

Case report

Leigh Syndrome: Report of a Rare Case with Late Onset Presentation

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ABSTRACT

Leigh's syndrome, or sub acute necrotizing encephalomyelopathy, is a rare inherited neurometabolic disease of infancy and early childhood with variable course and prognosis. Rarely, it occurs in juveniles and adults. The diagnosis is difficult and still remains to challenge the clinicians on the basis of history; hence the role of imaging is very essential. It is the neuroimaging, chiefly the Magnetic Resonance Imaging showing characteristic symmetrical necrotic lesions in the basal ganglia and/or brain stem that leads to the diagnosis. Late-onset varieties are rare and only few cases were reported all over the world. Here, I report a case of late onset (juvenile) Leigh syndrome presenting with an acute polyneuropathy. Neuroimaging confirmed it to be a case of Leigh syndrome.

Key words: Leigh syndrome, MRI, Children, Case report.

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Leigh's syndrome, or sub acute necrotizing encephalomyelopathy, described by Leigh in 1951, is characterized by symmetrical necrotic lesions in the central nervous system, involving areas such as the basal ganglia, brainstem, spinal cord and cerebellum. It is a mitochondrial disease related to various enzymatic defects that affect the oxidative metabolism [1,2]. Leigh syndrome is faced in approximately 1 in 40,000 births with no known gender or racial predilection [3]. It affects mainly infants and preschool children. But its presentation is very variable and may occur in children and young adults in atypical manner [2, 4]. The most common symptoms are motor with pyramidal and cerebellar dysfunction [1,5,6]. Beside this, the disease has distinctive findings on neuroimaging and cerebrospinal fluid (CSF) examination [5]. The treatment effectiveness is still controversial, and aims to decrease the anaerobic metabolism [6]. Despite its considerable clinical, genetic and biochemistry heterogeneity, the basic neuropathological features in children affected are almost identical; which are focal, bilateral, and symmetric necrotic lesions associated with demyelination, vascular proliferation and gliosis in the brainstem, diencephalon, basal ganglia, and cerebellum [7]. It is possible to rise the diagnosis of probable Leigh syndrome during life on the basis of clinical signs and symptoms, type of inheritance, metabolic abnormalities, and neuroimaging findings [8]. I report a rare case which presented clinically as a polyneuropathy disorder and diagnosed as Leigh syndrome on MRI.

Case Presentation

A 12-year-old girl, 2nd product of a non-consanguineous marriage, had a history of having started altering in gait. She began to do involuntary movements with the left upper and lower limbs especially when she walked. After six months, the right side was also involved. The patient evolved with progressive worsening in walking, frequent falls, no longer write or eat alone or perform private hygiene care such as bathing or brushing teeth by her. Her father reported unspecific symptoms like attention

deficit, decrease in alertness, and mild attacks of breathlessness, but there is no seizure. The perinatal history was uneventful. Physical examination showed dystonic movement in the 4 limbs, more severe on the left side. His strength, tone or reflexes were normal. Eye movements were normal, with no nystagmus. The fundus and the slit lamp examination were unremarkable. Routine laboratory investigations revealed hemoglobin 9 gm/dL, total leukocyte count 22,400 cells per mm³ with marked neutrophilia (80%) and lymphocyte count 12%. Serum ceruloplasmin and copper were normal while serum lactate (3.4 mmol/L) and creatinine kinase (240 U/L) levels were mildly raised. Liver and renal function tests were within normal limits. Arterial blood gas analysis indicated mild metabolic acidosis. EEG showed slowing on background rhythm and no epileptic activity. The magnetic resonance imaging (MRI) of the brain showed symmetrical hyperintense signals in the basal ganglia, thalami, brain stem and cerebellum on T2- and FLAIR images with no associated atrophic changes (Fig 1). Based on the above clinical, laboratory and imaging findings, the diagnosis of Leigh syndrome was established. Mitochondrial cocktail therapy, including thiamine, riboflavin, and vitamin C, was started. She showed mild improvement at 6-month follow-up, with spasticity mildly reduced, swallowing and breathing function regained, and normal background activity re-established on EEG.

Discussion

Although rare, Leigh syndrome is probably the most common mitochondrial disease in childhood [1,7]. Age of onset of symptoms is usually less than 2 years (infantile form), but others may present in childhood (juvenile form) and unusually in adulthood. In the infantile form (about 50% of cases), symptoms may become apparent within two years of life. In this situation, there may be hypotonia, regression of neuropsychomotor development, ataxia, seizures and breathing dysfunctions [1,2,7]. On the juvenile form, which is much less common, patients have mainly an extrapyramidal

syndrome with dystonia and stiffness. There are no specific markers for this disease, and the lactate's elevation in serum and CSF may not be detected, especially when the patient is not under stress of oxidative metabolism [1]. Its etiology is genetic and is related to an enzyme defect in any part of the cell respiration. The most common defects are biochemical deficiencies of pyruvate dehydrogenase complex, complex IV (or cytochrome C oxidase), in the complex I of respiratory chain or in the ATPase [8,9]. The genetic inheritance of this syndrome may be autosomal recessive, X-linked or mitochondrial [7]. As the sensitivity of genetic tests available is low, in most cases this diagnosis is suspected by MRI, especially in late or atypical forms [1, 9]. Neuroimaging plays an important role in diagnosis of patients with Leigh syndrome [10-12]. Typical imaging findings have been considered to be the diagnostic hallmark and consist of symmetric areas of hyperintense signal on T2 in the basal ganglia (especially the putamen), thalamus, and brainstem nuclei at various levels. It is believed that the preference for such sites is due to an increased metabolic activity in these areas, which are more sensitive to ATP's synthesis failure [10]. These high T2 signals on MRI reflect the spongiform changes and vacuolation in the affected brain structures [11, 12].

In general, the diagnostic criteria of this syndrome are: (1) Progressive neurological disease with motor and intellectual developmental delay; (2) Signs and symptoms of brainstem and/or basal ganglia disease; (3) Raised lactate levels in blood and/or cerebrospinal fluid; (4) Characteristic symmetric necrotic lesions in the basal ganglia and/or brainstem [2, 7-10].

There is currently no effective treatment. The results and prognosis are variable. The aim of symptomatic

treatment is to improve the ATP production and to lower the lactate levels [13-16].

The case described in this report represents atypical form of presentation of this syndrome. In this case, the patient has the onset of symptoms only at the age of 12 years old, characterizing the late form of presentation. Its first manifestation was only the dystonia and the evolution of neurological symptoms was slow and gradual.

This case illustrates how the patient with this syndrome may progress in bursts or a slow and gradual progression. This slow progression seems to occur more frequently in the late form of presentation. Greater knowledge of this entity, might improve the prognosis of these patients, changing the natural history of this disease as well the genetic counseling in prenatal period.

Conclusion: The diagnosis of Leigh's syndrome should be considered in appropriate clinical and laboratory settings whenever symmetrical hyper intensities are encountered in the basal ganglia and brain stem on MRI. Further investigations such as measurement of blood and/or CSF lactate, and respiratory chain enzymes activities should be conducted. Neuro-radiological discriminative observation is very useful in guiding the clinicians for the most appropriate enzymatic and genetic study in their patients.

Conflict of interest: The author declares that there is no conflict of interest.

Consent: Written informed consent was obtained from the father of the patient for publication of this case report and any accompanying images.

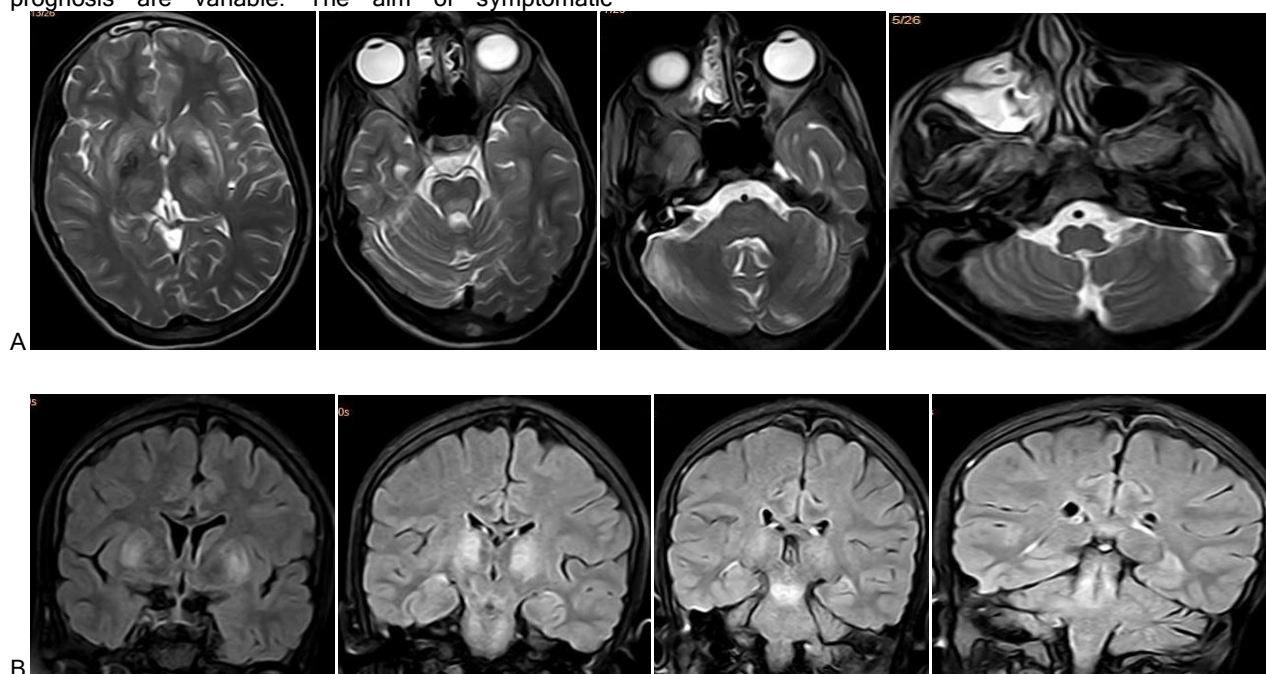


Figure 1: (A) Serial axial non-contrast T2 MR Images and (B): Serial coronal FLAIR images show abnormal bilateral symmetrical hyperintense signals involving the basal ganglia (mainly the putamen), thalamus, cerebellar peduncles, mid brain, pons, medulla and the cerebellum.

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