An interesting case of Leigh-like syndrome

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Abstract

A 12-year-old female child with motor developmental delay presented with persistent vomiting, recurrent falls and unsteadiness in dark since 2 years of age. There was decline in scholastic performance, bulbar symptoms and aggravation of symptoms during intercurrent illness. Clinically, she had frontal and parietal lobar dysfunction, dysarthria, optic atrophy and LMN VII, IX, X, XII cranial nerve involvement. There was generalized hypotonia, distal muscle wasting, weakness, cerebellar signs and impaired vibration/position sense in distal extremities. Biochemical investigations revealed elevated serum/cerebrospinal fluid (CSF) lactate and CSF lactate pyruvate ratio. Neuroimaging demonstrated bilateral symmetrical T2 hyperintensities in basal ganglia, subcortical white matter, cerebellar hemispheres and posterior aspect of spinal cord. As certain atypical features like bilateral symmetrical T2 hyperintensities in subcortical white matter were also seen, metachromatic leukodystrophy was considered in differential diagnosis but ruled out by nerve biopsy. This case is reported for the presence of atypical neuroimaging features that are rarely found in Leigh's disease.

Key Words

Basal ganglia, cerebellum, lactate, metachromatic leukodystrophy, white matter

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Ann Indian Acad Neurol 2012;15:310-2

Introduction

Leigh's disease, named after Denis Archibald Leigh, a British psychiatrist who first described the condition in 1951, is an inherited neurometabolic disorder that usually affects infants between the age of 3 months and 2 years but, in rare cases, teenagers and adults are affected as well. Mutations in mitochondrial DNA or in nuclear DNA cause degeneration of motor skills and, eventually, death. We hereby report a case of a 12-year-old girl with clinical, biochemical and radiological features characteristic of Leigh's disease.[1,2]

Case Report

Our patient is a 12-year-old female child born of third degree consanguinous parentage with history of delay in development of motor milestones. She had recurrent falls preceded by tripping of toes since she started walking and unsteadiness, especially in the dark. The child had persistent vomiting since 1 year of age immediately after taking food. There was one episode of generalised tonic clonic convulsions at 2 years of age and gradual decline in scholastic performance for the past 1 year. She developed worsening of unsteadiness with swaying to either side following a febrile illness 4 months back, which improved with treatment. For the past 1 month, she again developed worsening of preexisting symptoms along with development of dysphagia, nasal regurgitation and slurring of speech. There was no history of similar complaints in other family members.

General examination revealed pallor, bilateral pes cavus and clawing of toes. Higher mental function examination demonstrated predominantly frontal and parietal lobar dysfunction in the form of poor attention, perseveration, defective alternative sequencing, left sensory extinction, right left disorientation, bilateral astereognosis, impairment of calculation and constructional skills. Language was fluent, with normal comprehension and repetition. Reading and writing was severely impaired. Speech was dysarthritic involving labial, lingual and guttural components. She had bilateral optic atrophy with LMN VII, IX, X, XII cranial nerve involvement. There was generalized hypotonia with predominantly distal wasting and weakness. All deep tendon reflexes were absent, with plantar showing no response. Position and vibration sense was impaired distally and signs of cerebellar dysfunction were present bilaterally. Intermittent choreoathetotic movements involving both foot were also present.

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Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.104344

Investigations

Complete blood count, renal and liver function tests were normal. Magnetic resonance imaging of the brain and spine revealed T2 and FLAIR symmetrical hyperintensities in frontal and parietal subcortical white matter, bilateral basal ganglia and cerebellar hemispheres with diffuse cortical atrophic changes. T2 hyperintensities in the posterior column region extending throughout the length of spinal cord were also noted. [Figures 1-4]. Cerebrospinal fluid (CSF) protein was 600 mg/dL, with elevated lactate 45 mg/dL (normal range: 15–22 mg/dL) and lactate pyruvate ratio 25.28 (normal 17). Serum lactate was also elevated, 55.7 mg/dL (normal range: 4.5–19.8 mg/dL). EEG showed bilateral symmetrical slowing in the range of 5–6 HZ. Nerve conduction study revealed motor axonal neuropathy in lower limbs and diffuse sensory axonal neuropathy. Muscle biopsy was negative for ragged red fibers. Nerve biopsy was negative for abnormal metachromatic storage material.

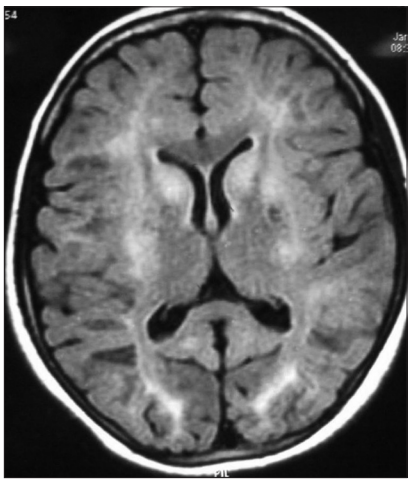

Figure 1: Axial T2 FLAIR image shows bilateral symmetrical subcortical and basal ganglia hyperintensities. Diffuse cortical atrophic changes are also seen

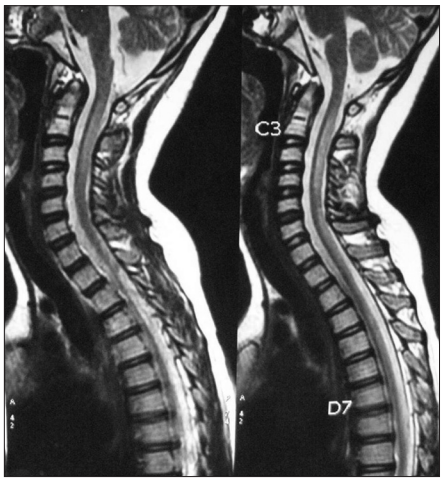

Figure 3: Sagittal T2 image shows hyperintensities in the posterior column region of the spinal cord extending for the entire length of the spinal cord

Discussion

Leigh syndrome is an extremely rare neurodegenerative disorder with a prevalence of 1:100,000 to 1:140,000 births. Initial features may be nonspecific, such as failure to thrive and persistent vomiting. Decompensation during an intercurrent illness is typically associated with psychomotor retardation.[3]

Stringent diagnostic criteria were defined by Rahman *et al*.:[1]

1. Progressive neurologic disease with motor and intellectual developmental delay.
2. Signs and symptoms of brainstem and/or basal ganglia disease.
3. Raised lactate concentration in blood and/or CSF.
4. One or more of the following:
   a. characteristic feature on neuroimaging (b/l symmetrical hyperintense signal abnormality in brainstem and/or basal ganglia on T2).
   b. Typical neuropathologic changes: multiple focal symmetric necrotic lesions in the basal ganglia, thalamus, brainstem, dentate nuclei and optic nerves.
   c. Typical neuropathology in a similarly affected sibling.

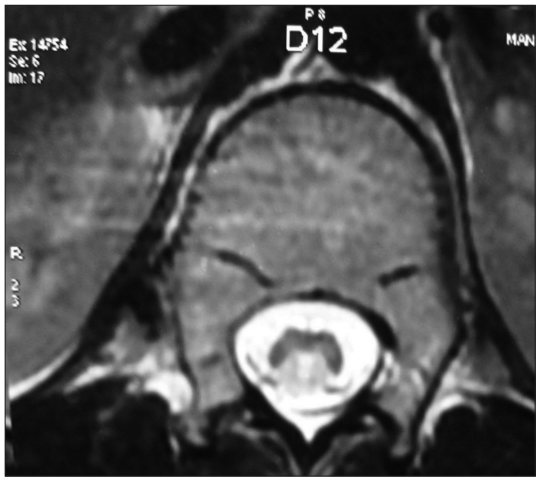

Figure 2: Axial T2 image of spinal cord at the thoracic level shows hyperintensities involving the posterior column

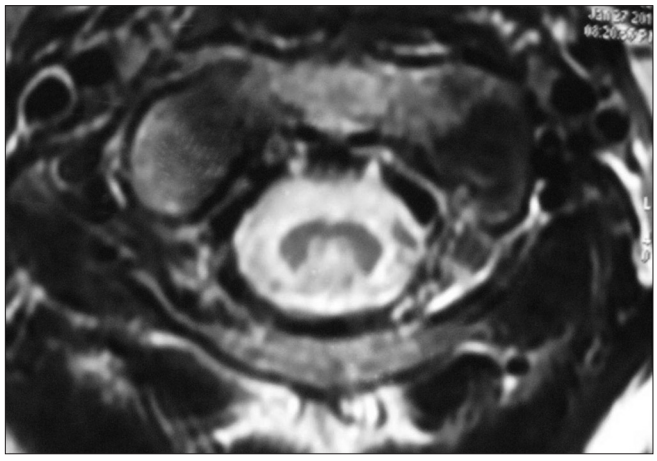

Figure 4: Axial T2 image of the spinal cord at the cervical level shows hyperintensities involving the posterior column

Our patient had clinical and biochemical features suggestive of Leigh's disease, such as progressive neurological disease with motor/intellectual developmental delay, signs and symptoms of brainstem/basal ganglia involvement, decompensation during an intercurrent illness and elevated serum/CSF lactate and CSF lactate pyruvate ratio. Neuroimaging also revealed typical features such as bilateral symmetrical basal ganglia hyperintensities. In addition, certain atypical radiological features like bilateral symmetrical T2 white matter hyperintensities in the frontoparietal region along with diffuse cortical atrophic changes and posterior column involvement extending for the entire length of the spinal cord were also present in this patient. As supratentorial leukodystrophy was present in our patient, we performed nerve biopsy to rule out metachromatic leukodystrophy. But, nerve biopsy was negative for metachromatic granules. Enzyme analysis for metachromatic leukodystrophy was not done due to economic constraints. We were not able to perform genetic confirmation for mitochondrial DNA because of nonavailability. This patient has typical clinical and biochemical features suggestive of Leigh's disease, with certain atypical features on neuroimaging. As the genetic confirmation was not done, the diagnosis can be suggested as Leigh-like syndrome. Such atypical variants of Leigh syndrome have been reported in very few cases previously. Huntsman *et al*. in his case series review have reported evidence of spinal cord involvement in magnetic resonance imaging among four of his five patients.[4] Hence, we report this case of Leigh-like syndrome with unusual neuroimaging features showing involvement of subcortical white matter, spinal cord and cortical atrophy. Thus, Leigh syndrome can involve any level of neuraxis resulting in a wide variety of clinical presentations, of which the clinician should be aware.[4-6]

Treatment

No specific treatment exists. Supportive management includes treatment of acidosis and antiepileptic drugs. A range of compounds are often used in the hope of improving mitochondrial functions, like coenzyme Q10, riboflavin, thiamine, etc.[7]

Conclusion

We report this case of Leigh-like syndrome disease with classical clinical, biochemical and neuroimaging features for its rarity of presentation. Certain atypical neuroimaging features like supratentorial subcortical white matter hyperintensities were also present in this patient.

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How to cite this article: Bharani K, Gnanashanmugam G, Kamaraj V, Balasubramanian S. An interesting case of Leigh-like syndrome. Ann Indian Acad Neurol 2012;15:310-2.
Received: 20-12-11, **Revised:** 01-01-12, **Accepted:** 14-01-12
Source of Support: Nil, **Conflict of Interest:** Nil