 2020).

CONCLUSIONS

Leigh syndrome, due to its heterogeneous nature, remains a challenging mitochondrial disorder to diagnose and treat. Despite ongoing advancements in diagnostic techniques, effective treatments are still lacking. Therefore, it is important to continue research using animal models of the disease to identify appropriate and effective diagnostic and therapeutic strategies.

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DYSFUNKCJA MITOCHONDRIALNA W ZESPOLE LEIGHA: OD PODŁOŻA GENETYCZNEGO DO PODEJŚĆ TERAPEUTYCZNYCH

Streszczenie. Zespół Leigha (LS), inaczej dziecięca podostra encefalomielopatia martwicza, jest rzadką genetycznie uwarunkowaną chorobą metaboliczną, wynikającą z pierwotnej lub wtórnej dysfunkcji mitochondrialnego łańcucha transportu elektronów. Choroba ujawnia się zazwyczaj we wczesnym dzieciństwie, przed ukończeniem 2. roku życia, i głównie dotyka układu nerwowego, często prowadząc do przedwczesnej śmierci. Model myszy z wyciszonym genem *NDUFS4* wykazuje objawy analogiczne do ludzkiego LS, takie jak ataksja, zahamowanie wzrostu, dysfunkcja oddechowa oraz podwyższony poziom mleczanu we krwi i płynie mózgowo-rdzeniowym, z podobnie wysoką śmiertelnością sięgającą około 90%. Zespół Leigha może być dziedziczony autosomalnie recesywnie, mitochondrialnie lub recesywnie w sprzężeniu z chromosomem X, przy czym większość przypadków wiąże się z mutacjami w jądrowym DNA, rzadziej w mitochondrialnym DNA. Zidentyfikowano mutacje w ponad 75 genach, z czego najczęstsze dotyczą genu *MT-ATP6*, odpowiedzialnego za mitochondrialny zespół Leigha (MILS) dziedziczony po matce. Diagnostyka LS obejmuje badania prenatalne, obrazowe (np. rezonans magnetyczny mózgu) oraz biochemiczne, koncentrujące się na poziomie mleczanu we krwi i płynie mózgowo-rdzeniowym. Obecnie brak skutecznej terapii – dostępne leczenie obejmuje suplementację witamin i leczenie objawowe, mające na celu złagodzenie symptomów oraz poprawę jakości życia pacjentów. Celem pracy jest przedstawienie aktualnego stanu wiedzy na temat zespołu Leigha, w tym jego etiologii, obrazu klinicznego, diagnostyki oraz dostępnych metod terapeutycznych. Szczególny nacisk położono na genetyczne podłoże choroby oraz różnorodność mutacji związanych z jej występowaniem, co może przyczynić się do lepszego zrozumienia mechanizmów choroby i potencjalnych kierunków dalszych badań.

Słowa kluczowe: zespół Leigha, choroba mitochondrialna, mutacje genów, mtDNA, łańcuch transportu elektronów.