Case report

Leigh syndrome responsive to vitamin therapy

K C S Dalpatadu[1], **P D Ratnayake**[1], **P M G Punchihewa**[1]

Sri Lanka Journal of Neurology, 2012, **1**, 45-47

Abstract

We report a case of Leigh syndrome in a girl aged four years and eight months who presented to us with progressive ptosis and worsening ataxia with frequent falls on a background of development delay. The clinical profile, bio-chemical analysis and MRI findings were consistent with a diagnosis of Leigh syndrome. Her clinical course was that of infantile onset, mild, slowly progressive form. She was given multivitamin supplement aiming to provide high dose thiamine and showed a remarkable response with disappearance of ptosis and marked improvement in function in the speech domain and motor skills.

Introduction

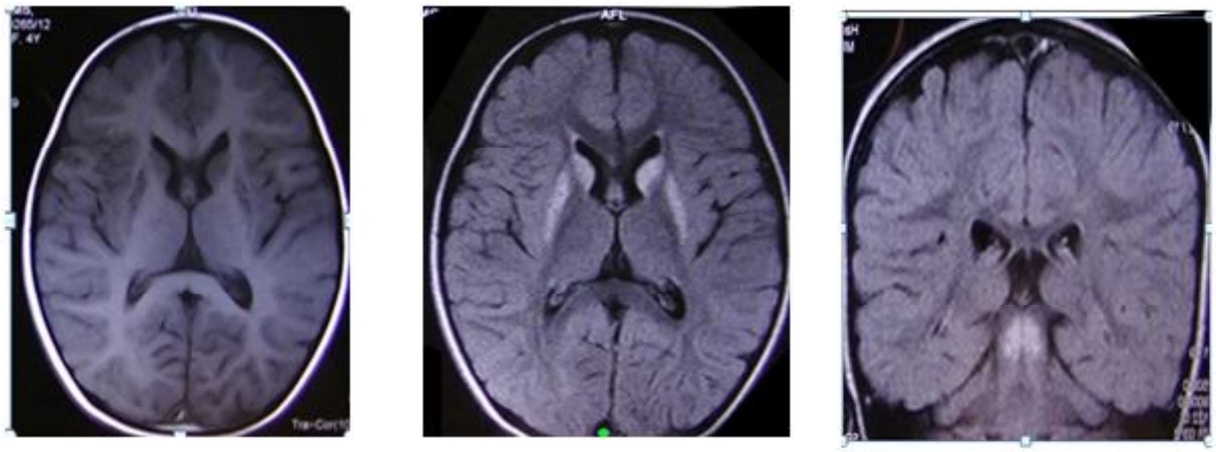
Leigh syndrome also known as sub acute necrotising encephalomyelopathy, is a rare neurodegenerative condition with a widely variable presentation. Some patients respond to vitamin supplementation. Due to the many underlying enzymatic defects giving rise to similar clinical profiles, it is difficult to clinically predict response to vitamin treatment.

Case report

The second born girl of parents who were distantly related was referred with a progressive ptosis of two months duration to the Neurology Unit at Lady Ridgeway Hospital for Children. Mother also complained of unsteadiness and frequent falls noted from around two years of age. There was also mild development delay noted mainly in gross motor and speech domains. The antenatal and perinatal period had been normal. There was no suggestive family history and her elder sister was in good health.

The clinical examination revealed a well nourished girl with bilateral partial ptosis with sparing of pupils. There was no ophthalmoplegia and the optic fundus was normal. Lower limb reflexes were symmetrically exaggerated with positive Babinski response. Gait ataxia was also seen. No other physical signs were present.

MRI showed bilateral symmetrical signal intensity changes in both heads of caudate nucleus and putamen as well as the brain stem. These were of low intensity in T1 and of high signal intensity in T2 and Flair. The mammillary bodies were spared (Figure). Laboratory evaluations showed an elevated CSF lactate (35.18 mg/dl; reference: 10-25 mg/dl).



A1 A2 B

Figure. MRI changes involving caudate and putamen symmetriclly A1) T1 hypo intensity, A2) FLAIR hyper intensity. B) brain stem: peri aqueductal FLAIR hyper intense symmetric lesion.

[1] *Lady Ridgeway Hospital for Children, Colombo 8, Sri Lanka.*

An EEG done showed nonspecific changes with asynchronous and long sleep spindles. ECG as well as visual and auditory evoked potentials were normal. Urine amino acid chromatography was also normal. Investigations for Wilson disease and repetitive nerve stimulation and nerve conduction tests done previously had been negative.

The child was commenced on vitamin supplementation aiming to supply high dose of thiamine. After one month on treatment she showed a remarkable response with complete resolution of ptosis. There was also a marked improvement in the ataxia with no further falls. Mother also noted a significant gain in speech abilities.

Discussion

Leigh was the first to describe this rare disorder in a seven month old infant who had a rapid onset and a fatal outcome[1]. Subsequent work described this disorder to have a wide variability in its age of onset, clinical presentation and progression[2].

A number of enzyme defects at many different sites in the respiratory pathway are recognised to give rise to the neuropathological findings grouped together as Leigh syndrome. The related genetic defect is seen in nuclear DNA in majority though mitochondrial genes are involved in 20 to 25%. However, a genetic cause for a number of cases of Leigh syndrome continue to remain unknown[3]. The mode of inheritance of nuclear DNA defect is autosomal recessive in majority with X linked recessive pattern seen in few.

The age of disease onset is usually during the first two years of life though juvenile or adult onset may be seen occasionally. The initial findings may be non specific with slow growth, feeding difficulty, vomiting and development delay. More characteristic features such as ptosis, ophthalmoplegia, visual loss, pigmentary retinopathy, ataxia and basal ganglia syndromes would eventually appear[4]. The clinical course may be rapidly fulminant or protracted for years.

Our patient did not have clinical features of severe involvement such as dysphagia, muscle and movement problems and respiratory insufficiency. Her clinical features suggest a mild form with slow disease progression.

The biochemical evidence of elevated lactate in CSF is found in most cases as in our patient and adds weight to the diagnosis. Lactate to pyruvate quotient in blood and CSF aids refinement of the diagnosis[6]. Gold standard for diagnosis is identification of mutations in mitochondrial DNA and biochemical investigations of muscle biopsies[3,7]. These are currently not available in Sri Lanka. Combination of typical clinical features and characteristic imaging together with elevated lactate level is considered sufficient for diagnosis in the absence of specific investigations.

The MRI features found in our patient was characteristic with symmetrical caudate and putaminal lesions as well as brain stem peri aqueductal lesions. The other common sites of involvement include thalami, cerebellum and even cerebral white matter[9,10,11]. The putamen involvement is seen in almost all patients.

Thiamine is the most commonly used agent to treat this disorder. However, its effect is variable and seen only in some. Thiamine responsive patients usually have pyruvate dehydrogenase deficiency[13]. Symptomatic treatment of abnormal movements can contribute to enhance the quality of life.

Other available treatment options such as riboflavin, carnitine, biotin and ketogenic diet have been demonstrated to be useful in the presence of different enzymatic defects[14,15,16,17]. Most however progress and the commonest cause of death is respiratory insufficiency[18].

Conclusion

Leigh syndrome is a rare disorder with many aetiologies. Our patient probably had the form of disease with infantile onset and slow progression though the age at diagnosis was close to 5 years. She showed a remarkable response to thiamine suggesting pyruvate dehydrogenase deficiency. Improved availability of investigations and better awareness will help to enable early diagnosis, genetic counselling and directed treatment.

References

1. Leigh D. Sub acute necrotizing encephalomyelopathy in an infant. *J Neurol Neurosurg Psychiatry* 1951; **14**: 216.

2. Huntsman RJ, Sinclair DB, Bhargava R, Chan A. Atypical presentations of Leigh syndrome: a case series and review. *Pediatric Neurology* 2005; 334-40.

3. Pronicka E, Piekutowska-Abramczuk D, Pronicki M. Metabolic diseases in children including Leigh syndrome – biochemical and molecular background. *Postepy Biochemii* 2008; **54**(2): 161-8.

4. vanErven PM, Cillessen JP, Eekhoff EM, et al. Leigh syndrome, a mitochondrial encephalomyopathy: a review of the literature. *Clin Neurol Neurosurg* 1987; **89**: 217-30.

5. Rahman S, Blok RB, Dahl HH, et al. Leigh syndrome: clinical features and biochemical and DNA abnormalities. *Ann Neurol* 1996; **39**(3): 343-51.

6. Tomczak R, Rieber A, Zeitler H, et al. Neuge borene smitzerebraler symptomatic. *Radiologe* 1996; **36**(7): 591-2.

7. Naess K, Freyer C, Bruhn H, et al. Mt DNA mutations are a common cause of severe disease phenotypes in children with Leigh syndrome. *Biochimica et Biophysica Acta* 2009; **1787**(5): 484-90.

8. Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA anbormalities. *Ann Neurol* 2001; **49**(3): 377-83.

9. Davis PC, Hoffman JC Jr, Braun IF, et al. MR of Leigh's disease (subacute necrotizing encephalomyelopathy). *Am J Neuroradiol* 1987; **8**: 71-5.

10. Medina L, Chi T, DeVivo D, et al. MR findings in patients with subacute necrotizing encephalomyelopathy (Leigh syndrome): correlation with biochemical defect. *Am J Neuroradiol* 1990; **11**: 379-84.

11. Geyer CA, Sartor KJ, Prensky AJ, et al. Leigh disease (subacute necrotizing encephalomyelopathy). CT and MR in five cases. *J Comput Assist Tomogr* 1988; **12**: 40-4.

12. Lim CC. Magnetic resonance imaging findings in bilateral basal ganglia lesions. *Ann Acad Med Singapore* 2009; **38**(9): 795-8.

13. Di Rocco M, Lamba LD, Minniti G, Caruso U, Naito E. Outcome of thiamine treatment in a child with Leigh disease due to thiamine-responsive pyruvate dehydrogenase deficiency. *Eur J Paediatr Neurol* 2000; **4**(3): 115-7.

14. Bar-Meir M, Elpeleg ON, Saada A. Effect of various agents on adenosine triphosphate synthesis in mitochondrial complex I deficiency. *J Pediatr* 2001; **139**(6): 868-70.

15. Wijburg FA, Barth PG, Bindoff LA, Birch-Machin MA, van der Blij JF, Ruitenbeek W, Turnbull DM, Schutgens RB. Leigh syndrome associated with a deficiency of the pyruvate dehydrogenase complex: results of treatment with a ketogenic diet. *Neuropediatrics* 1992; **23**(3): 147-52.

16. Pinard JM, Marsac C, Barkaoui E, Desguerre I, Birch-Machin M, Reinert P, Ponsot G. Leigh syndrome and leukodystrophy due to partial succinate dehydrogenase deficiency: regression with riboflavin. *Arch Pediatr* 1999; **6**(4): 421-6.

17. Toth G, Morava E, Bene J, Selhorst JJ, Overmars H, Vreken P, Molnar J, Farkas V, Melegh B. Carnitine-responsive carnitine insufficiency in a case of mtDNA 8993T > C mutation associated Leigh syndrome. *J Inherit Metab Dis* 2001; **24**(3): 421-2.

18. Lee HF, Tsai CR, Chi CS, Lee HJ, Chen CC: Leigh syndrome: clinical and neuroimaging follow-up. *Pediatr Neurol* 2009; **40**(2): 88-93.