Adult-onset Leigh's disease: A rare entity

Shaik Afshan Jabeen, G. Sandeep, Kandadai Rukmini Mridula, Angamuttu Kanikannan Meena, Rupam Borgohain, Challa Sundaram[1]

Department of Neurology, Millennium Block, [1]Department of Pathology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Andhra Pradesh, India

Abstract

Leigh syndrome (LS) is a heterogeneous familial or sporadic neurodegenerative disorder. It is typically seen in infancy or childhood, although rare cases of adult onset have been described. The authors describe a 37-year-old woman who presented with protracted gastrointestinal symptoms followed by acute brain stem syndrome with severe metabolic acidosis and who subsequently showed dramatic clinical and neuroradiological improvement.

Key Words

Adult onset, brain stem hyperintensities, bulbar palsy, Leigh's disease, serum lactate

For correspondence:
Dr. Shaik Afshan Jabeen, Department of Neurology, Millennium Block, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 50082, Andhra Pradesh, India.
E-mail: drjabeennims@gmail.com

Ann Indian Acad Neurol 2016;19:140-142

Introduction

Leigh syndrome (LS); also known as Leigh's disease (LD) or subacute necrotizing encephalomyelopathy; is a rare neurodegenerative disorder with a prevalence of 1:100,000 to 1:140,000 births. It is a familial or sporadic mitochondrial disorder characterized by psychomotor regression and lesions in the basal ganglia and brainstem. Some cases display a maternal inheritance, others follow an autosomal (pyruvate carboxylase, SURF1 gene mutations with cytochrome C oxidase (COX) deficiency, and complex I deficiencies) or sex-linked (pyruvate dehydrogenase E1 gene mutations) pattern of inheritance.[1] Over 50% of cases present in the 1st year of life, usually before 6 months of age. Late-onset varieties are rare and only few cases were reported all over the world.[2] Here, we report an adult-onset LD with supportive biochemical and muscle histochemistry evidence, who responded to treatment.

Case Report

A 37-year-old female presented with protracted pain abdomen and vomiting since 3 months; followed by giddiness, headache, and diplopiasince 15 days. There was no fever, seizures, limb weakness, or sensory symptoms. Personal and family history was unremarkable. General and other systemic examination was normal. Neurological examination revealed bilateral horizontal gaze palsy with gait ataxia. Rest of the examination was normal. Magnetic resonance imaging (MRI) brain showed dorsal brain stem (midbrain and pons) T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities. In view of recurrent vomiting, clinical and MRI picture, a diagnosis of Wernicke's encephalopathy was made and she was treated with parenteral thiamine. There was marked improvement and she was discharged. Few days later she presented with diplopia, increased swaying while walking, bulbar palsy, breathlessness, and shock. Arterial blood gas (ABG) analysis showed severe metabolic acidosis. Fasting serum lactate was elevated (8 mmol/L; normal: 0.8-2.4 mmol/L). MRI revealed increased brainstem hyperintensities with MR spectroscopy (MRS) of the lesion showing peak lactate [Figure 1]. Cerebrospinal fluid (CSF) lactate was also elevated (4.4 mmol/L; normal: 1.1-2.3 mmol/L). Hemogram and renal and liver function tests were normal. CSF cytology and biochemistry were normal. Further, metabolic work up revealed normal serum copper, ceruloplasmin, and urine copper levels. Serum aquaporin antibodies were negative. A provisional diagnosis of adult-onset LD was considered and patient was treated with mitochondrial cocktail (intravenous thiamine, coenzyme-Q, riboflavin, L-carnitine, and L-arginine) along with ventilator support for respiratory failure. Patient improved dramatically in neurological symptoms and was slowly weaned from the ventilator. Muscle biopsy revealed reduced COX and COX-succinate dehydrogenase (SDH) activity without any evidence of ragged red fibers [Figure 2]. Muscle biopsy was sent to Centre

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.175437

for Cellular and Molecular Biology (CCMB), Hyderabad, India; where muscle deoxyribonucleic acid (DNA) was extracted and sequential analysis for complete mitochondrial genome was done; no pathogenic mutations were observed, however, nuclear partofmitochondrial DNA (mtDNA) of blood was not analyzed. Repeat MRI after 3 months revealed complete disappearance of the hyperintensities [Figure 3]. A diagnosis of adult-onset LS was made based on classical radiological appearance, biochemical and histochemical evidence, and excellent response to mitochondrial cocktail. At 1-year follow-up, she was asymptomatic neurologically, but had moderate obstructive sleep apnea with an apnea–hypopnea index of 20/h on overnight polysomnography. Cardiac evaluation which included two-dimensional (2D) echocardiogram, treadmill test, and 24-hHolter monitoring were normal.

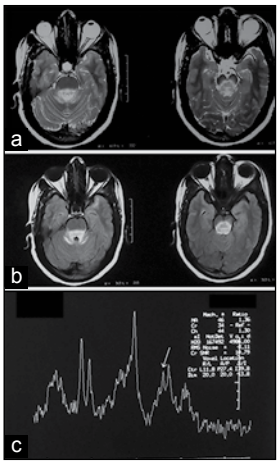

Figure 1: Showing MRI brain T2-weighted (a) and FLAIR (b) showing brainstem and cerebellar peduncle hyperintensities with raised lactate peak in MRS (c). MRI = Magnetic resonance imaging, FLAIR = fluid attenuated inversion recovery, MRS = MR spectroscopy

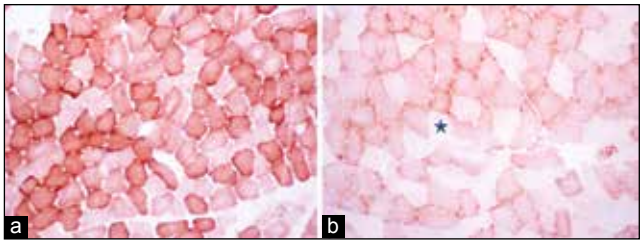

Figure 2: Showing the COX-negative fibers (*) in the patient (b) in comparison with a normal muscle biopsy specimen showing COX-positive fibers (a). COX = Cytochrome C oxidase

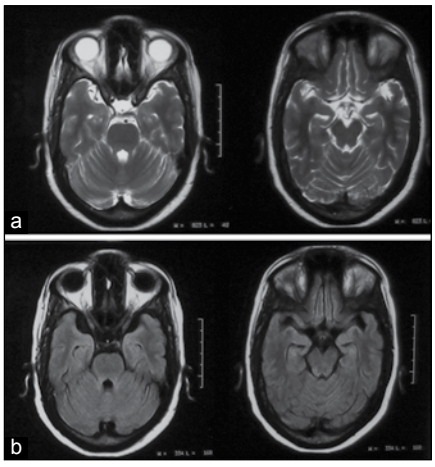

Figure 3: Repeat MRI brain T2-weighted (a) and FLAIR (b) sequencesshowing disappearance of brainstem hyperintensities after treatment

Discussion

Adult LD was defined as patients who survived longer than 18 years.[1] Sakushima *et al*.,[2] extensively reviewed the literature on adult-onset LD and they found that adult LD was rare and its clinical manifestations were different from those of children. They divided the cases into those which fulfilled the Rahman *et al*., criteria (Rahman's criteria group (RCG)) and those which were diagnosed with the identification of genetic abnormality (laboratory-diagnosed group (LDG)). Adult-onset LD tends to have less incidence of developmental delay, COX deficiency, serum lactate elevation, and basal ganglia lesions. In contrast they have cranial nerve disturbance, pyramidal signs, and cerebellar dysfunction. The diagnostic criteria by Rahman *et al* 1996.[3] for LS are as follows:

1. Progressive neurologic disease with motor and intellectual developmental delay;
2. Signs and symptoms of brain stem and/or basal ganglia dysfunction;
3. Elevated lactate levels in the blood and/ or CSF; and
4. One or more of the following:
   a. Characteristic features of LS on neuroimaging[4] (symmetric hyperintense lesions in basal ganglia and/ or brainstem in T2 sequence),
   b. Typical neuropathological changes at postmortem examination, and
   c. Typical neuropathology in a similarly affected sibling.

   The criteria proposed by Sakushima *et al*., 2011 are:
   1. History of cryptogenic thrive failure or signs of mental retardation, pyramidal signs, cerebellar disturbances, ophthalmoplegia, deafness, dysarthria, or other neurological symptoms are present; and
   2. Bilateral basal ganglia lesions or brainstem lesions with serum or CSF lactate elevation are present (lactate stress test (LST) should be considered when resting lactate levels are normal);
   3. Mitochondrial abnormalities are present in muscle pathology or in biochemical analyses, or known LD gene mutations are present; and
   4. Metabolic disorders, toxins, infection, multiple sclerosis, and Wernicke's encephalopathy can be excluded.

   Our patient fulfilled the later criteria as she did not have history of failure to thrive or motor/ intellectual delay as required in Rahman *et al*., criteria. Rather she had recurrent vomiting and brainstem signs.

Most of the reported cases excluded infections, autoimmune diseases, and toxins as in our case. Some cases were first misdiagnosed as multiple sclerosis and few are

in distinguishable from Wernicke's encephalopathy as occurred in our patient during the first admission. Our patient satisfied clinical, radiological, and biochemical criteria for LS. Muscle histochemistry reinforced the diagnosis. Also striking imaging findings described previously with LS were found in our patient as well, moreover excellent response with complete resolution of both MRI and clinical signs and symptoms to mitochondrial cocktail[5] confirmed our patient as a case of LS. The excellent response to treatment in our patient is similar to the case reported by Goldenberg *et al*.,[5] where there was a partial deficiency of COX. Recent literature also supported the frequent occurrence of sleep apnea syndrome and abdominal symptoms in patients with mitochondrial diseases as occurred in our patient.[5]

The major mutations known to occur in LD patients are T8993C, T8993G, T10191C, G13513A, A8344G, and A3243G in mitochondrial genes, and SURF1in the nuclear genome. Currently, there are 24 known mutations in mitochondrial genes and 21 in nuclear genes.[6] The underlying genetic etiology could not be ascertained in our patient. Recent studies have shown that recognized mtDNA mutations only account for a small proportion of cases of mitochondrial disease.[7] In addition, nuclear DNA mutations account for a substantial number of mitochondrial disorders which could not be done in our patient due to unavailability. Moreover, mitochondrial respiratory chain analysis in muscle or fibroblasts could not be done in our patient. Adult-onset LD is extremely rare and requires high index of suspicion.

Acknowledgment

The authors acknowledge the help of Centre for Cellular and Molecular Biology (CCMB), Hyderabad, India for analysis of complete mitochondrial genome.

References

1. Turner C, Schapira AH. Mitochondrial disorders. Neurology in Clinical Practice. Bradley, 6th ed. p. 1473-87.
2. Sakushima K, Tsuji-Akimoto S, Niino M, Saitoh S, Yabe I, Sasaki H. Adult leigh disease without failure to thrive. Neurologist 2011;17:222-7.
3. Rahman S, Blok RB, Dahl HH, Danks DM, Kirby DM, Chow CW, *et al*. Leigh syndrome: Clinical features, biochemical and DNA abnormalities. Ann Neurol 1996;39:343-51.
4. Arii J, Tanabe Y. Leigh syndrome: Serial MR imaging and clinical follow-up. AJNR Am J Neuroradiol 2000;21:1502-9.
5. Goldenberg PC, Steiner RD, Merkens LS, Dunaway T, Egan RA, Zimmerman EA, *et al*. Remarkable improvement in adult Leighs syndrome with partial cytochrome c oxidase deficiency. Neurology 2003;60:865-8.
6. Finsterer J. Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol 2008;39:223-35.
7. Baertling F, Rodenburg RJ, Schaper J, Smeitink JA, Koopman WJ, Mayatepek E, *et al*. A guide to diagnosis and treatment of Leigh syndrome. J Neurol Neurosurg Psychiatry 2014;85:257-65.

How to cite this article: Jabeen SA, Sandeep G, Mridula KR, Meena AK, Borgohain R, Sundaram C. Adult-onset Leigh's disease: A rare entity. Ann Indian Acad Neurol 2016;19:140-2.
Received: 10-12-14, **Revised:** 25-12-14, **Accepted:** 18-02-15

Source of Support: Nil, **Conflicts of Interest:** None declared.