Heliyon 10 (2024) e23137

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

A case of Leigh syndrome presented with paroxysmal body swing

Jia Zhang [a,b,c], Jing Gan [a,b,c], Jianjun Wang [a,b,c,*]

[a] Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, 610041, China
[b] Key Laboratory of Obstetrics & Gynecologic and Pediatric Diseases and Birth Defects of the Ministry of Education, Sichuan University, Chengdu, Sichuan, China
[c] Key Laboratory of Development and Maternal and Child Diseases of Sichuan Province, China

ARTICLE INFO

Keywords:
Leigh syndrome
MT-ND5
de novo
Paroxysmal episode

ABSTRACT

Background: Leigh syndrome (LS) is a heterogeneous neurodegenerative disease that is the most common manifestation of mitochondrial disease in children.
Methods: We report a case of Leigh syndrome with paroxysmal body swing in a 1-year-old boy.
Results: The boy presented with paroxysmal body swing, and the electroencephalogram showed no epileptic discharge during the paroxysmal episode. It was determined to be a nonepileptic seizure, which was the first LS phenotype described. After treatment with a vitamin cocktail, the paroxysmal body swing improved.
Conclusion: LS should be considered for children with onset of infantile and paroxysmal body swing combined with developmental regression, and early mitochondrial genetic testing can aid in diagnosis and guide early intervention.

1. Introduction

Leigh syndrome (LS) is a common mitochondrial encephalomyopathy in childhood caused by mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) variants. It is a severe and progressive neurodegenerative disease that occurs mostly in infants. In recent years, the application of next-generation sequencing (NGS) technology has improved the diagnostic level of mitochondrial diseases, laid a foundation for the further study of genotype and phenotype, and provided an evidence base for genetic counseling and prenatal diagnosis.

2. Case report

A 1-year-old boy presented to the hospital because of “paroxysmal whole body swing” (Supplementary Material). The body swing was irregular, and his eyes were closed, occurring mostly during sleep with no cyanosis and incontinence. Each episode lasted approximately 1–2 hours and could be relieved with human intervention. After stimulation, a similar onset was observed, but the duration was short, approximately a few seconds to tens of seconds. Prenatal examination showed that the right ventricle was widened, and color Doppler ultrasound showed no abnormalities. The child was G1P1, full term, with a birth weight of 2.7 kg. The growth and development of the child were as follows: at 2 months old, he could hold his head up; at more than 7 months old, he could turn over; and at 11 months old, he could walk with assistance and shout “baba” and “mama”. After disease onset, the child exhibited

* Corresponding author. No. 20, Section Three, South Renmin Road, Chengdu, 610041, China.
E-mail address: wauscpx@aliyun.com (J. Wang).

https://doi.org/10.1016/j.heliyon.2023.e23137
Received 8 December 2022; Received in revised form 15 October 2023; Accepted 27 November 2023
Available online 7 December 2023

comprehensive development regression; could not stand or walk with assistance; was unstable when sitting and standing; and did not cry, laugh, speak, or recognize people. No feeding difficulties were observed. There was no family history of hereditary diseases.

The results of the physical examination at admission were as follows: clear consciousness, no facial abnormality, normal skull size, negative pupil examination on both sides, and no nystagmus or strabismus. The muscle tension of the limbs was high, the limbs were moveable, the knee-tendon reflex was normal, and the pathological sign and the meningeal irritation sign were negative. After admission, relevant examinations were completed as follows: blood ammonia was 53.1 μmol/L (10–47 μmol/L), lactic acid was 3.65 mmol/L (0.5–22 mmol/L), pyruvate was 115.42 μmol/L (20–100 U/L), and β-hydroxybutyric acid was 2.16 mmol/L (0–0.27 mmol/L). Cerebrospinal fluid (CSF) lactic acid was 3.23 mmol/L, and CSF cytology, biochemistry, and pathogen nucleic acid showed no abnormalities. Autoimmune encephalitis antibodies were negative. Electrocardiogram and echocardiography showed no abnormalities. Auditory evoked potentials were abnormal. Visual evoked potentials were normal. The video electroencephalogram (EEG) showed that the background wave was slightly slower (4–5 Hz), and no epileptic discharge was observed during the episode. Cranial MRI showed abnormal signals of the bilateral thalamus, midbrain, periaqueductal gray, and superior cervical medulla. DTI imaging showed decreased white matter fiber bundles in the brainstem, mainly in the midbrain (Fig. 1).

Inherited metabolic diseases were considered, and the patient was treated with a multivitamin cocktail (coenzyme Q10 10 mg/kg/d, Vitamin E 10 mg/kg/d, Vitamin B1 5 mg/kg/d, Vitamin B2 10 mg/kg/d, Vitamin C 25 mg/kg/d, levocarnitine 50 mg/kg/d) after admission. A mutation of *MT-ND5* (m.13513G > A) was found by NGS; the proportion of the mutation was 68.6 % (18646/27164), and the mother and father were wild type. Combined with genetic testing, a diagnosis of Leigh syndrome was made, and oral vitamin cocktail therapy and rehabilitation training were continued. The child did not exhibit paroxysmal body swing after discharge, but psychomotor development was not significantly improved. Unfortunately, after 6 months of follow-up, the child died of COVID-19-related pneumonia.

3. Discussion

The mitochondrial ND5 subunit is one of the seven subunits of complex I encoded by mitochondria. It is the largest (1811 nt) gene, and its mutation can affect the assembly or stability of complex I [1,2]. By far, the most common mutation in the *MT-ND5* gene is the m.13513G > A mutation [1]. Studies have shown that the *MT-ND5* m.13513G > A mutation can cause disease even under low mutational load, and there is no significant correlation between the degree of mutation heterogeneity and the age of onset and disease severity[1,3]. To date, this mutation has been reported in at least 50 patients, including multiple patients with mitochondrial encephalomyopathies, most commonly seen in MELAS and LS. Ariel et al. identified the m.13513G > A mutation in 5 (1.88 %) of 265 LS patients [3]. Studies have shown that the m.13513G > A mutation in LS is most frequently combined with optic atrophy and/or Wolff–Parkinson–White (WPW) syndrome [4]. However, the phenotype of m.13513G > A is variable due to the particularity of mitochondrial genetics. The visual evoked potential, electrocardiogram, and cardiac color Doppler ultrasound of this child were not abnormal at the time of admission to the hospital, but with the progression of the disease, most patients will experience multiple system involvement, so it is necessary to continue with follow-up observations.

Studies on the first symptoms of LS showed that motor abnormalities accounted for 82.8 %, including hypotonia, spasticity of

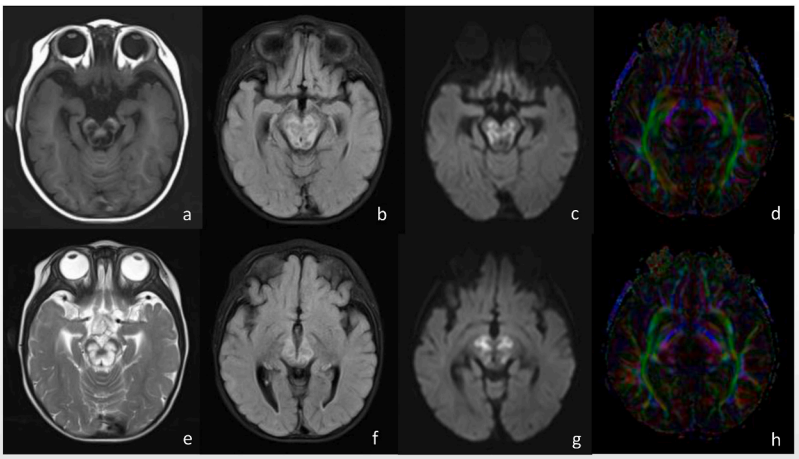

Fig. 1. Cranial MRI (a, T1; b, T2; c, d, T2-Flair; e, f, DWI) showed abnormal signals of the bilateral thalamus, midbrain, periaqueductal gray, and superior cervical medulla. DTI imaging (f, g) showed decreased white matter fiber bundles in the brainstem, mainly in the midbrain.

dystonia, ataxia, and chorea, followed by ocular symptoms, feeding difficulties, seizures, and development retardation [5]. In this case, the patient presented with paroxysmal body swing combined with developmental regression, typical brain MRI changes, and mitochondrial gene detection suggesting *MT-ND5* m.13513G > A, resulting in a diagnosis of LS. No epileptic discharge was found in the EEG of the child during the onset of the paroxysmal body swing attack, and a nonepileptic episode was considered. No similar phenotype of LS has been described to date, and the motor symptoms are believed to be related to the cerebellar-thalamic-cortex pathway. Brain MRI showed bilateral involvement of the thalamus, midbrain, and cervical medulla. DTI imaging showed decreased white matter fiber bundles in the brainstem and increased muscle tension. Subcortical myoclonus is considered a brain stem injury resulting in disconnection between cortical and subcortical structures or the symptoms of stimulation of the olivary nucleus loop under the dentate nucleus caused by metabolic abnormalities. The underlying mechanisms are unclear and may be related to abnormal energy metabolism, so this hyperkinetic movement disorder was controlled after treatment with a vitamin cocktail. A recent study and analysis of 209 LS patients in China showed that the worst survival rate was associated with mutations in *MT-ND5*, *MT-ATP6* (m.8993T > C and m.9176T > C), *SURF1* and *ALDH5A1* [6]. After treatment with the vitamin cocktail, the child's paroxysmal movement disorder was improved, and no paroxysmal body swing was observed after discharge. However, psychomotor development was not significantly improved; since onset occurred at an early age, the prognosis was poor.

4. Conclusion

In this patient, paroxysmal body swing was the main clinical manifestation, which added to the clinical manifestation spectrum of LS. This case suggests that LS should be considered for children with onset of infantile and paroxysmal body swing combined with developmental regression, and early mitochondrial genetic testing can aid in diagnosis and guide early intervention. However, this study is a case report, and there is no similar phenotype description at present; further follow-up observation with larger sample sizes is still needed.

Ethics approval and consent to participate

Not applicable.

Consent to publish

The parents gave their written consent for their child personal and clinical details. A copy of the signed, written informed consent for publication form is available for review by the editor.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Funding

This work was supported by the National Science Foundation of China (No. 82071686), the Grant from Science and Technology Bureau of Sichuan province (No. 2021YFS0093), the Grant from Research Fund of West China Second University Hospital (No. KL115, KL072).

CRediT authorship contribution statement

Jia Zhang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jing Gan:** Funding acquisition, Project administration, Resources, Validation. **Jianjun Wang:** Conceptualization, Project administration, Resources, Supervision, Visualization, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the patients' parents for provision of clinical data.

Abbreviations

LS:Leigh syndrome;
mtDNA:mitochondrial gene;
nDNA:nuclear gene;
NGS:next-generation sequencing;
CSF:Cerebrospinal fluid;
EEG:electroencephalogram;
MRI:magnetic resonance imaging;
DTI:diffusion tensor imaging;
MELAS:mitockondrial encephalomyopathy with lactic acidsis and strokelink episodes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23137.

References

[1] M.J. Blok, L. Spruijt, I.F. de Coo, et al., Mutations in the ND5 subunit of complex I of the mitochondrial DNA are a frequent cause of oxidative phosphorylation disease, J. Med. Genet. 44 (4) (2007 Apr) e74, https://doi.org/10.1136/jmg.2006.045716.
[2] V. Petruzzella, G. Di Giacinto, S. Scacco, et al., Atypical Leigh syndrome associated with the D393N mutation in the mitochondrial ND5 subunit, Neurology 61 (7) (2003 Oct 14) 1017–1018, https://doi.org/10.1212/01.wnl.0000080363.10902.e9.
[3] A. Brautbar, J. Wang, J.E. Abdenur, et al., The mitochondrial 13513G>A mutation is associated with Leigh disease phenotypes independent of complex I deficiency in muscle, Mol. Genet. Metabol. 94 (4) (2008 Aug) 485–490, https://doi.org/10.1016/j.ymgme.2008.04.004.
[4] E.M. Ruiter, M.H. Siers, C. van den Elzen, et al., The mitochondrial 13513G > A mutation is most frequent in Leigh syndrome combined with reduced complex I activity, optic atrophy and/or Wolff-Parkinson-White, Eur. J. Hum. Genet. 15 (2) (2007 Feb) 155–161, https://doi.org/10.1038/sj.ejhg.5201735.
[5] K. Sofou, I.F. De Coo, P. Isohanni, et al., A multicenter study on Leigh syndrome: disease course and predictors of survival, Orphanet J. Rare Dis. 9 (2014 Apr 15) 52, https://doi.org/10.1186/1750-1172-9-52.
[6] L. Stenton Sarah, Ying Zou, Hua Cheng, et al., Leigh syndrome: a study of 209 patients at the Beijing children's hospital, Ann. Neurol. 91 (2022) 466–482, https://doi.org/10.1002/ana.26313.