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Leigh syndrome: Resolving the clinical and genetic heterogeneity paves the way for treatment options

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ABSTRACT

Leigh syndrome is a progressive neurodegenerative disorder, affecting 1 in 40,000 live births. Most patients present with symptoms between the ages of three and twelve months, but adult onset Leigh syndrome has also been described. The disease course is characterized by a rapid deterioration of cognitive and motor functions, in most cases resulting in death due to respiratory failure. Despite the high genetic heterogeneity of Leigh syndrome, patients present with identical, symmetrical lesions in the basal ganglia or brainstem on MRI, while additional clinical manifestations and age of onset varies from case to case. To date, mutations in over 60 genes, both nuclear and mitochondrial DNA encoded, have been shown to cause Leigh syndrome, still explaining only half of all cases. In most patients, these mutations directly or indirectly affect the activity of the mitochondrial respiratory chain or pyruvate dehydrogenase complex. Exome sequencing has accelerated the discovery of new genes and pathways involved in Leigh syndrome, providing novel insights into the pathophysiological mechanisms. This is particularly important as no general curative treatment is available for this devastating disorder, although several recent studies imply that early treatment might be beneficial for some patients depending on the gene or process affected. Timely, gene-based personalized treatment may become an important strategy in rare, genetically heterogeneous disorders like Leigh syndrome, stressing the importance of early genetic diagnosis and identification of new genes/pathways. In this review, we provide a comprehensive overview of the most important clinical manifestations and genes/pathways involved in Leigh syndrome, and discuss the current state of therapeutic interventions in patients.

Contents

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1. Introduction and history of Leigh syndrome

In 1951, Archibald Denis Leigh (1915–1998) described a devastating, neurodegenerative disorder as Subacute Necrotising Encephalomyelopathy (SNE) which was later designated Leigh syndrome [73]. The patient was a boy who developed normally until the age of six months, at which point he stopped crying, lay very still and was only awake when disturbed. Examinations revealed a bilateral optic atrophy, deafness and bilateral spasticity. The condition of the boy worsened rapidly and he died after a few days due to an encephalopathic illness. Neurological features included neuronal degeneration and gliosis of the thalamus, midbrain, pons, medulla and dorsal spinal cord, as well as loss of

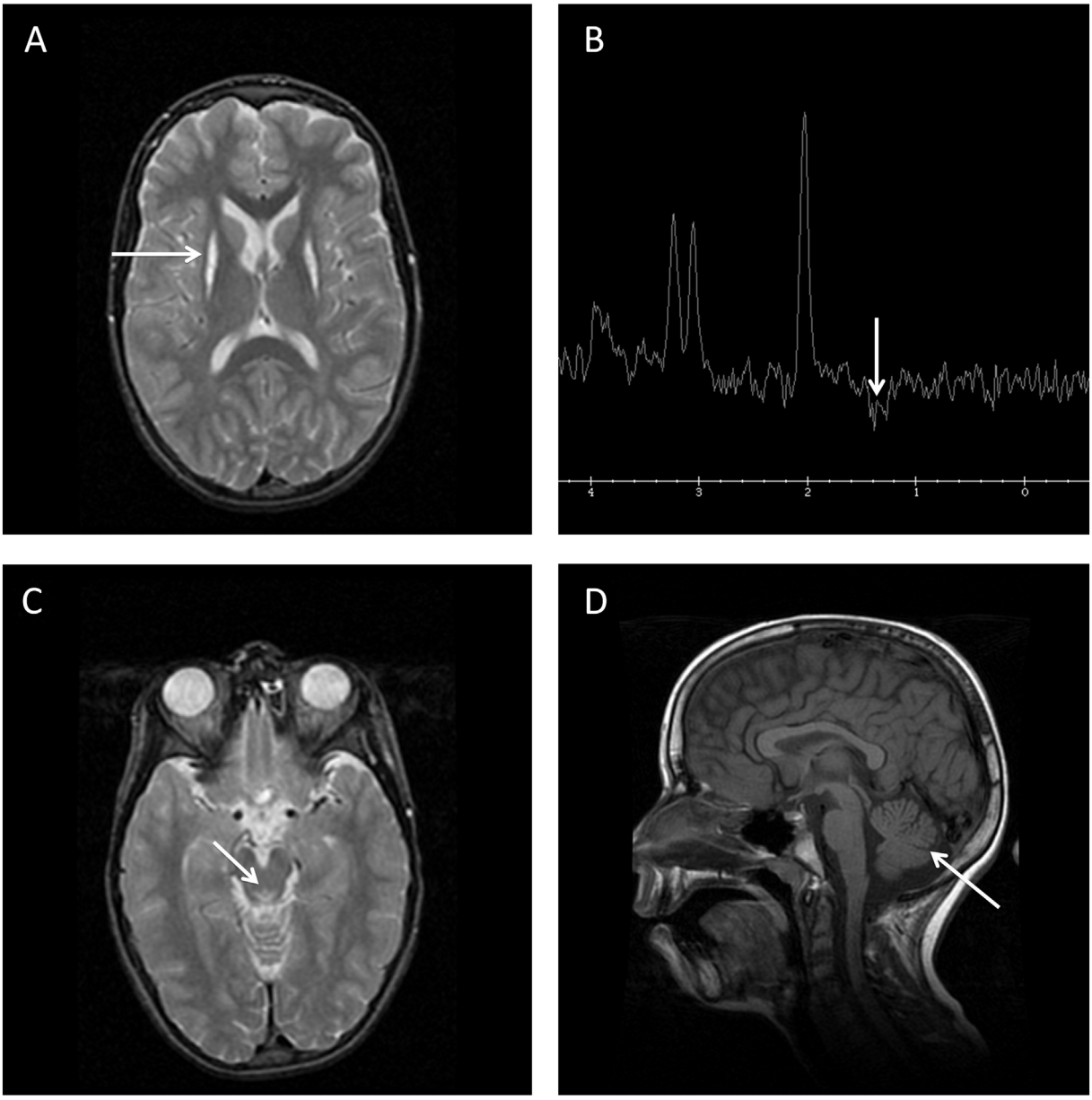

Fig. 1. Magnetic resonance images of the brain representing typical Leigh MRI/MRS pathology. A) Axial T2 weighted brain MRI shows hyperintensity in the putamen (arrow). B) MR-spectroscopy from the basal ganglia shows a lactate peak at 1.35 ppm (arrow). C) Axial T2 with hyperintensity of the periaquaductal region (arrow). D) Sagittal T1 slight cerebellar atrophy (arrow); notice increase in 4th ventricle volume.

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