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Adult-onset Leigh syndrome with recurrent seizures and peripheral neuropathy due to the 9176T > C mutation: a case report and literature review

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Abstract

Background Leigh syndrome (LS) is an inherited form of mitochondrial encephalopathy associated with various gene mutations of the oxidative phosphorylation system, typically occurring in infancy or early childhood and resulting in disability or even death. However, few late-onset cases have been reported.

Objective The objective of this case report was to investigate the radiological and clinical characteristics of an adult patient diagnosed with Leigh syndrome.

Case presentation This article describes a patient who presented with recurrent generalized seizures, peripheral neuropathy and hypertension and was ultimately diagnosed with Leigh syndrome with a mitochondrial gene variant, c.9176T > C (p.Leu217Pro), in 20,315 of the MT-ATP6 gene. Here, we discuss the possible pathogenesis of its clinical manifestations according to the related literature and review the current therapeutic approaches and prognosis of LS.

Conclusion A possible diagnosis of LS should be taken into consideration when patients with characteristic neuroimaging findings of LS demonstrate recurrent seizures, peripheral neuropathy, or hypertension, and genetic analysis should be carried out for differential diagnosis.

Keywords Leigh syndrome, MT-ATP6 gene, Peripheral neuropathy, Recurrent seizure, Hypertension, Basal ganglia, Mitochondrial diseases

Introduction

Leigh syndrome (LS), also known as subacute necrotizing encephalopathy (SNE), is a rare and complicated neurodegenerative disease caused by gene mutations in either nuclear or mitochondrial genome-encoded proteins in the oxidative phosphorylation system (OXPHOS) and is the most common mitochondrial disease in children [1, 2]. Bilateral, symmetrical necrotizing lesions distributed in the basal ganglia and brainstem and elevated lactate in the serum or cerebrospinal fluid (CSF) are clinical characteristics of LS. Its clinical manifestations range from a series of neurodegenerative symptoms including growth

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retardation, ataxia, seizures, dysphagia, ptosis, hypotonia or spasticity, dystonia, nystagmus, and sleep apnoea to other symptoms, such as feeding difficulties and failure to thrive. These symptoms vary from case to case, largely depending on the affected areas in the central nervous system [3, 4]. Most cases of LS have an early onset with rapid deterioration and ultimately disability or even death in infants. Late-onset LS is relatively rare, and the disease course is mild and has a better outcome. LS is often misdiagnosed as other diseases because of its lack of specificity in terms of clinical manifestations.

Here, we report an adult female patient with late-onset LS. The possible pathogenesis of LS's clinical manifestation and the relevant literature were reviewed and discussed.

Case presentation

A 21-year-old female with bilateral weakness in the lower extremities and recurrent seizures was admitted to our hospital in October 2021. One month before her admission, she went to another hospital due to lobar pneumonia. At that time, she experienced weakness in both lower extremities because of hypokalaemia which improved after supplementation with potassium. Ten days later, her lower limbs were weak again, and she experienced chest tightness, abdomen distention, and headache, and facial flushing. Her blood pressure (BP) increased to 190/150 mmHg and did not improve after taking nifedipine (0.03 g/day). She was subsequently sent to a local emergency room, where she experienced generalized tonic–clonic seizures (GTCSs) with unconsciousness and urinary incontinence. After intravenous administration of diazepam, the seizures ended, and consciousness gradually recovered. One hour later, the seizure recurred, with symptoms similar to those seen previously. The patient was subsequently transferred to our hospital for further diagnosis and treatment.

According to her parents' description, the patient had congenital external ophthalmoplegia in her left eye but had no diplopia, and her eyesight was normal. She had learned to walk until 18 months of age but still could not run, indicating that her development of motor function was slower than that of normal children. Furthermore, the patient has no history of alcohol intake and was allergic to cephalosporins and Salvia miltiorrhiza bunge(a kind of plant traditional Chinese medicine). Her grandparents and uncle had hypertension, and her mother had ischaemic stroke and hypertension. She had hypertension for almost 6 months before admission, and the highest recorded blood pressure was 150/110 mmHg. The physical examination revealed normal consciousness and cognitive function. There was symmetrical weakness in her distal lower extremities (muscle strength 4/5 grades) and diminished muscle tone in both the upper and lower extremities. Additionally, the knee jerk disappeared on the left side and was weak on the right side, whereas Babinski signs were positive on both sides. She had no sensory impairment but showed unsteadiness in the bilateral heel–knee–shin tests. The patient also presented with several congenital abnormalities, including external ophthalmoplegia in the left eye and bilateral pes cavus.

In the imaging examinations, there were low signals at T1 (Fig. 1. A), high signals at T2 (Fig. 1. B) and high signals on fluid attenuated inversion recovery (FLAIR) sequences (Fig. 1. C) of brain magnetic resonance imaging (MRI) in the dorsal brainstem, mesencephalic aqueduct and bilateral basal ganglia, but there was no obvious enhancement in the contrast images. Diffusion-weighted imaging (DWI) (Fig. 1. D) show dotted and limited diffusion signals in the above areas. The cervical, thoracic, and lumbar spinal cord MR images were all normal. Electromyogram examinations revealed reduced motor unit action potential (MUAP) amplitude in the upper extremities, reduced compound muscle action potential (CMAP) amplitude with slowed velocity in the lower extremities, and reduced sensory nerve action potentials (SNAPs) amplitude in the upper extremities. The chest X-ray revealed bilateral pneumonia, the pituitary MR showed suspectable pituitary adenoma, and the thyroid gland ultrasound showed hyperplastic nodules. The adrenal glands contrast-enhanced CT, electrocardiogram, abdominal aorta, iliac artery and lower extremity artery ultrasound and transthoracic echocardiograph of the adrenal glands were all normal.

Routine laboratory tests revealed hyperlipidaemia and hypercholesterolaemia. Insulin-like growth factor 1 (IGF-1) was highly expressed at a concentration of 479 ng/ml. Other hormone series tests, including oral glucose tolerance tests (OGTTs), serum C-peptide tests, serum insulin measurements, cortisol circadian rhythm tests, low-dose and high-dose dexamethasone suppression tests, plasma catecholamine determination, plasma aldosterone/renin ratio (ARR) tests and 24-h urine free cortisol tests, were all normal.

First, the patient was referred to the Department of Endocrinology and Metabolism, and the diagnosis of "hypertensive encephalopathy" was taken into consideration because of abnormal hypertension and recurrent seizures. Both nifedipine (30 mg/day) and doxazosin mesylate (4 mg/day) were given orally to decrease blood pressure. However, the antihypertensive effect was slight, and other clinical symptoms were not relieved either. She was subsequently transferred to the Department of Neurology due to peripheral neuropathy and abnormal signals on brain magnetic resonance imaging (MRI). Cerebral spinal fluid (CSF) assessment revealed a high protein concentration of 648 mg/L, while the results

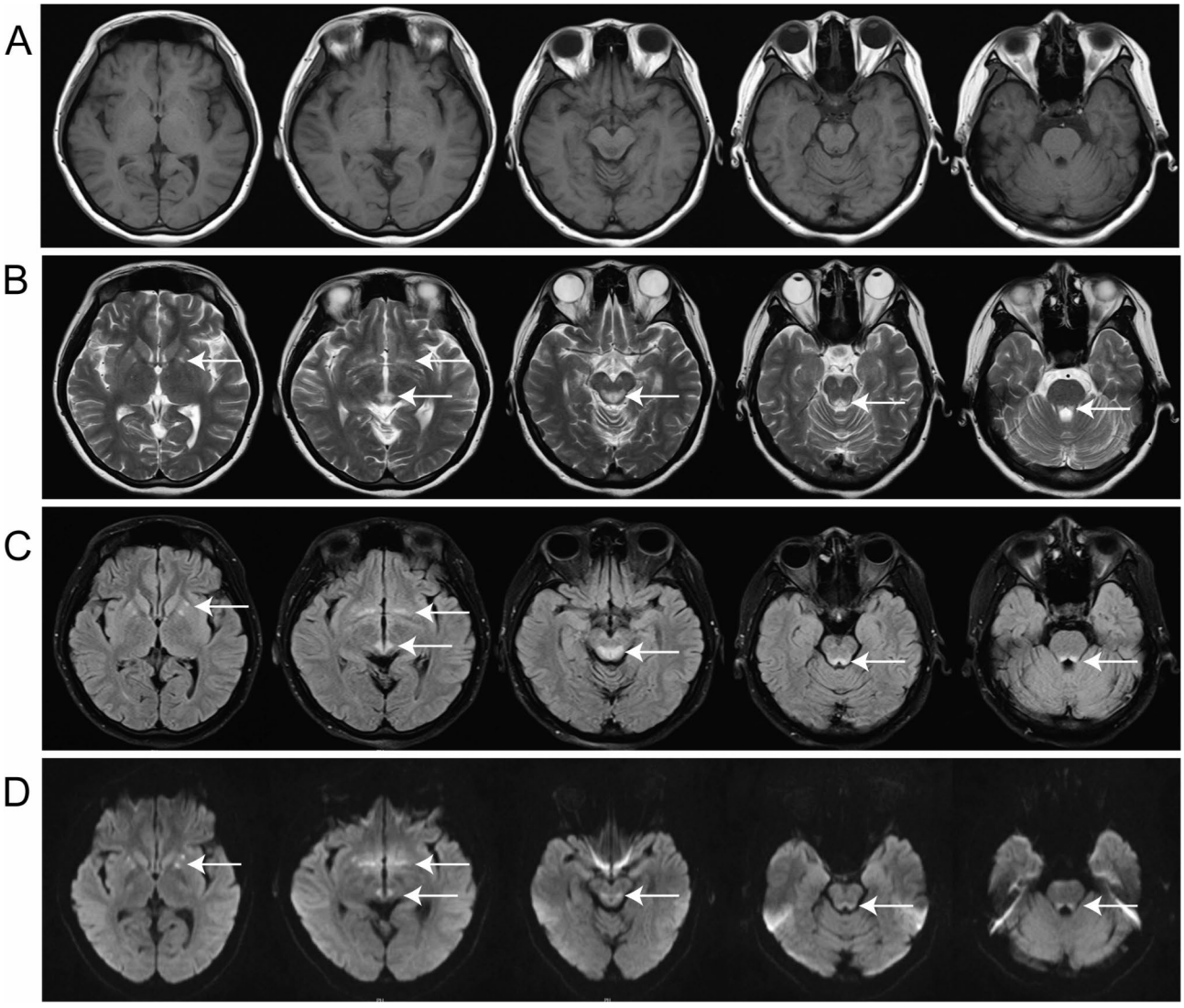

Fig. 1 Brain MR image of the patient in October 2021 showing bilateral symmetrical lesions with abnormal signals in the dorsal brainstem, mesencephalic aqueduct and bilateral basal ganglia on T1 (**A**), T2 (**B**), FLAIR (**C**) and DWI images (**D**)

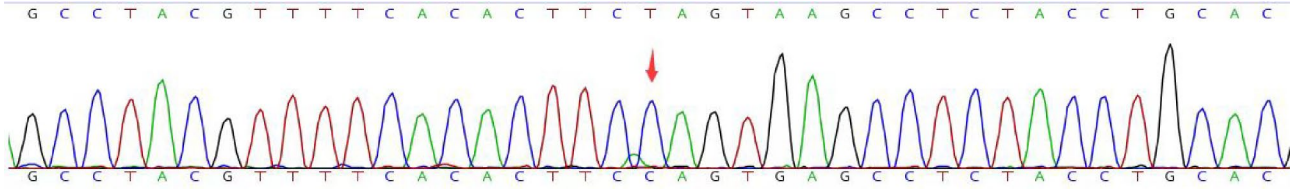

Fig. 2 Sequencing results of the MT-ATP6 gene in the patient. The sequencing revealed a heterozygous mutation, c.9176T > C (p.Leu217Pro)

of cytology, biochemistry and culture examinations were all normal. The autoimmune antibodies associated with central nervous system demyelinating diseases [myelin oligodendrocyte glycoprotein (MOG), aquaporin 4 (AQP4), glial fibrillary acidic protein (GFAP) and myelinbasicprotin(MBP)] and autoimmune peripheral neuropathy [anti-Sulfatide antibodies, anti-GMs(GM1, GM2,GM3,GM4)antibodies, anti-GDs(GD1,GD2,GD3) antibodies, anti-GTs(GT1a, GT1b) antibodies and anti-GQ1b antibodies] as well as the oligoclonal bands in the serum and CSF were all negative.

At last, genetic analysis was carried out, and the results revealed a heterozygous missense mutation, c.9176T > C, in the MT-ATP6 gene, supporting the diagnosis of LS syndrome (Fig. 2). The final diagnosis of LS, hypertension, peripheral neuropathy and hypercholesterolemia

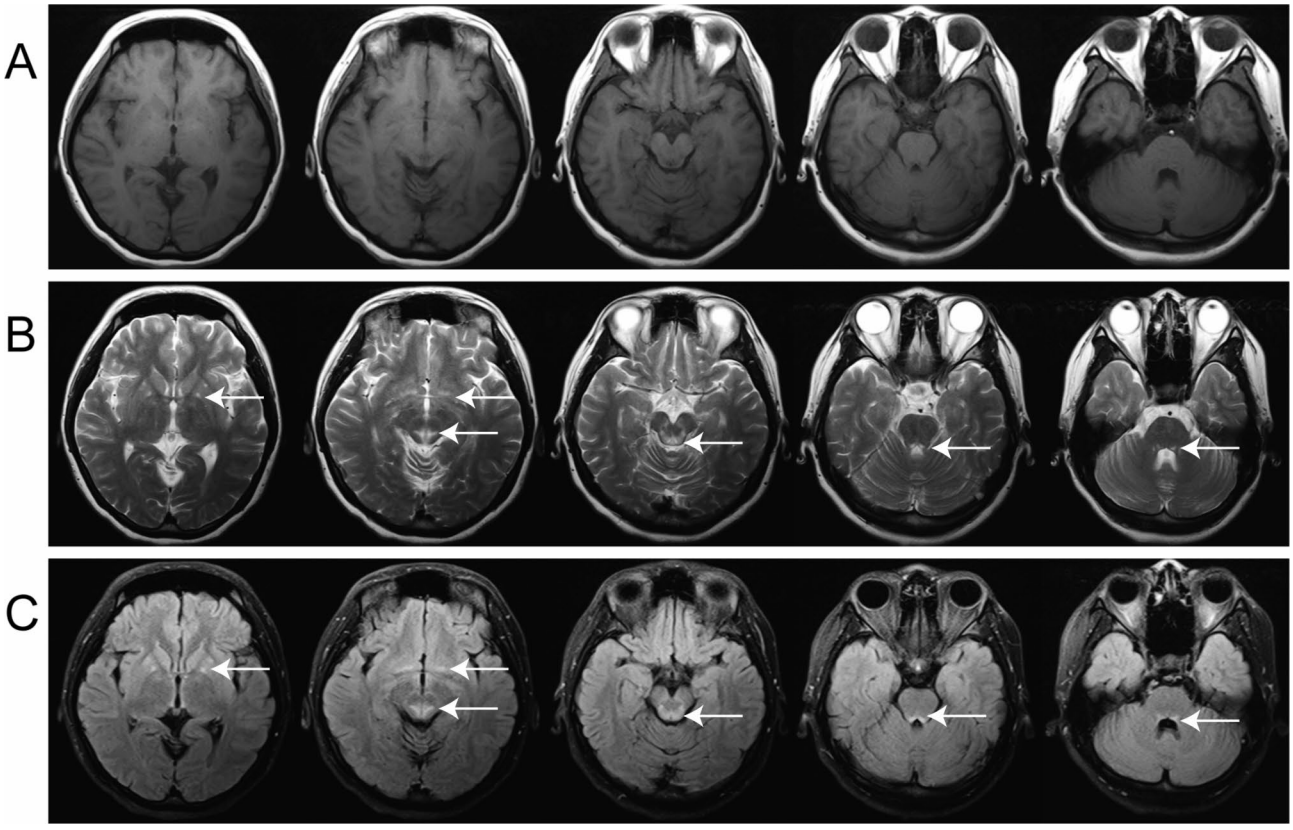

Fig. 3 Compared with the previous images, the following lesions have been alleviated: cranial T1-weighted (**A**), T2-weighted (**B**) and FLAIR (**C**) MR images reveal bilateral symmetrical shrunk lesions with abnormal signals in the dorsal brainstem, mesencephalic aqueduct and bilateral basal ganglia

was confirmed. The patient was subsequently treated with doxazosin mesylate to control blood pressure, mecobalamin to treat defects in peripheral neuropathy, and rosuvastatin to regulate the level of cholesterol. Twelve days after admission to our hospital, brain MRI was examined and revealed slight regression of the former lesions. When we called back for the follow up, no seizures occurred again, and the power of her lower limbs has been improved progressively.

One month after hospitalization, the brain MRI was repeated and revealed a reduction in the former lesions (Fig. 3). One year later, at a follow-up visit the weakness in her lower limbs had completely recovered, her blood pressure was normal, and the seizures had not occurred again.

Discussion and literature review

LS covers a diverse phenotypic spectrum due to its clinical and genetic heterogeneity. To date, more than 75 LS-associated genes have been identified [3]. LS can be inherited in any of the following inheritance types: maternal trait, autosomal recessive trait, or X-linked inheritance. The presentation of LS differs with various degrees of mutant loads [5]. Generally, typical onset occurs before 2 years of age (early onset) or even earlier in the neonatal period, resulting in delayed development, such as feeding difficulties and failure to thrive [5]. In more diverse forms, late-onset patients may develop neurological symptoms, including behavioural psychiatric disorders, intelligence reduction, movement disorders, headache, and memory loss, or even multiple sclerosis phenotypes [5, 6]. In addition, there is a condition that involves multisystemic deficits without neurological symptoms, which is defined as Leigh-like syndrome (LLS), including cardiac, hepatic, gastrointestinal, and renal tubular dysfunction; haematological abnormalities; and dysmorphic distinctions [7].

LS is often triggered by stress conditions, such as acute infection, vaccination, anaesthesia, drugs, and surgery, which demand more energy be generated by the mitochondria [2, 7]. The neuroimaging hallmarks of LS are bilateral, symmetrical hyperintensities in the basal ganglia and brainstem, especially in the putamen, substantia nigra, nucleus ruber and medulla oblongata, on T2-weighted images; and FLAIR sequences of magnetic resonance imaging (MRI), the thalamus and the spinal cord can also be affected. A lactate peak may also be found in affected areas via magnetic resonance spectroscopy (MRS) [2, 4, 5, 8].

In our case, the patient had late onset and had no obvious inducing factors but presented typical neuroimaging findings of LS, as mentioned above. Notably, one special clinical manifestation in this patient was peripheral neuropathy.

In the peripheral nervous system, myelin Schwann cells (SCs) form myelin sheaths that facilitate rapid and efficient conduction of action potentials in peripheral axons. SCs demand high metabolic energy generated by mitochondria to maintain axonal structure and function [9]. Therefore, abnormal mitochondria could cause defects in peripheral nerves. Peripheral neuropathy is a unique manifestation and occurs very rarely in mitochondrial diseases induced by MT ATP6 mutations, including NARP, MILS (Maternally Inherited Leigh Syndrome), CMT2-like (Charcot–Marie–Tooth neuropathy) and dHMN-like (distal hereditary motor neuropathy), which usually demonstrate striking sensory axonal or motor axonal deficits [10]. Avril Ea et al. described a Canadian family with predominant ataxia and peripheral neuropathy who was diagnosed with LS due to a 9185T > C missense mutation at high heteroplasmy in the MT ATP6 gene [11]. LS with peripheral neuropathy commonly occurs in children and is often mild and easy to miss. However, a 26-year-old man diagnosed with LS due to a mitochondrial 9176T > C mutation was reported to have central fever and peripheral neuropathy and died of respiratory failure 5 months after the onset of disease [12]. Therefore, a mitochondrial disorder should be considered when patients present with peripheral neuropathy together with some congenital abnormalities, such as ptosis, ophthalmoplegia, gastrointestinal dysmotility, cerebellar ataxia, decreased visual acuity, pigmentary retinopathy, and hearing loss, especially with white matter abnormal signals on MRI [10].

Another special clinical feature of this case was recurrent seizures. There was no relevant lesion in the patient's brain that can explain her epilepsy. Therefore, whether epilepsy is related to LS is uncertain. Notably, epilepsy often has a multisystem clinical presentation and is among the most common neurological features of primary mitochondrial diseases [13]. Mitochondria can produce energy in the form of ATP and maintain the homeostasis of cellular ions. Specifically, as a highly energy-demanding organ, the brain is more vulnerable to mitochondrial disorders that cause the frequent occurrence of epileptic seizures in LS [14]. On the basis of current evidence, seizures in primary mitochondrial diseases can be explained mainly by ATP depletion resulting from defective OXPHOS. On the other hand, epileptic seizures themselves can lead to mitochondrial dysfunction through the release of deleterious compounds and disruption of mitochondrial metabolism, generating a self-perpetuating cycle [15]. With respect to auxiliary examinations, epilepsy in primary mitochondrial diseases is not associated with pathognomonic electroencephalography (EEG) findings, and not all seizures involve epileptogenic lesions. A review revealed that epilepsy may occur in primary mitochondrial diseases, including mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibres (MERRF), POLG-related disorders and Leigh syndrome (LS). Approximately 40% of LS patients present with seizures during their disease course, which may occur as a combination of distinct seizure types [16]. In a retrospective study of 110 patients with a diagnosis of LS, 21.6% experienced seizures (24 patients), the second most common symptom at disease onset. Among those twenty-four patients, eleven patients had focal seizure loci, eight patients had generalized seizures, two patients had partial seizures with secondary generalization, and three patients had unclassified epileptic seizures [6]. A history of epileptic seizures and pathological signs at birth are strongly related to a poor prognosis of LS, and the corresponding therapy is more challenging [4, 16]. In brief, epilepsy is a common symptom of LS that should be considered when patients have recurrent seizures and other congenital anomalies.

The aetiology of the hypertension in this patient remains uncertain. Because she was very young and all of the related hormone tests and examinations were normal, identifying the cause of hypertension was difficult. Hypertension is an uncommon symptom of LS. To date, only seven cases of LS with hypertension have been reported, six of which involved children. Among these six patients, five presented with hypertension accompanied by respiratory abnormalities [17–21], and another presented with WPW-like conduction defects, cardiomyopathy and hyponatraemia [22]. On the other hand, five children patients died within several months, and only one child recovered 70 days later. Notably, the initial symptom of these patients was not hypertension, which often occurs in the terminal stage of LS and is usually accompanied by a poor outcome. A 26-year-old woman with reversible cerebral vasospasm syndrome (RCVS), transient cardiac wall hypertrophy (posterior wall dominance), marked hypertension (206/142 mmHg) and ECG abnormalities was diagnosed with LS. However, her blood pressure returned to normal after admission without antihypertensive agents [23]. After months of treatment, her neurological symptoms were also relieved, and her abnormal brain MRI findings were dramatically alleviated, similar to our patient. These findings suggest that adults with LS and hypertension tend to have a milder disease course and better prognosis than children. Hypertension accompanied by LS may result from brainstem lesions involving the medulla that modulate sympathetic nerve activity under hypoxia [24].The relationship

between LS and hypertension needs to be further investigated in the future.

Therapeutic approaches

To date, there are still no specific and effective therapeutic strategies for LS. The available options are symptomatic therapies consisting of supplements (CoQ10 and its derivatives), vitamins, pyruvate, dichloroacetate, and a ketogenic diet (KD) [2]. Mitochondrial replacement therapy, gene therapy, hypoxia treatment and immunotherapies such as plasma exchange and intravenous immunoglobulin are promising options for LS and other mitochondrial disorders and are promising for improving the prognosis of these diseases [2, 5, 25, 26]. There are some strategies for targeting seizures/ epilepsy in mitochondrial disease. An international Delphi-based consensus concerning the safety of drug use in patients with primary mitochondrial disease revealed that seizures/ epilepsy in primary mitochondrial diseases should be treated similarly as in non-mitochondrial epilepsy [27]. Levetiracetam is regarded as a safe treatment, and it is a first choice for myoclonus, especially in MERRF [16]. Levetiracetam combined with clonazepam, clobazam, or topiramate are as the first-line therapy. Lamotrigine is safe and effective, but it may enhance myoclonic seizures. There are some reports indicate that perampanel, zonisamide and lacosamide are effective to treating MELAS or drug-resistant seizures are effective. Drugs' toxicity and potential negative effect on myoclonus should be taken more attention when using other antiseizures medications like oxcarbazepine, phenytoin or phenobarbital [16, 28]. Patients with POLG mutations should avoid sodium valproate due to mitochondrial toxicity [29]. Most patients are prone to demand multiple antiseizures medications and even progress to drug-resistant epilepsy. The ketogenic diet was confirmed effective and has been widely used in patients with mitochondrial intractable epilepsy. Moreover, there are study reported that vagal nerve stimulation (VNS), deep brain stimulation (DBS) and palliative surgery were used to treat drug-resistant epilepsy [16]. In conclusion, treatments for mitochondrial epilepsy are challenging, it is significant for clinicians to choose best antiseizures drugs to control seizure attacks.

Prognosis

The prognosis for LS remains poor. All over the world, the mortality of LS before adulthood ranges from 23.8 to 39.2% [30–32]. Compared with early-onset patients, particularly those younger than 6 months of age, late-onset patients have markedly better survival. Erika Ogawa. et al. reported the mortality data of 166 Japanese patients, 40.3% of the 62 patients in the early-onset group died, while only 14.3% of the 98 patients with onset after 6 months of age died, and nearly 90% of deaths occurred by age 6 [32]. Conversely, Sarah L. Stenton et al. reported a study of 209 Chinese patients who did not support poorer survival in patients with earlier onset before 6 months [31]. Moreover, the survival of LS varies with genotype. Patients who have defects in MT-ND5 and MT-ATP6 (m.8993T > C and m.9176T > C) have poorer survival, whereas patients with SURF1 deficiency have relatively mild symptoms and better survival [31].

Conclusion

Here we reported a case of adult-onset Leigh syndrome with heterozygous variants in the MT-ATP6 gene: c.9176T > C. When patients present with peripheral neuropathy, sudden hypertension and recurrent seizures, together with characteristic neuroimaging findings of white matter changes in the basal ganglia and brainstem, LS should be taken into consideration by clinicians, and genetic analysis should be carried out in time to confirm the diagnosis.

Abbreviations

LS	Leigh syndrome
OXPHOS	Oxidative phosphorylation system
CSF	Cerebrospinal fluid
CNS	Central nervous system
nDNA	Nuclear DNA
mtDNA	Mitochondrial DNA
BP	Blood pressure
GTCS	Generalized tonic–clonic seizure
MRI	Magnetic resonance imaging
FLAIR	Fluid attenuated inversion recovery
DWI	Diffusion-weighted imaging
EEG	Electroencephalography
MUP	Motor unit potential
MCAP	Motor conduction action potential
SNAPs	Sensory nerve action potentials
LLS	Leigh-like syndrome
MELAS	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
NARP	Neuropathy, ataxia, and retinitis pigmentosa syndrome
CMT	Charlot–Marie–Tooth neuropathy
MILS	Maternally inherited Leigh syndrome
dHMN	Distal hereditary motor neuropathy
MERRF	Myoclonic epilepsy with ragged red fibres
IVIG	Intravenous immunoglobulin
RCVS	Reversible cerebral vasospasm syndrome

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Author contributions

YL drafted the manuscript, edited the radiological images and searched the related literature. Yaxin Lai and XC collected the clinical data of the patients. SZ revised and finalized the manuscript and supervised the study. All the authors have read and approved the final manuscript.

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Data availability

Data is provided within the manuscript. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
We hereby confirm that the present report conforms to the ethical standards and guidelines of the journal.

Consent for publication
Written informed consent for publication was obtained from the patient. A copy of the written consent is available for review by the editor upon request.

Competing interests
The authors declare no competing interests.

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