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Spectrum of Leigh Syndrome: A Portuguese Population in an Evolutionary Genetic Age

Valeria Helen*

Department of Neurology, São João University Hospital, EPE, 4050-011 Porto, Portugal

Introduction

Leigh Syndrome (LS), also known as subacute necrotizing encephalomyelopathy, represents a severe neurological disorder typically diagnosed in infancy or early childhood. It is characterized by progressive degeneration of the central nervous system, leading to developmental regression, movement disorders, seizures and respiratory failure. The syndrome was first described by Archibald Denis Leigh in 1951 and has since been recognized as a heterogeneous disorder with varying genetic causes and clinical manifestations. Leigh syndrome manifests with a wide spectrum of clinical features, which can vary depending on the underlying genetic mutation and its impact on mitochondrial function. Common symptoms include. These often present early in infancy and may include developmental delay or regression, hypotonia (weak muscle tone), ataxia (uncoordinated movements) and seizures. Respiratory distress and failure are common due to the progressive involvement of brainstem respiratory centers. Some patients exhibit abnormal eye movements or optic atrophy. Impaired mitochondrial function leads to metabolic abnormalities, such as lactic acidosis, which can be detected in blood or cerebrospinal fluid. The underlying pathophysiology of Leigh syndrome is primarily associated with mitochondrial dysfunction. Mitochondria are organelles responsible for producing energy in the form of ATP through Oxidative Phosphorylation (OXPHOS). Genetic mutations affecting genes encoding mitochondrial proteins or those involved in mitochondrial DNA (mtDNA) maintenance can disrupt OXPHOS, leading to energy failure and subsequent neurodegeneration [1].

Description

Leigh syndrome is genetically heterogeneous, with mutations identified in both nuclear and mitochondrial genomes. Approximately 75% of cases are associated with mutations in nuclear DNA, affecting genes encoding subunits of the mitochondrial respiratory chain complexes or proteins involved in mitochondrial function. These mutations typically follow autosomal recessive inheritance patterns. Mutations in this gene lead to cytochrome c oxidase deficiency, a key enzyme in the respiratory chain. Mutations in these genes affect various subunits of complex I and II of the respiratory chain. Mutations in SCO2 impair cytochrome c oxidase assembly, leading to respiratory chain dysfunction. In addition to nuclear DNA mutations, Leigh syndrome can also result from mutations in Mitochondrial DNA (mtDNA). These mutations are maternally inherited and can affect any of the mitochondrial genes encoding essential proteins involved in OXPHOS. The severity and progression of Leigh syndrome can vary depending on the specific genetic mutation, with some mutations leading to more severe forms of the disease than others. The prevalence and spectrum of Leigh syndrome can vary across different populations due to genetic diversity and environmental factors. In the context of the Portuguese population, epidemiological studies have provided valuable insights into the genetic landscape and clinical characteristics of Leigh syndrome [2-4].

Estimating the prevalence and incidence of Leigh syndrome within Portugal provides a basis for understanding its burden on the healthcare system and affected families. Analysing the spectrum of genetic mutations associated with Leigh syndrome in Portuguese patients can identify prevalent mutations and genetic hotspots, facilitating genetic counseling and carrier screening. Characterizing the clinical phenotype of Leigh syndrome in Portuguese patients can highlight any unique features or patterns specific to this population, aiding in early diagnosis and management. Evaluating current treatment approaches and clinical outcomes in Portuguese patients with Leigh syndrome can inform strategies for improving patient care and prognosis. Diagnosing Leigh syndrome poses significant challenges due to its heterogeneous presentation and overlap with other neurological disorders. Clinical suspicion based on characteristic symptoms, neuroimaging findings (such as bilateral symmetrical lesions in basal ganglia and brainstem) and biochemical markers (e.g., elevated lactate levels) is crucial for initiating genetic testing. However, genetic testing itself can be complex and costly, requiring specialized laboratories capable of sequencing both nuclear and mitochondrial genomes. Furthermore, treatment options for Leigh syndrome are currently limited to supportive care and symptomatic management, as there are no curative therapies targeting the underlying mitochondrial dysfunction [5].

Conclusion

In conclusion, Leigh syndrome represents a complex and heterogeneous group of disorders characterized by mitochondrial dysfunction and progressive neurological degeneration. In the context of the Portuguese population, understanding the genetic variability, clinical spectrum and epidemiological factors of Leigh syndrome is essential for improving diagnosis, management and patient outcomes. Through comprehensive genetic studies, clinical phenotyping and collaborative research efforts, clinicians and researchers can further elucidate the underlying mechanisms of Leigh syndrome and develop targeted therapies. Ultimately, advancing knowledge in Leigh syndrome not only enhances our understanding of mitochondrial biology but also brings us closer to personalized approaches in the diagnosis and treatment of this devastating neurological disorder. Despite these challenges, ongoing research offers promising avenues for improving the diagnosis, management and understanding of Leigh syndrome. Next-generation sequencing technologies continue to advance, enabling faster and more comprehensive genetic testing for Leigh syndrome and other mitochondrial disorders. Research into mitochondrial-targeted therapies, such as mitochondrial replacement therapies or pharmacological interventions to enhance mitochondrial function, holds potential for future treatment strategies. Tailoring treatment based on individual genetic profiles and disease mechanisms could optimize therapeutic outcomes and improve quality of life for patients with Leigh syndrome. Establishing national or international patient registries and collaborative research networks facilitates data sharing, accelerates genotype-phenotype correlations and promotes clinical trial recruitment

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***Address for Correspondence:** Valeria Helen, Department of Neurology, São João University Hospital, EPE, 4050-011 Porto, Portugal; E-mail: h.valeria709@gmail.com*

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Conflict of Interest

None.

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