Atypical Leigh Syndrome Diagnosed in an Infant with Prominent Cardiac Hypertrophy as Initial Symptom: A Case Report with Novel LRPPRC Variants

Guoyu Sun

Peking University First Hospital

Yi Ma

Fuwai Hospital State Key Laboratory of Cardiovascular Disease

Xinlin Hou

Peking University First Hospital

Zhou zhou (✉ zhouzhou@fuwaihospital.org)

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

<https://orcid.org/0000-0002-7674-9857>

Case report

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Abstract

Background: Leigh syndrome is a kind of severe neurological disorder with various inheritable patterns usually affects children, especially the infants. Lack of characteristic neurodegenerative symptoms cause the delay and inaccurate diagnosis of Leigh syndrome, which is essential for the prognosis in pediatric clinical practice.

Case presentation: A 10-day-old Chinese boy was first admitted to hospital with feeding difficulty, elevated lactate and prominent cardiac hypertrophy as initial symptom but without neurological abnormality. Subsequent identification of novel *LRPPRC* compound heterozygous variants c.2582T>A (p.Val861Asp) and c.1582+4A>G by whole exome sequencing seemed to favor French-Canadian Leigh syndrome. This diagnosis was further supported by the rapid progression of neuropathology manifesting as epileptic seizures 5 months later and the significantly reduced mitochondrial complex-IV activity.

Conclusion: This tortuous process of diagnosis should raise the recognition of rare untypical type of Leigh syndrome, and emphasize the important role of genetic testing in current pediatric clinic. The observation also broadens the spectrum of *LRPPRC* variants associated with Leigh syndrome outside of French-Canadian areas.

Introduction

Leigh syndrome (OMIM#256000) is a kind of severe inheritable neurological disorder which usually affects usually affects children, especially the infants, and its diagnosis is mainly based on typical clinic observations of neuropathology and elevated lactate. Leigh syndrome can be divided into different subtypes according to the genetic backgrounds with various inheritance patterns [1]. Among them, French-Canadian type (OMIM#220111) was an autosomal recessive Leigh syndrome caused by biallelic *LRPPRC* variants [1]. Lack of characteristic neurodegenerative symptoms cause the delay and inaccurate diagnosis of Leigh syndrome, which is essential for the prognosis in pediatric clinical practice.

Patient Presentation

A 10-day-old Chinese boy was referred to our hospital due to groaning with feeding difficulty. He was the first child of healthy, nonconsanguineous parents without any family history of cardiac disease or relevant symptoms. He was born at full term and weighed 3400 g. He experienced feeding difficulties with retention in the stomach after birth. He had poor responses to the outside world and hypomyotonia with non-concave edema at the distal extremities. His breath increased to 70–90 beats/min, with audible systolic murmurs (grade II-III/VI) in the precardiac area. Hepatomegaly was found palpable 3 cm under the rib without splenomegaly.

The laboratory test results showed significantly increased plasma lactose (maximum 15.6 mmol/L), as well as creatine kinase MB isoenzyme, cardiac troponin I and B-type natriuretic peptide (> 4988 pg/ml), but the blood glucose level was normal. The urine levels of lactate and pyruvate were both dramatically

elevated (647.48 mmol/mol and 382.29mmol/mol, respectively). These results suggested disorders of mitochondrial energy metabolism.

Electrocardiogram (ECG) revealed high voltage in the right ventricle and ST-T changes with sinus rhythm. Echocardiography results further confirmed the significant hypertrophy in both ventricles and septum (maximum 10 mm) along with atrial septal defect and patent ductus arteriosus (Fig. 1A and B) but normal ejection fraction of 58%. The head magnetic resonance imaging (MRI) taken 41 days after birth revealed no abnormal signals in the basal ganglia and brain stem (Fig. 1C).

After symptomatic treatment with fluid restriction, digoxin and β -blocker, supplemented with coenzyme Q10, multivitamins, etc, he was discharged 46 days after birth, still fed by nasal feeding.

To assist with the differentiation, genetic testing of mitochondrial DNA and genomic DNA was performed (See supplementary for details) with informed consent of the patient's parents. The results revealed novel compound heterozygous variants c.2582T > A (p.Val861Asp) and c.1582 + 4A > G in *LRPPRC* (Fig. 2) with uncertain pathogenicity related to autosomal recessive French-Canadian type of Leigh syndrome with complex IV deficiency (OMIM#220111) by whole exome sequencing (WES) and negative results for mitochondrial DNA sequencing.

Consistent with the suggestive Leigh, he manifested frequent seizures as a series of convulsions and was hospitalized again 5 months 18 days after birth without obvious signs of heart failure. However, the cerebral MRI results still showed no abnormal signals in the basal ganglia and brain stem, only widened sulci, fissures and cisterns with the white matter myelination slightly later than normal peers (Fig. 1D). The electroencephalogram (EEG) was found to be of highly irregular rhythms with outbreak suppression trends, and a series of isolated spasms were detected, and one attack of myoclonus was observed.

Moreover, the analysis of mitochondrial respiratory chain enzyme activity revealing significantly reduced complex IV activity (24.5% of control) with a potential secondary relatively lower complex V activity (63.6% of control) also supported the suspicion of Leigh syndrome with complex IV deficiency, potentially due to *the LRPPRC* variants.

Taken together, Leigh syndrome can be diagnosed. This patient was treated with Topamax and Levetiracetam for seizure, and the seizure didn't stop until 9 months after birth. Unfortunately, he experienced repeated respiratory tract infections leading to respiratory and cardiac arrest, and died 20 months after birth.

Discussions

Leigh syndrome (OMIM#256000), also known as subacute necrotizing encephalomyelopathy, has a relatively homogeneous phenotype characterized by pediatric-onset progressive neuropathology as the initial and prominent sign but various genotypes associated with mitochondrial- or nuclear-encoded genes involved in energy metabolism [1]. Multiple organ systems can also be affected, including heart,

live, kidney, intestines and stomach [2, 3], and the relatively prevalent cardiac manifestation, cardiac hypertrophy, is rarely presented as the initial symptom [1]. The diagnosis of Leigh syndrome is mainly based on the clinic observations and imaging findings, although genetic testing can help with the final diagnosis and classification. In our case, even the lactic acidosis did raise the suspicion of Leigh syndrome at the first hospital admission, the normal head MRI without any evident neurologic abnormalities but only with severe cardiac hypertrophy (Fig. 1) seemed to withhold the diagnosis of Leigh leading to the delay of accurate diagnosis.

When significant cardiac hypertrophy is clinically observed, attention should be paid to the differential diagnosis of certain hereditary diseases, such as Noonan syndrome, Pompe disease and mitochondrial disease [4]. However, the patient in this case had neither abnormal appearance nor internal organ malformation except cardiac hypertrophy. In addition, Noonan syndrome and Pompe disease were not supported by the consistently normal blood glucose levels. The final diagnosis of Leigh syndrome was not made until genetic testing revealed *LRPPRC* compound heterozygous variants and the patient showed epileptic seizures 5 months later.

LRPPRC encodes a multifunctional protein playing an important role in the energy metabolism and transcriptional regulation of both nuclear and mitochondrial genes [5]. So far, more than 50 *LRPPRC* variants have been reported associated with French-Canadian type Leigh syndrome (OMIM#220111) (Fig. 3) [6–8], and cardiovascular involvement, including mitral regurgitation, bicuspid aortic valve, complex cardiac malformations and cardiomyopathy, was occasionally reported [7] (Supplementary Table 1). Although some recognized founder mutations identified in Québec areas are reported missense [6], most of them are truncating ones (e.g. frameshift, stop-gain and splicing) leading to nonsense-mediated mRNA decay [7, 8]. In this case, due to lack of previous reports and functional studies, these identified compound heterozygous *LRPPRC* variants are classified as variants of uncertain significance according to American College of Medical Genetics and Genomics (ACMG) recommendations [9], but still with a high likelihood of pathogenicity. *LRPPRC* c.1582 + 4A > G is predicted to cause aberrant splicing by multiple in silico tools including Human Splicing Finder (<http://www.umd.be/HSF/>), potentially leading to a frameshift insertion of GTAG at the end of exon 13. The patient's later-onset seizures (5 months later) and mitochondrial complex-IV deficiency further supported the pathogenicity of Leigh-associated *LRPPRC* variants. Therefore, genetic testing may serve as a useful tool for accurate diagnosis in pediatric clinic.

Here, we reported an infant with prominent cardiac hypertrophy and elevated level of lactic acid as the initial symptom but without neurological abnormality. WES results favored *LRPPRC*-associated French-Canadian Leigh syndrome, which was further supported by the relatively late-onset epileptic seizures. Our observations of novel compound heterozygous variants c.2582T > A (p.Val861Asp) and c.1582 + 4A > G also broadened the spectrum of *LRPPRC* variants outside of French-Canadian areas.

Conclusion

This tortuous process of diagnosis should raise the recognition of rare atypical type of Leigh syndrome, and early-onset cardiac hypertrophy and elevated level of lactic acid may also be the clue. Moreover, genetic testing plays an important role in the current pediatric clinic.

Declarations

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Authors' contributions

GYS was primary involved in the clinical data collection, manuscript draft and funding. YM was primary involved in the genetic testing, data management, manuscript draft and revision. XLH and ZZ supervised clinical as well as genetic assessment, revised the final manuscript and provided the funding for the study. All authors approved the final manuscript as submitted.

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Availability of data and materials

The analyzed datasets in this study are included in the article/supplementary material.

Ethics statement

Ethical clearance was sought from the ethics committee of the institutional review board at Fuwai Hospital, China. Written informed consent was obtained from both parents of the patient to publish this case report.

Disclosure

All authors declare that they have no conflict of interest.

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Figures

Figure 1

Initial echocardiography result of the patient at 10 days (A and B) and head MRI results at 41 days (C) and 5 months 11 days (D). Echocardiography indicates (A) significant left ventricular septal hypertrophy (10 mm, indicated by the arrow) and (B) patent ductus arteriosus (6.5*2.1mm); (C): There were abnormal signals at bilateral periventricular area (indicated by the arrow) suggesting the possibility of old hemorrhage, but no abnormal signals in the basal ganglia and brain stem, no expansion of the ventricle, and no widening and deepening of the sulci and fissures. (D): The bilateral ventricles were slightly widened, and the widening of sulci, fissures and cisterns were increased (indicated by arrows). The bilateral hemisphere structure was symmetrical with no obvious abnormal signals in the brain

parenchyma, and the myelinization of the white matter of the brain was slightly later than normal ones of the same age.

Figure 2

Novel compound heterozygous LRPPRC variants c.2582T>A (p.Val861Asp) and c.1582+4A>G identified in the patient inherited from his healthy father and mother, respectively.

Figure 3

Summary of all available LRPPRC variants illustrated in a graphical representation of the gene structure. The variants from Clinvar (Top lane) are classified according to recorded pathogenicity, while those from GnomAD (middle lane) are shown in different allele frequency. Those potentially causative LRPPRC variants for Leigh syndrome recorded in Clinvar (excluded benign or likely benign ones) and HGMD are illustrated according to various functional domains, as well as those newly identified compound heterozygous variants in this boy (bottom lane).

Supplementary Files

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