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【 CASE REPORT 】

# Adult-onset Leigh Syndrome with a m.9176T＞C Mutation Manifested As Reversible Cerebral Vasoconstriction Syndrome

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**Abstract:**

A 26-year-old woman developed a sudden headache, ptosis, and diplopia. Magnetic resonance imaging and angiography demonstrated a symmetrical lesion from the midbrain to the brainstem, involving the solitary nucleus and multifocal cerebral artery narrowing. Reversible cerebral vasoconstriction syndrome (RCVS) was suspected, and the patient improved after vasodilatation. Leigh syndrome was suspected due to the elevated serum pyruvate level, so mitochondrial DNA was analyzed, and an m.9176T>C mutation was detected. The final diagnosis was adult-onset Leigh syndrome manifesting as RCVS. An uncontrolled baroreflex due to a solitary nuclear lesion or endothelial dysfunction may have contributed to her unique presentation.

**Key words:** Leigh syndrome, reversible cerebral vasoconstriction syndrome, thunderclap headache, mitochondrial disease

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## Introduction

Leigh syndrome is a rare disorder characterized by subacute necrotizing encephalopathy (1). It is caused by mitochondrial dysfunction and named after Leigh, who first described it in 1951 (2). Clinically, it manifests with various symptoms, including psychomotor regression or retardation, optic atrophy, opthalmoplegia, ptosis, and respiratory failure due to brainstem dysfunction. The prevalence of this disease is estimated to be 1 in 40,000 newborn children, and most documented case have been of infantile-onset ones between 3 and 12 months old. The prognosis is generally poor with high mortality, and most patients die before five years old (3).

Recently, advances in molecular genetics, including the discovery of several mutations in the mitochondrial and nuclear genes, have expanded the concept of Leigh syndrome (4). Dysfunction of the mitochondria respiratory chain in complex I, II, IV, and V (including the *ATP6* mutation, which comprises about 5-10% of Leigh syndrome cases) as well as coenzyme Q and pyruvate dehydrogenase have been reported to contribute to the pathogenesis, and more than 60 genes have been discovered to cause Leigh syndrome (5, 6). Consequently, we now recognize that Leigh syndrome can cause non-neurological symptoms, in-

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cluding cardiac abnormality (mainly hypertrophic cardiomyopathy), and the disease can be diagnosed in adult cases, with an elderly-onset case in a 74-year-old patient being reported (7).

We herein report a unique case of adult-onset Leigh syndrome that manifested as reversible cerebral vasoconstriction syndrome (RCVS), probably due to solitary nucleus dysfunction or endothelial dysfunction of the cerebral artery.

## Case Report

A previously healthy 26-year-old woman with normal development felt that her eyelids were getting heavy 1 month before hospital admission (day X-30). On day X-8, she developed diplopia; on day X-6, a sudden-onset thunderclap headache with mild chest discomfort prompted a visit to the hospital.

Her systolic blood pressure and heart rate were 206/142 mmHg and 130 beats/min, respectively. Brain computed tomography did not reveal any abnormalities, and the patient was managed conservatively. However, on day X-2, the recurrence of the thunderclap headache prompted the patient's admission for a further examination.

On admission (day X), her blood pressure had normalized to 115/81 mmHg; however, her heart rate remained elevated at 103 beats/min. A neurological examination revealed bilateral blepharoptosis and inferior oblique muscle palsy. Diagnostic tests revealed hypo-osmolar hyponatremia (serum sodium, 118 mEq/L; osmolality, 273 mmol/L) and decreased plasma renin activity (1.9 ng/mL/h). The urine sodium concentration increased to 43 mEq/L, with an increased osmolality of 368 mmol/L, suggesting renal salt wasting or syndrome of inappropriate antidiuretic hormone. Brain natriuretic peptide (486.9 pg/mL) and pyruvate (1.6 mg/dL; normal range: 0.3-0.9 mg/dL) were elevated, but with normal lactate and thiamine levels. She was negative for autoantibodies against the nucleus, neutrophilic cytoplasm, aquaporin 4, and myelin oligodendrocyte glycoprotein.

An electrocardiogram (ECG) showed U waves on V1-V3 leads despite a normal serum potassium level (3.9 mEq/L). A cerebrospinal fluid (CSF) analysis showed a normal cell count (1/$mm^3$) and protein level (40 mg/dL); lactate and pyruvate levels in the CSF were not measured. The IgG index was 0.72, and the oligoclonal bands were negative. Magnetic resonance imaging (MRI) detected symmetrical lesions from the medulla oblongata, including the solitary nucleus and pons, to the midbrain tegmentum along the ventricle (Figure A-D) but sparing the inferior olivary nucleus, area postrema, mammillary bodies, pituitary gland, and hypothalamus. The apparent diffusion coefficient (ADC) value in each lesion was low. Magnetic resonance angiography (MRA) revealed severe multifocal narrowing of the right vertebral, superior cerebellar, and posterior cerebral arteries (Figure E), although the brain lesions did not match the vascular territory.

Since her clinical course (repeated thunderclap headache) and MRA findings suggested RCVS, treatment with calcium channel blockers (verapamil 120 mg/day) was initiated on day X+4. Consequently, the vessel morphologies on MRA were nearly normal by day X+8 (Figure F), with the headache improving within two weeks.

After hospitalization, the sodium levels were slowly corrected and normalized. Magnetic resonance spectroscopy (MRS) on day X+37 with the region of interest set at the midbrain showed a lactate peak (Figure G). The ECG patterns continued to change: U-waves resolved on day X+5, but T-waves in leads V1-V5 progressed. Transthoracic echocardiography showed a diffusely hypertrophic myocardium in the posterior (13 mm) and interventricular septal (11 mm) walls with increased echogenicity.

Based on these clinical findings, elevated serum pyruvate levels, symmetrical brain lesions on MRI, and the lactate peak on MRS, all of which were compatible with Leigh syndrome (1), mitochondrial DNA from a blood sample was analyzed. Consequently, the m.9176T>C mutation was confirmed, which was previously described as an *ATP6* gene mutation in Leigh syndrome and was associated with the substitution of the highly conserved leucine to proline at amino acid position 217 of subunit α (8, 9). Blood, urine, and cardiac tissues from an endomyocardial biopsy were further analyzed for mitochondrial genome mutations using both next-generation sequencing and Sanger sequencing. All samples revealed a homoplasmic state of m.9176T>C substitution.

Immunostaining of the cardiac muscle using an antibody against mouse *MT-ATP6* (MT-ATP6 polyclonal antibody, PA5-109432; Invitrogen, Thermo Fisher, Waltham, USA) was preserved. Although no data concerning immunostaining in a case with an m.9176T>C mutation were available at the time, we suspected that this pattern might have been due to an issue with the antigen-binding site, as one amino acid mutation might not have influenced the result.

The patient was ultimately diagnosed with adult-onset Leigh syndrome with a m.9176T>C mutation, manifesting as RCVS. We speculated that the possibility of posterior reversible encephalopathy syndrome or secondary damage due to ischemic stroke by RCVS was relatively unlikely, given the ADC value and the fact that the lesion distribution did not match the vascular territory. It might have been valuable to check for the m.9176T>C mutation in her family members, especially her mother, but her mother was asymptomatic and thus was not further analyzed.

After months of multi-vitamin supplementation and 5-aminolevulinic acid hydrochloride treatment, her neurological symptoms resolved, including dramatic reductions in her brain MRI findings (Figure H).

## Discussion

We encountered a unique case of adult-onset Leigh syndrome manifesting as RCVS. Leigh syndrome is historically regarded as an infant disease, but current opinion is that this

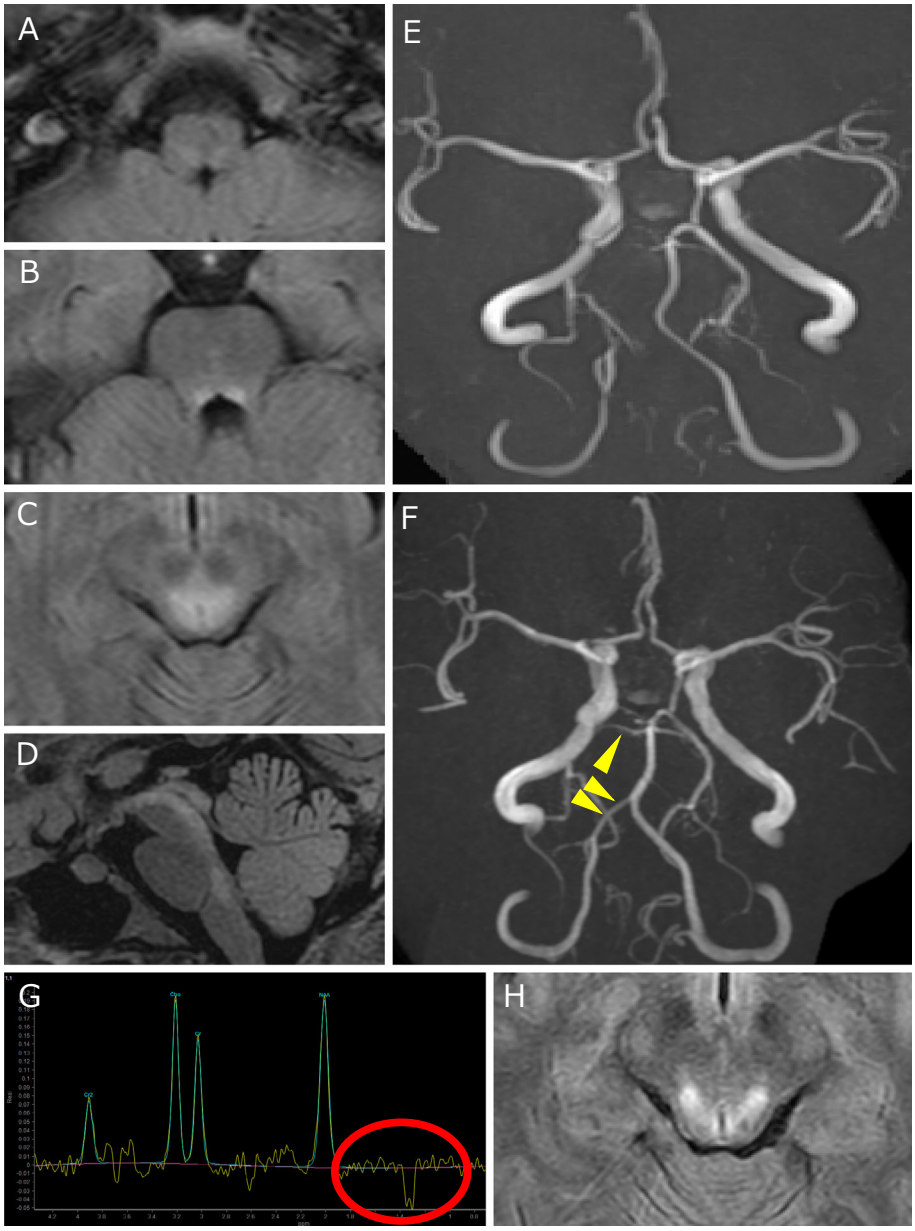


**Figure.** **A-D are fluid attenuated inversion recovery images. A-C were taken on day X-1 and depict a symmetrical brainstem lesion from the medulla oblongata to the midbrain. D was taken on day X+8 and depicts a longitudinal lesion from the pons to the midbrain along the ventricle. E and F depict magnetic resonance angiography results on day X-1 and X+8, respectively. Focal stenosis in posterior circulation was improved (yellow arrow). G is the date of magnetic resonance spectroscopy (long echo-time of 144 msec, region of interest at the midbrain lesion), showing a downward lactate peak. H was taken on day X+43, demonstrating near resolution of the brainstem lesion.**

syndrome could comprise various phenotypes, including unusual, non-infantile-onset cases. Indeed, over 50 case reports of adult Leigh syndrome can be found in Medline (10), and a nationwide study in Japan noted that 13 of 166 cases of Leigh syndrome were adult-onset (3).

The m.9176T>C substitution, as seen in our case, induces an *MT-ATP6* gene mutation, which encodes a subunit of the Fo ATP-synthase complex in complex V of the electron transport chain (11). In addition, eight pathogenic variants have been reported in *ATP6*. The clinical features of *ATP6* gene mutations vary; 55% have classic Leigh syndrome, 18% have Leigh-like syndrome, and 8% have neuropathy, ataxia, and retinitis pigmentosa syndrome, with a broad range of the onset age, from the prenatal period to 75 years old (11). Among these variants, on limiting the discussion to Leigh syndrome with the m.9176T>C mutation, nine adult-onset cases of Leigh syndrome have been reported (8). However, the clinical course and symptoms were variable, and none of these patients developed RCVS.

Our case had two interesting features. The first is a longitudinal brain lesion along the ventricle observed on MRI. This impressive symmetric lesion from the brainstem to the

diencephalon is reminiscent of a metabolic disorder. Generally, Leigh syndrome affects the putamen, substantia nigra, red nucleus, and medulla oblongata. Variable areas in the brainstem or basal ganglia may also be affected (1). However, longitudinal lesions along the ventricle, as observed in our case, have not been reported. The reason for this is unclear, but it might be associated with individual differences in areas where oxidative metabolism is prominent (1).

The second feature is the narrowed supratentorial vessel, visualized using MRA. Typical headaches and effective therapy with vasodilators suggest an underlying vasoconstrictive mechanism in RCVS (12). RCVS has not yet been reported as a clinical manifestation of Leigh syndrome. However, marked hypertension associated with a lesion of the solitary nucleus has been described in two other reports of Leigh syndrome (13, 14). Given these findings, we speculate that our patient suffered from an uncontrolled baroreflex due to solitary nucleus dysfunction that led to marked hypertension as well as secondary spasms of the intracranial arteries through dysregulation of arterial tone (15). Interestingly, there is a case report of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes manifesting as RCVS possibly due to endothelial dysfunction by decreased nitric oxide levels (16). Similar cases of endothelial dysfunction have been reported in Leigh syndrome (17). Therefore, the pathology stemming from endothelial dysfunction might be a plausible alternative explanation. Furthermore, transient cardiac wall hypertrophy (posterior wall dominance) and ECG abnormalities were observed in our case. This is consistent with the cardiac findings in cases of mitochondrial disease, and the ECG findings might be attributed to the cardiac load with sudden hypertension and vulnerabilities due to mitochondrial gene abnormalities in the myocardium itself. However, this is only a single case report, so a further analysis of similar cases is warranted.

In conclusion, we reported a case of adult-onset Leigh syndrome. The spectrum of Leigh syndrome is expanding, and it should be considered as a differential diagnosis in cases of RCVS and brainstem lesions along the ventricles.

**The authors state that they have no Conflict of Interest (COI).**

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