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Leigh Syndrome Complicated by Takotsubo Cardiomyopathy: A Case Report and Literature Review

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Abstract

BACKGROUND: Leigh syndrome (LS) is one of the most common mitochondrial disorders in the pediatric population, primarily affecting infants and children. It presents with diverse clinical manifestations and is often misdiagnosed or underdiagnosed in clinical practice.

CASE PRESENTATION: In the present investigation, a retrospective analysis was conducted on a pediatric case manifesting symptoms akin to Takotsubo cardiomyopathy (TTC) characterized by an acute onset. The clinical manifestations and radiographic imaging data of the pediatric patient were analyzed. In addition, genetic screening on the patient and her family members was conducted. Based on these findings, the patient was conclusively diagnosed with LS. Subsequently, the relevant literature was reviewed, and the clinical characteristics of this disease were summarized.

CONCLUSION: There were no prior reports of LS concomitant with TTC. TTC is a severe complication of LS. Early detection and comprehensive treatment are crucial for the successful recovery of patients with TTC. The case examined in this study provides valuable insights into the successful treatment of LS concomitant with TTC.

Abbreviations:

LS	- Leigh syndrome
mtDNA	- mitochondrial DNA
nDNA	- nuclear DNA
HR	- Heart Rate
TTC	- Takotsubo cardiomyopathy

CASE REPORT

INTRODUCTION

Leigh syndrome (LS) is a severely debilitating neurodegenerative disorder caused by mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). It constitutes one of the most commonly encountered manifestations of mitochondrial disease syndromes in the pediatric population, specifically in infants and children. Incidents of LS among Chinese patients are relatively frequent based on reported cases (Yang & Sun, 2006). LS is characterized by diverse clinical manifestations, such as cognitive delay or regression, motor impairments and stunted physical growth, epilepsy, muscle tone disorders, ophthalmic abnormalities, and others. Patients with LS succumb to respiratory or cardiac failure (Schubert Baldo & Vilarinho, 2020; Chen & Cui, 2018). However, cases of LS triggered by Takotsubo cardiomyopathy (TTC) are rare in clinical practice. LS triggered by TTC is often misdiagnosed or goes undiagnosed. In this study, a retrospective analysis of a case involving LS triggered by TTC was conducted. The aim is to assist clinicians in early detection and encourage proactive treatment strategies.

CASE-STUDY PRESENTATION

The pediatric patient was a six-year-old girl, admitted to the Pediatric Surgery Department of the First Affiliated Hospital of the University of Science and Technology of China on September 17, 2022, at 18:00 hours, with a history of abdominal distension accompanied by difficulty in breathing for 5 days. Five days before admission to the hospital, the patient experienced abdominal distension and difficulty breathing. The patient was taken to a local hospital where the doctors suspected that the patient was experiencing a respiratory tract infection based on the findings from her chest X-ray. She underwent nebulization based on her symptoms but did not experience any significant improvement. Subsequently, the patient visited a local clinic where she was prescribed oral probiotics based on her symptoms. On September 17, she sought outpatient care at our hospital, followed by an abdominal ultrasound examination. The ultrasound findings are listed below: (1) An elevated echogenicity was observed in the pancreas. The presence of echogenicity in the pancreatic tail raised suspicion. Further examination was advised. (2) No obvious abnormalities in the biliary system, abdominal cavity, or retroperitoneum were observed. Since early September this year, the patient has been experiencing lower limb weakness and a tendency to fall easily while walking. The patient was the first child of a G1P1 mother, born at full term following an uncomplicated pregnancy and delivery. Her growth and developmental milestones have been typical for a child her age. Family history indicates a non-consanguineous marriage of the parents, both of whom were previously in good health and denied any family history of hereditary diseases. The patient had received routine vaccinations.

Approximately one hour after admission to our hospital, the patient presented with mental confusion, a pale complexion, and rapid breathing. Immediate measures were taken, including oxygen therapy, airway

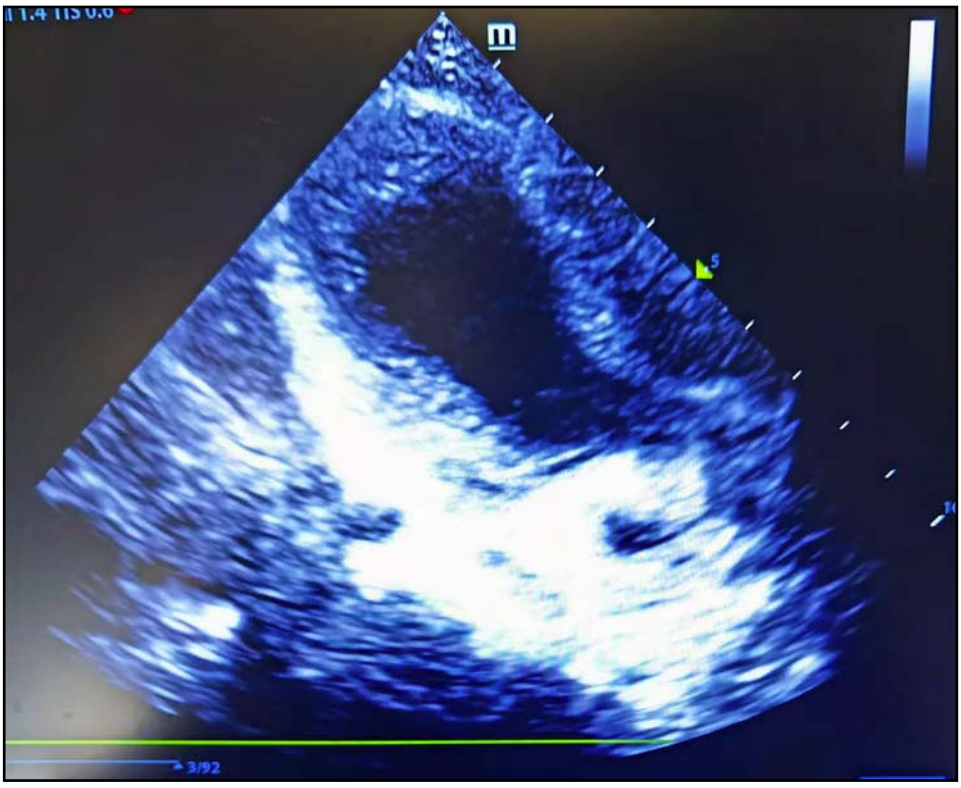

Fig. 1. Echocardiogram findings revealed that the myocardium in the anterior wall of the left ventricle exhibited approximately normal thickness and echogenicity, coupled with a reduction in motion amplitude. Additionally, the midsection of the left ventricle underwent spherical expansion.

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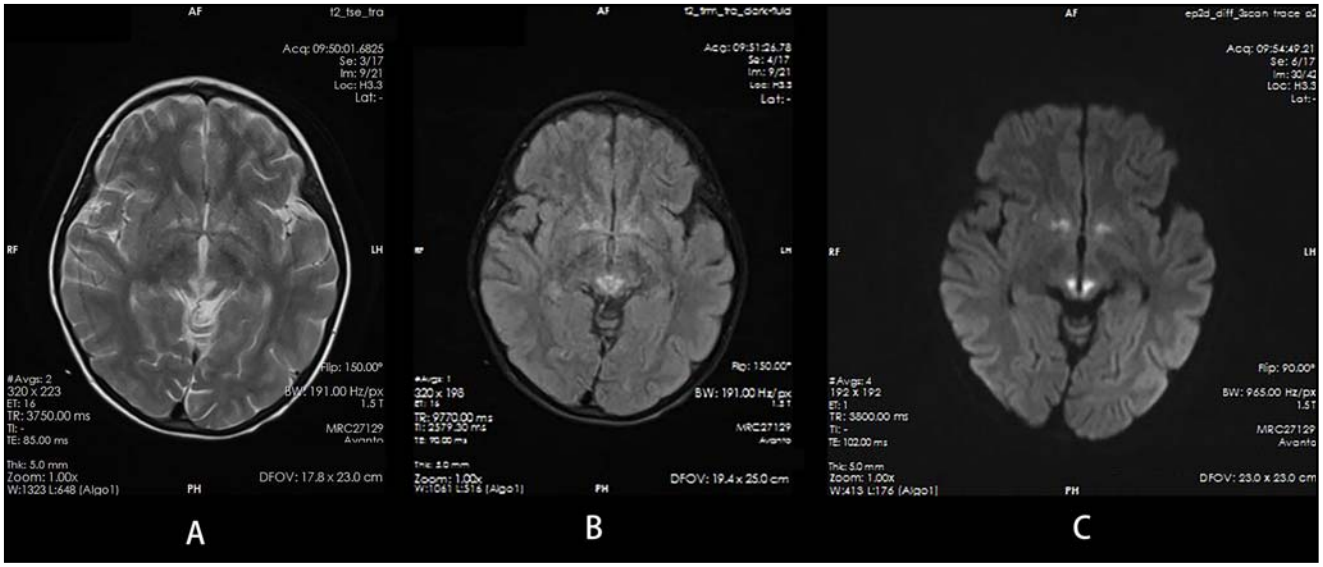

Fig. 2. Non-contrast MRI scans of the head of the patient alongside diffusion-weighted imaging (DWI)—A: Prolonged T2 signal intensities within the bilateral basal ganglia and the interpeduncular fossa located between the cerebral peduncles. B: T2W-Flair sequence shows slightly elevated signal intensity. C: DWI shows slightly elevated signal intensity.

suctioning, and cardiac monitoring, and the patient was transferred to the pediatric intensive care unit for further treatment. The patient exhibited blood-tinged foamy phlegm, a hypotensive blood pressure of 70/50 mmHg, and suboptimal oxygen saturation. Consequently, expedited initiation of mechanical ventilation was undertaken by employing a mechanical ventilator. On examination, the patient appeared confused, pupils exhibiting uniform size and shape along with a normal response to light, and a supple neck devoid of discernible jaundice, rash, or cutaneous bleeding spots. Bilateral lung sounds were symmetrical with moist rales. The heart rate (HR) was 165 beats per minute, with muffled heart sounds but no murmurs. The abdomen was distended and soft. The liver, characterized by a moderate texture, was palpable 4.5 cm below the ribs, while the spleen did not manifest palpability below the ribs. Bowel peristaltic sounds were observed with reduced intensity. The extremities were cold to the touch. The capillary refill time was about 4 seconds. The patient was diagnosed with cardiogenic shock based on these manifestations and was provided with life support measures, including dexamethasone for its anti-inflammatory properties and dexmedetomidine to alleviate sympathetic nervous system stimulation. On September 21st, invasive mechanical ventilation was discontinued. Levocarnitine was added to regulate metabolism, in addition to vitamins B1 and B12 to bolster nerve function. Despite the aforementioned therapy, the child continued to have a flat affect and vacant gaze. Her upper limbs were normal in terms of muscle strength and muscle tone, while her lower limbs were 2+ in terms of strength.

Findings of the patient's bedside echocardiography on the night of September 17th: the left ventricle of the heart demonstrated enlargement. The myocardium in the anterior wall of the left ventricle exhibited approximately normal thickness and echogenicity, coupled with decreased motion amplitude. Spherical expansion was noted in the mid-section of the left ventricle. The myocardium in the remaining segments of the left ventricular wall displayed normal thickness, echogenicity, and motion. Left ventricular ejection fraction (LVEF) was 43%. The echocardiography indicated symptoms of TTC (Figure 1). The electrocardiogram indicated HR at 187 beats per minute and narrow QRS complex tachycardia.

The electrocardiogram recorded on September 23rd displayed no abnormalities. Findings based on blood routine analysis were: white blood cell count (WBC): 42.87*10^9/l, N%: 78.2%, red blood cells (RBC): 4.83*10^12/L, hemoglobin (Hb):143 g/l, platelet count (PLT): 544*10^9/l, C-reactive protein (CRP): normal. Troponin: 2.08 ug/l, creatine kinase-myocardial band (CK-MB): 41.34 IU/L, myoglobin: 219.70 ug/l, and lactic acid: 3.7 mmol/l. Brain natriuretic peptide (BNP), biochemistry, serum amylase, urine amylase, and disseminated intravascular coagulation were normal. Cerebrospinal fluid routine, biochemistry, slide test, and culture exhibited no abnormalities.

Findings based on enhanced whole abdomen computed tomography (CT): 1. 1. The pancreas exhibited fullness, and an accessory spleen was identified. 2. The abdominal intestinal region displayed mild distension attributable to the presence of gas and dilation. Magnetic resonance imaging (MRI) of the head revealed symmetrical patchy areas with prolonged T1 and T2 signal intensities within the bilateral basal ganglia and the interpeduncular fossa situated between the cerebral peduncles. The T2-weighted-fluid-attenuated inversion recovery (T2W-Flair) sequence revealed slightly elevated signal intensity (Figure 2).

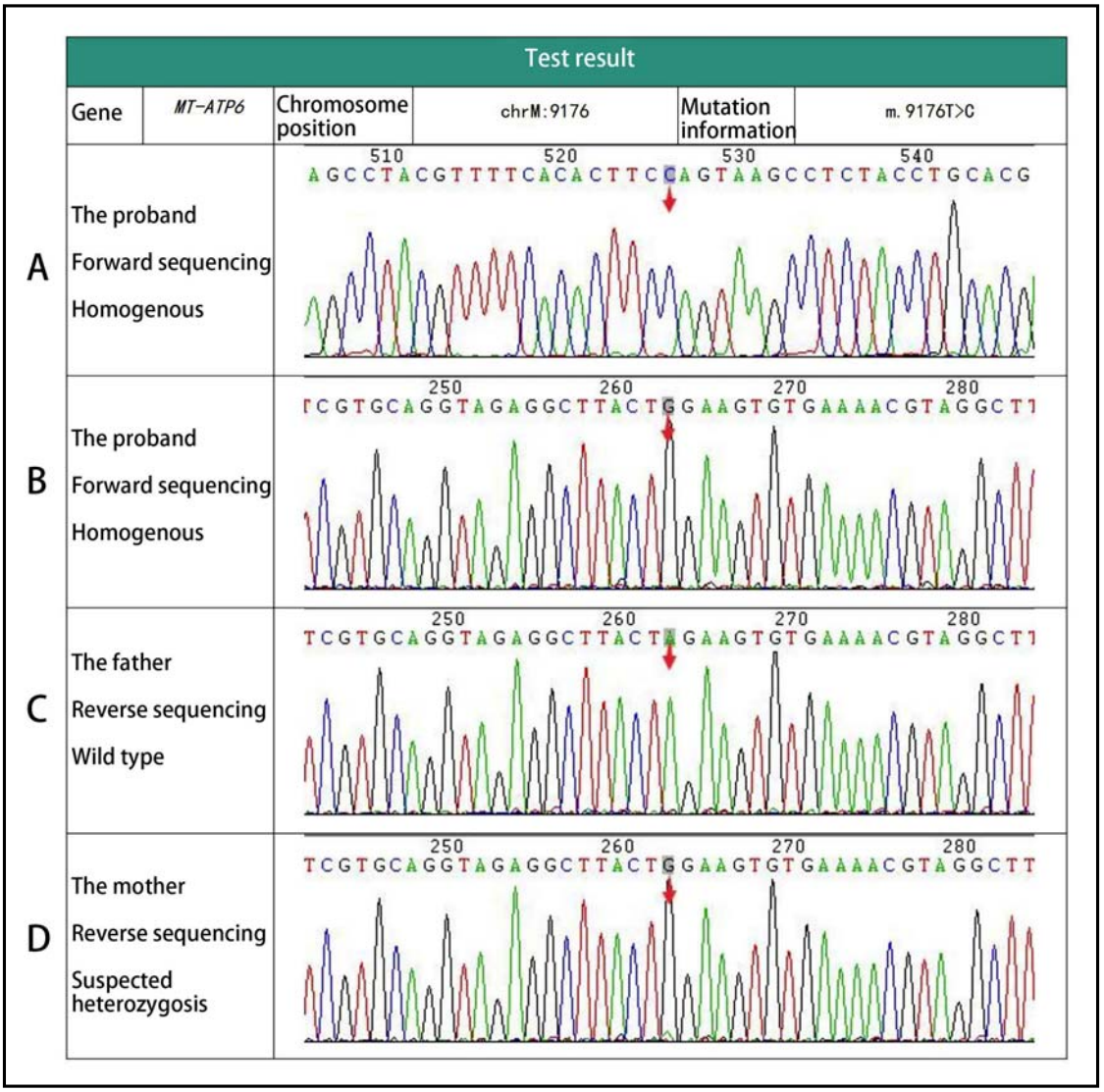

Fig. 3. The molecular genetic testing report for the pediatric patient and parents indicates m.9167T>C (p.Leu217Pro) on the MA-ATP6 gene. This mutation follows a mitochondrial inheritance pattern and is believed to have been inherited from the patient's mother. A: Proband's forward sequencing is homogenous. B: Proband's reverse sequencing is homogenous. C: Father's reverse sequencing is wild type. D: Mother's reverse sequencing shows suspected heterozygosis.

After the treatment, the head MRI revealed no discernible improvement. Suspecting a metabolic disorder, we performed genetic sequencing. Results identified a missense mutation at the chrM: 9716 chromosome position, specifically m.9176T>C (p.Leu217Pro) on the MT-ATP6 gene. This mutation follows a mitochondrial inheritance pattern and is believed to have been inherited from her mother (Figure 3). As a result, the diagnosis was revised to LS. Subsequent screening revealed that the patient's asymptomatic 3-year-old brother carries the same mutation, and comprehensive laboratory and imaging examinations have not been conducted.

DISCUSSION

Mitochondrial diseases are a group of multisystem disorders arising from deficiencies in adenosine triphosphate synthesis and insufficient energy production caused by functional defects in mitochondrial metabolic enzymes. These conditions are often caused by alterations in mtDNA or nDNA. LS is among the most prevalent forms of mitochondrial encephalomyopathy in children, primarily resulting from cytochrome oxidase deficiency. The clinical presentations of LS vary depending on the extent of metabolic disturbance in affected individuals and the specific organs involved (Saneto *et al.* 2008). There are currently no standardized diagnostic criteria for LS. Baertling *et al.* proposed potentially effective criteria in 2014 to aid in the diagnosis of LS with normal or decreased lactic acid levels. The criteria are delineated as follows: ① Manifestation of diverse symptoms emanating from neurodegenerative diseases linked to mitochondrial dysfunction. ② Mitochondrial dysfunction attributable to inherited genetic anomalies. ③ Identification of lesions in the bilateral central nervous system through imaging examinations (Baertling *et al.* 2014). The pediatric patient in this study experienced an acute onset of illness with preceding motor function regression. MRI of the head revealed symmetrical abnormalities in both the bilateral basal ganglia and the interpeduncular fossa located between the cerebral

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peduncles. The diagnosis was confirmed by integrating genetic testing with the aforementioned findings.

TTC, also known as stress-induced cardiomyopathy, is a form of cardiac injury resembling myocardial infarction or myocarditis caused by intense physical or psychological stress. It typically manifests as reversible left ventricular systolic dysfunction and ballooning-like motion abnormality of the left ventricular wall, similar to symptoms seen in acute coronary syndrome (Kenigsberg *et al.* 2019; Gharaibeh *et al.* 2018). The most common form of TTC detected in echocardiography is the cardiac-apex type, accounting for approximately 80%, followed by the mid-ventricular type, accounting for around 15% (Sattar *et al.* 2020; Ali *et al.* 2020). Despite extensive research on stress-induced cardiomyopathy, its precise pathophysiological mechanisms remain unclear. Potential mechanisms include elevated levels of catecholamines in circulation alongside toxic effects on myocardial cells due to heightened activity of the sympathetic nervous system, epicardial coronary artery spasm alongside microvascular dysfunction, and estrogen deficiency alongside endothelial dysfunction (Dawson, 2018; Kono & Sabbah, 2014). In 2019, Topal *et al.* proposed diagnostic criteria for pediatric TTC (Topal *et al.* 2020): (1) Echocardiography: Transient dysfunction of the left ventricle or right ventricle, characterized by reduced motion, motion loss, or reverse motion. The syndrome may present as ventricular apical ballooning or abnormal wall motion, which can be apical, focal, or basal. Potential transitions between all wall motion patterns are observed. The distribution of wall motion abnormalities typically aligns with multiple epicardial vessels. (2) There are triggering factors, encompassing emotional, physical, or a combination of both. (3) Electrocardiographic changes include the presence of atypical patterns such as ST-segment elevation, ST-segment depression, T-wave inversion, and prolonged QTc, among others. (4) Laboratory tests: elevated cardiac biomarkers (troponin, creatine kinase, and BNP). (5) No evidence of infectious myocarditis. As revealed by echocardiography, the patient in this study exhibited brainstem injury, left ventricular enlargement, and spherical dilation in the midsection of the left ventricle of the heart. The diagnosis becomes apparent when these findings are concomitant with markedly elevated troponin levels.

Acute neural injury can enhance sympathetic nervous system activity, precipitating a "catecholamine storm" that triggers TTC. While TTC is a known complication of status epilepticus and CNS infections, this appears to be the first report of LS-induced TTC. Reports of TTC caused by conditions, such as status epilepticus, central nervous system infections, and cerebrovascular diseases, among others, are not uncommon, but there have been no relevant reports of LS followed by TTC. As a severe complication of LS, TTC itself may increase treatment costs, exacerbate neural damage, and add to the difficulty in treating LS. Therefore, early detection and comprehensive treatment are crucial for successful treatment and improved prognosis. The case in this study provides valuable insights into the successful treatment of TTC concomitant with LS.

CONCLUSION

LS is a common form of mitochondrial encephalomyopathy seen in pediatric patients, with diverse clinical manifestations. To our knowledge, this is the first report of TTC complicating LS in the Chinese population. This case expands the known clinical phenotype of LS through a retrospective analysis of clinical data of a pediatric patient. The exploration encompassed specific genetic mutations associated with the disease. This enhanced comprehension contributes to the prospect of early diagnosis and intervention, thereby mitigating the challenges faced by affected children and their families.

DECLARATIONS

Ethics approval and consent to participate

This study was conducted with approval from the Ethics Committee of The First Affiliated Hospital of USTC. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from the patient's legal guardians.

Consent for publication

All patient guardians signed a document of informed consent.

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Yong Lv and Xue-Song Wang conceived the idea and conceptualized the study. Zhen-Zhen Jin and Hua-Bing Tang collected the data. Zhen-Zhen Jin and Xue-Song Wang interpreted the data. Zhen-Zhen Jin and Hua-Bing Tang analyzed the data. Zhen-Zhen Jin drafted the manuscript, and then Yong Lv reviewed the manuscript. All authors read and approved the final draft.

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