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LEIGH'S DISEASE: A RARE MITOCHONDRIAL DISEASE CASE REPORT

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ABSTRACT We report a rare case of Leigh's disease who was diagnosed with imaging.

KEYWORDS :

INTRODUCTION

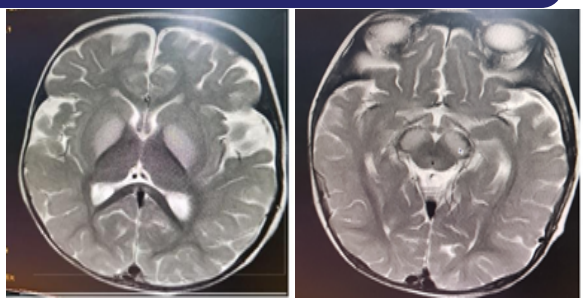
Leigh disease also termed as Sub Acute Necrotizing Encephalopathy (SNP) is a rare, inheritable, progressive neurodegenerative disorder , first reported in 1951 by Denis Leigh (1). It usually presents in infancy or early childhood and is the most common pediatric presentation of mitochondrial diseases. It is possible to come to a diagnosis of probable SNE during life on the basis of clinical signs and symptoms, mode of inheritance, metabolic abnormalities, and neuroimaging findings (2). We report a rare case of Leigh's disease diagnosed on CT and MRI and discuss the role of imaging in its diagnosis.

CASE

A 7-month-old female child presented with history of fever, vomiting's for 7 days and seizures, generalized tonic in nature, for one day. She was the first child, a product of consanguineous marriage, with uneventful perinatal history and normal development. On examination, she was febrile with stable vitals. On CNS examination, GCS was 10/15. There was no obvious cranial nerve palsy or focal neurological deficit. There was generalised hypotonia, with absent DTR's while plantars were mute. Pupils were 3mm equal in size and reacting to light. Fundus examination revealed temporal pallor in both eyes. Rest systemic examination was normal. Keeping a possibility of meningitis, she was started on injection Ceftriaxone. Seizures were controlled with phenytoin. The child needed ventilatory support for 72 hours for respiratory failure and developed ventilator associated pneumonia for which antibiotics were given for 2 weeks. At discharge, she was accepting orally. On follow-up after 4 weeks, the child had lost previously acquired milestones.

Investigations

Hb: 8gm%, macrocytic picture TLC 15,000 DLC N=70% L=24% Blood sugar, electrolytes, renal and liver function tests: WNL. CSF: Normal study. ABG:(pH=6.96, HCO3=4.6mmol/lt, pCO2=20.3 mm of Hg) S/o Metabolic Acidosis. Blood lactate levels: High. CECT HEAD: Symmetrical hypodensities involving lentiform nucleus ,periventricular white matter on left side and bilateral cerebellar peduncles with likely possibility of mitochondrial encephalopathy. MRI head: Symmetrical T2 and T2 FLAIR hyperintensities involving bilateral globus pallidi, putamina, cerebellar peduncles and midbrain, with diffusion restriction. MRS showed lipid lactate peak.



MRI Showing symmetrical b/l T2/T2 FLAIR hyperintensities involving b/l Globus pallidi, b/l putamina, peduncles, midbrain with diffusion restriction.

DISCUSSION

Leigh's disease is a rare progressive neurological disorder of childhood, with an estimated prevalence 2.05 cases per 1,00,000(3). The preschool incidence of Leigh syndrome was 1 out of 32,000(4). Age of onset of is usually less than 2 years (infantile form), but milder forms may present in childhood (juvenile form) and unusually in adulthood (5). Affected children usually become symptomatic within the first year of life with feeding difficulties, vomiting and failure to thrive, followed by psychomotor regression, abnormal muscle tone, weakness, dystonia, brainstem and cerebellar dysfunction (ataxia), visual loss and seizures(6) . Death usually occurs within a few years after onset of symptoms, typically from progressive respiratory failure (7).

In Leigh's disease, proton MRS has shown decreased NAA and elevated lactate, with lactate elevation most pronounced in those areas most severely affected on the imaging studies. Because most other non-mitochondrial disorders involving the basal ganglia (Wilson's disease, other causes of lactic acidemia, chronic infarction, maple syrup urine disease) do not have increased basal ganglia lactate, spectroscopy may be useful in confirming the diagnosis of Leigh's disease and other mitochondrial diseases (including MERRF, Kearns–Sayre syndrome, MELAS and Leigh's disease(8)(9). The lactate represents the end product of anaerobic metabolism. In our patient, the most prominent finding was markedly increased lactate peaks. Takahashi et al. reported an elevation in the lactate level in Leigh's syndrome at MRS, which is more prominent in the basal ganglia and brainstem, and they claimed that MRS is a useful indicator for the follow up of a response to treatment and prognosis (10). Recently, Lin et al. reported a high level of lactate by proton MRS in patients with mitochondrial disease (11).

Neuroimaging plays an important role in diagnosis of patients with Leigh syndrome (12)(13)(14)(15). The most characteristic neuro-radiological findings are bilateral, symmetric focal hyperintensities in the basal ganglia,

thalamus, substantia nigra, and brainstem nuclei at various levels on T2- MRI. These high T2 signals on MRI reflect the spongiform changes and vacuolation in the affected brain structures(16)(17)(18). In the basal ganglia, the putamen is particularly involved. In one series, 100% of the patients with proven SNE had putaminal involvement(12) . Ghosh and Pradhan reported two children with Leigh syndrome suspected clinically and confirmed by MRI in 1996(19). Low attenuation in the putamina on CT is considered to be characteristic of the disease(19)(20). In India, Bhavsar VM, Kumta NB described the role of CT scan of the brain in the diagnosis of Leigh syndrome in 1991(13). In 2005, Hombal and Narvekar reported Leigh syndrome in a 3-year-old child with regression of milestones and involuntary movements. The diagnosis in their case was based on neuroimaging(15).

Laboratory analysis shows metabolic acidosis with elevated blood & CSF lactate concentrations. The diagnostic criteria are: (1) Progressive neurological disease with motor and intellectual developmental delay/ regression; (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 or brainstem

CONCLUSIONS

The diagnosis of Leigh's disease should be considered in a child presenting with progressive neurodevelopment regression and signs and symptoms of brain stem and/or basal ganglia involvement with raised lactate levels in blood. Bilateral symmetric T2 prolongation involving multiple brainstem nuclei/structures associated with basal ganglia abnormalities in a child with neurological problems should prompt the clinician to consider Leigh disease and conduct further investigations .Mitochondrial disease cannot be cured completely but with appropriate investigations, accurate diagnosis and prompt institution of adequate supportive therapy, symptomatic amelioration can be achieved, thereby adding life to the limited years of survival of these children. Efforts for prevention and prenatal diagnosis are still in the nascent stage. Nucleus transplantation into enucleated oocyte is emerging as a new option for prevention of mitochondrial disorders.

REFERENCES

1. LEIGH D. Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatry. 1951;14(3):216–21.
2. van Erven PMM, Cillessen JPM, Eekhoff EMW, Gabreëls FJM, Doesburg WH, Lemmens WAJG, et al. Leigh syndrome, a mitochondrial encephalo(myo)pathy. A review of the literature. Clin Neurol Neurosurg. 1987;89(4):217–30.
3. Castro-Gago M, Blanco-Barca MO, Campos-González Y, Arenas-Barbero J, Pintos-Martínez E, Eirís-Puñal J. Epidemiology of pediatric mitochondrial respiratory chain disorders in northwest Spain. Pediatr Neurol. 2006 Mar;34(3):204–11.
4. The Incidence of Mitochondrial Encephalomyopathies in Childhood: Clinical Features and Morphological, Biochemical, and DNA Abnormalities - PubMed [Internet]. [cited 2020 Jun 1]. Available from: https://pubmed.ncbi.nlm.nih.gov/11261513/
5. Medina L, Chi TL, DeVivo DC, Hilal SK. MR findings in patients with subacute necrotizing encephalomyelopathy (Leigh syndrome): Correlation with biochemical defect. Am J Roentgenol. 1990;154(6):1269–74.
6. Sofou K, De Coo IFM, Isohanni P, Ostergaard E, Naess K, De Meirleir L, et al. A multicenter study on Leigh syndrome: Disease course and predictors of survival. Orphanet J Rare Dis. 2014 Apr 15;9(1):52.
7. Shrikhande DY, Kalakoti P, Syed MMA, Ahya K, Singh G. A rare mitochondrial disorder: Leigh syndrome--a case report. Ital J Pediatr. 2010;36(1):62.
8. Grodd W, Krägeloh-Mann I, Klose U, Sauter R. Metabolic and destructive brain disorders in children: Findings with localized proton MR spectroscopy. Radiology. 1991;181(1):173–81.
9. Mitochondrial Disorders: Analysis of Their Clinical and Imaging Characteristics - PubMed [Internet]. [cited 2020 Jun 1]. Available from: https://pubmed.ncbi.nlm.nih.gov/8237691/
10. Takahashi S, Oki J, Miyamoto A, Okuno A. Proton magnetic resonance spectroscopy to study the metabolic changes in the brain of a patient with Leigh syndrome. Brain Dev. 1999 Apr 1;21(3):200–4.
11. Proton MR Spectroscopy in the Diagnostic Evaluation of Suspected Mitochondrial Disease - PubMed [Internet]. [cited 2020 Jun 1]. Available from: https://pubmed.ncbi.nlm.nih.gov/12533324/
12. Medina L, Chi TL, DeVivo DC, Hilal SK. MR findings in patients with subacute necrotizing encephalomyelopathy (Leigh syndrome): Correlation with biochemical defect. Am J Roentgenol [Internet]. 1990 Jun [cited 2020 Jun 1];154(6):1269–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2159689
13. Leigh's Subacute Necrotizing Encephalomyelopathy: Possible Diagnosis by C.T. Scan - PubMed [Internet]. [cited 2020 Jun 1]. Available from: https://pubmed.ncbi.nlm.nih.gov/1937652/
14. Manzi S V., Hager KH, Murtagh FR, Mazalewski JG. MR imaging in a patient with Leigh's disease (subacute necrotizing encephalomyelopathy). Pediatr Radiol. 1990 Dec;21(1):62–3.
15. Hombal A, Narvekar V. Leigh s disease (subacute necrotising encephalomyelopathy)-a case report. Indian J Radiol Imaging [Internet]. 2005 [cited 2020 Jun 1];15(2):217. Available from: http://www.ijri.org/text.asp?2005/15/2/217/28806
16. Symmetric Lesions of the Subthalamic Nuclei in Mitochondrial Encephalopathies: An Almost Distinctive Mark of Leigh Disease With COX Deficiency - PubMed [Internet]. [cited 2020 Jun 1]. Available from: https://pubmed.ncbi.nlm.nih.gov/7502989/
17. Savoiardo M, Zeviani M, Uziel G, Farina L. MRI in leigh syndrome with SURF1 gene mutation [3]. Vol. 51, Annals of Neurology. Ann Neurol; 2002. p. 138–9.
18. Rossi A, Biancheri R, Bruno C, Di Rocco M, Calvi A, Pessagno A, et al. Leigh syndrome with COX deficiency and SURF1 gene mutations: MR imaging findings. Am J Neuroradiol [Internet]. 2003 [cited 2020 Jun 1];24(6):1188–91. Available from: https://pubmed.ncbi.nlm.nih.gov/12812953/
19. Ghosh D, Pradhan S. Antemortem diagnosis of Leigh's disease: Role of magnetic resonance studies. Indian J Pediatr. 1996 Sep;63(5):683–9.
20. Paltiel HJ, O'Gorman AM, Meagher-Villemure K. Subacute necrotizing encaphalomyelopathy (Leigh disease): CT study. Radiology. 1987;162(1):115–8.