Original Article

A Novel Mutation of Mitochondrial T14709C Causes Myoclonic Epilepsy with Ragged Red Fibers Syndrome in a Chinese Patient

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Abstract

Background: Myoclonic epilepsy with ragged red fibers (MERRF) syndrome is characterized by myoclonus, generalized epilepsy, cerebellar ataxia, and ragged red fibers (RRFs) in the muscle. T-to-C transition at nucleotide position 14709 in the mitochondrial tRNA glutamic acid ($tRNA^{Glu}$) gene has previously been associated with maternally inherited diabetes and deafness. However, the association between MERRF and mitochondrial T14709C mutation (m.T14709C) has never been reported before.
Methods: Clinical information of a 17-year-old patient was collected; muscle biopsy and next-generation sequencing (NGS) of whole mitochondrial and neuromuscular disease panel were then conducted. Finally, sanger sequencing was carried out to confirm the mutations.
Results: The patient presented a typical MERRF phenotype with muscle weakness, epileptic seizure, clonic episodes, cerebellar ataxia, and spinal scoliosis. Muscle biopsy showed RRFs which indicated abnormal mitochondrial functions. NGS of whole mitochondrial gene revealed m.T14709C mutation, confirmed by Sanger sequencing.
Conclusion: We present a sporadic patient with typical MERRF presentation carrying the mutation of m.T14709C, which expanded the spectrum of m.T14709C.

Key words: m.T14709C; Myoclonic Epilepsy with Ragged Red Fibers Syndrome; Novel Mutation

Introduction

Myoclonic epilepsy with ragged red fibers (MERRF) syndrome is characterized by myoclonus, generalized epilepsy, cerebellar ataxia, and RRF in the skeletal muscle.[1] Other features include visual nerve involvement, impaired hearing, and cervical lipomas. It is estimated that the m.A8344G mutation was responsible for over 80% of MERRF patients. T-to-C transition at nucleotide position 14709 in the mitochondrial tRNA glutamic acid (tRNAGlu) gene has previously been associated with maternally inherited diabetes and deafness (MIDD). The association between m.T14709C and MERRF has seldom been reported before. Here, we present a sporadic patient with typical MERRF presentation carrying a heteroplastic mutation of m.T14709C which expands the spectrum of m.T14709C mutation.

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Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of Chinese People's Liberation Army General Hospital (No. S2017-070-01). Informed written consent was obtained from all patients prior to their enrollment in this study.

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Patient description

Our patient is a 17-year-old boy who was the only child of a healthy, nonconsanguineous couple. The family history was unremarkable. Although experienced an uneventful pregnancy and full-term normal delivery, he was found with motor retardation and marasmus after his birth. He then developed slower than his peers – cannot stand until the 18th month after birth and cannot walk until 2 years old. He experienced gradually aggravated limb weakness followed by unsteady movement from his childhood, he could not pass physical education lessons since primary school. Nine years ago (age of eight years), the patient experienced recurrent episodes of loss of consciousness (in the absence of seizure), presenting with dropping out things in hands. The time of duration was about 1 min while the seizure frequency was around 5–6 times per year. Five years ago (age of 12 years), his weakness aggravated, he had difficulty climbing stairs and carrying basin, together with myoclonic seizures in head, and slight clonic episodes in four extremities. This symptom occurred during both day and night time. He also suffered instability in holding chopsticks and bowls, walking in faltering steps, and feeling difficult to walk straight. Two years ago (age of 10 years), he appeared to have inarticulate speech. All the above symptoms aggravated progressively. There was no family history. Physical examination showed that his blood pressure was 120/80 mmHg, his height was 165 cm, and weighing 40 kg, he had normal vision and hearing, but his thoracic spine was left bending. Neurological examination revealed slurred speech, other cranial nerve functions were all normal. He was found with muscle atrophy in four extremities; circumference of both proximal lower limbs on location that 10 cm up to the kneecaps was 31 cm and circumference of both distal lower limbs on location that 10 cm below to the kneecaps was 27.5 cm. Bilateral motor power of the body rated by the Medical Research Council Scale is as follows: biceps and triceps muscles, 4−/5; hand and wrist muscles, 5−/5; iliopsoas muscles, 4−/5; quadriceps femoris muscles, 5/5; biceps femoris muscle, 4+/5; anterior tibial muscles, gastrocnemius, and soleus muscles, 5/5; and his muscle tone of the four extremities was low. The patient cannot complete either heel-knee-tibia test or finger-nose test on both sides. He behaved clumsy in rapid alternating movements on both sides, while beat back signs on both sides were positive. Romberg sign was positive as well. His deep and superficial senses were normal. The tendon reflexes were weakened, and the pathologic reflex was not drawn out. Both Kernig sign and Brudzinski sign were negative.

Laboratory test results revealed a normal thyroid function level and electrolyte level. Serum creatine kinase (CK) and aspartate aminotransferase (AST) levels were slightly elevated (CK 431 U/L [normal range: 24–194 U/L] and AST 63.9 U/L [normal range: 0–35 U/L]). Basal lactate in serum was elevated (>5 mmol/L, normal range: 0.7–2.1 mol/L), and blood glucose was among normal level. Electrocardiogram showed normal sinus rhythm. Color ultrasound revealed benign cystic lesion in the thyroid right leaf. Results of electromyogram were consistent with myopathy. Brain magnetic resonance imaging (MRI) and computed tomography scan were normal, and ambulatory electroencephalogram (AEEC) was normal as well. Spinal X-ray showed scoliosis in thoracic vertebra (left bending), a shape of "S" can be found in the frontal X-ray film.

Muscle biopsy

The proband underwent open biopsy. Standard histochemical staining included hematoxylin and eosin, periodic acid–Schiff stain, oil red O, Gomori trichrome stain, nicotinamide adenine dinucleotide dehydrogenase, nonspecific esterase, and adenosine triphosphatase after incubation at pH 4.3, 4.5, and 10.6. A morphometric evaluation of the muscle specimens was performed under a light microscope (OLYMPUS BX51, Japan). Ultra-thin sections were prepared from epon-embedded material, stained with osmic acid, and imaged by transmission electron microscopy.

DNA extraction

After getting informed consent from all patients, the total DNA was extracted from muscle using phenol chloroform standard procedures.

Genetic analysis

Whole mitochondrial genome next-generation sequencing (NGS) as well as targeted next-generation sequencing (which contains the most commonly seen neuromuscular disease gene mutations with metabolic myopathies genes and mitochondrial nuclear genes included) was conducted to detect causative genes (Illumina HiSeq 2000 sequencer, USA). Sanger sequencing (LifeTouch PCR instrument, China; Phanta Super-Fidelity DNA Polymerase, China; primer premier 5.0 software, Canada) was then performed to confirm both mitochondrial and nuclear mutations.

Results

Muscle pathological examination

Muscle biopsy findings showed that atrophic fibers in irregular forms were distributed sparsely, parts of which showed degeneration and coagulation, along with phagocytosis. Minority of muscle fibers showed hypertrophy and internal nuclei. Some fibers show subsarcolemmal mitochondrial accumulation which turned into aubergine basophilic materials in H and E staining [Figure 1a]. Many fibers showed evidence of typical ragged-red changes in Gomori staining [Figure 1b], the proportion of RRF is 10%. Nicotinamide adenine dinucleotide (NADH) showed that RRFs, which were mentioned above, appeared to have structural derangement and dark stain. In electronic speculum, we could see rectangular crystalline inclusion bodies in thick mitochondria [Figure 1c and 1d].

Gene findings

NGS of whole mitochondrial DNA found a m.T14709C mutation on ND6 and the sequencing depth was 2527/19449 (0.89). Nuclear mutation sequencing results which correlated with mitochondrial and other neuromuscular

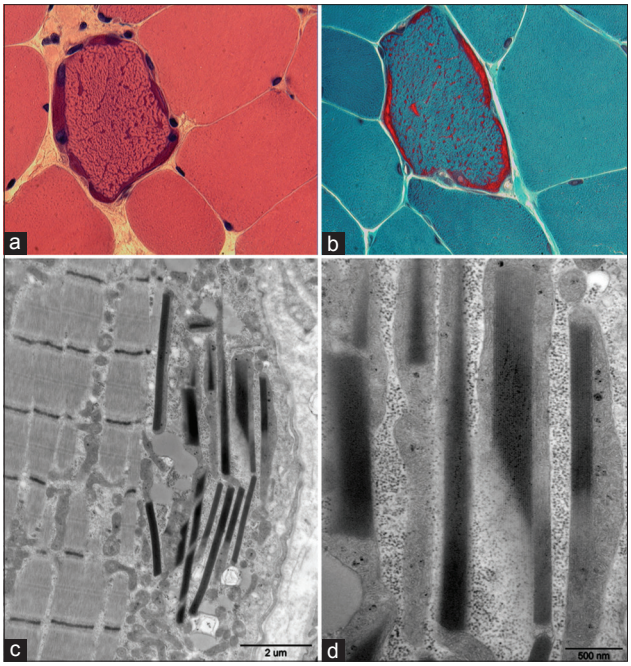

Figure 1: (a) In one fiber, many subsarcolemmal mitochondria turn into aubergine acidophilic materials (H and E, ×400). (b) One typical ragged-red fiber (Gomori, ×400). (c) Electronic speculum showing several mitochondrial malformation, with crystalline inclusion bodies inside (×15,000). (d) On enlargement of c, we can see clearer crystalline inclusion bodies in mitochondria (×50,000).

disorders were negative in our patient. Sanger sequencing was conducted to confirm the mitochondrial mutation [Figure 2].

Discussion

The mitochondrial syndrome MERRF is traditionally characterized by myoclonus, seizures, cerebellar ataxia, and mitochondrial myopathy (MM) with ragged-red fibers.[2] Hearing loss, peripheral neuropathy, exercise intolerance, and cardiomyopathy were also involved in MERRF. MERRF was first described in 1980 in two unrelated patients suffering from myoclonus, generalized convulsions, mental deterioration, intention tremor, ataxia, muscular atrophy, and foot deformities. In addition, optic atrophy, areflexia, and altered nerve conduction velocities were present. RRFs were seen in both patients.[3] In 1990, Shoffner *et al*. and Yoneda *et al*. described a point mutation of m.A8344G, which affects the mitochondrial DNA (mtDNA) encoding the RNA transporter of lysine (tRNALys) in the muscle of patients with MERRF.[4,5] MERRF is primarily an MT-TK disease, with pathogenic variants in this gene accounting for ~90% of MERRF patients,[6] it is estimated that the m.A8344G mutation was responsible for over 80% of MERRF patients with a prevalence of 0.7/100,000 in North East England based on a large population study;[7] other mutations such as m.T8356C, m.G8361A, and m.G8363A were responsible for approximately 10%, and mutations of m.G611A and m.G15967A accounted for another <5%,[8] yet up to 10% of MERRF patients had still no identifiable mutations in mtDNA.[9-12] In China, there are a total of 36

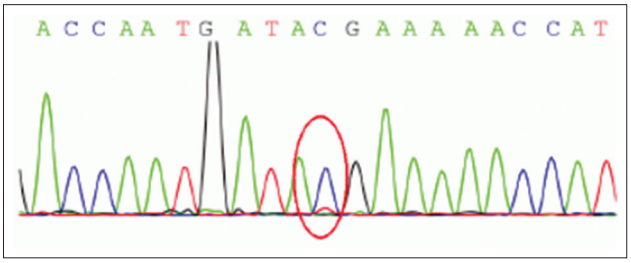

Figure 2: Sanger sequencing confirmed that the patient harbored m.T14709C mutation.

reported cases of MERRF, among which 20 cases (55.6%) harbored the mutation of m.A8344G, one case (2.8%) had m.A8344G and m.A3243G, and one case (2.8%) had m.T8356C mutation.[13-18]

Although clinical diagnosis of typical MERRF is based on four canonical features which are myoclonus, seizures, cerebella ataxia, and RRF in muscle tissue, phenotypes can vary in a large spectrum, as in a German cohort; seizures, myoclonus, cerebellar ataxia, and RRFs occurred in only 61%, 59%, 70%, and 63% of the MERRF patients with m.A8344G mutation, respectively. Nearly 88% had abnormal electroencephalography, 72% had hearing impairment, and 58% had muscle weakness. Brain MRI revealed cerebral and/or cerebellar atrophy in 43% in their patients.[19] Our patient presented with the typical clinical features of MERRF, including a long-standing history of muscle weakness, epileptic seizure, and clonic episodes. In addition, he was found with spinal scoliosis and cerebellar ataxia in PE; laboratory findings indicated elevated level of lactic acid, CK, and LDH; and electromyography showed myogenic change. Muscle biopsy showed RRF indicative of mitochondrial abnormalities. The most frequent seizure type in MERRF is generalized myoclonic seizure, but also focal myoclonic, focal atonic, generalized tonic-clonic, generalized atonic, generalized myoclonic-atonic, typical absences, or tonic-clonic seizures of unknown onset have been reported.[20] According to a study on epilepsy in patients with mitochondrial disorders, MERRF syndrome with m.A8344G mutation is the second major group in patients with uncontrolled epilepsy.[21] Although AEEC was normal in our patient, according to his presentation of loss of consciousness, dropping of objects from hand, and myoclonic seizures in head, we can diagnose him as epilepsy (absence seizure and myoclonic seizure) in clinical aspect and suppose that the AEEC might be conducted in nonepileptic status.

Spinal scoliosis is rarely seen in mitochondrial disorders. The exact etiology and pathogenesis of MM with scoliosis is still unknown,[22] but Longworth *et al*.[23] had reported the prevalence of scoliosis among patients with MM to be 5%, much higher than the incidence of scoliosis that among the general population (2%). Hiniker *et al*.[24] also reported a case of a 69-year-old woman who presented with axial MM developed rapidly progressive adult-onset scoliosis. Berio and Piazzi[25] had reported another case of chronic

progressive external ophthalmoplegia with severe scoliosis. Our patient is a MERRF case with scoliosis.

Motor retardation from birth is also less seen in MERRF. A Czech study is among one of the few reports to show motor retardation in MERRF – a patient with m.A8344G MERRF mutation (mutation load 95%) presented his first clinical symptoms – muscle hypotonia, cardiomyopathy, and mental and motor retardation – in infancy.[26] Our patient showed motor retardation and marasmus from his birth, which expanded MERRF's clinical spectrum.

The m.T14709C mutation on ND6 in the mt-tRNA^{Glu} gene was originally identified in a 29-year-old man with myopathy and diabetes mellitus.[27] Several other reports described families harboring the same m.T14709C mutation have been published since then, which was reported to be related with MM + diabetes mellitus and deafness/encephalomyopathy/dementia + diabetes + ophthalmoplegia (https://mitomap.org//MITOMAP). Some of the previously described patients with the m.T14709C mutations were in fact asymptomatic. Only in their third or fourth decade, they started to develop diabetes mellitus or other neurological problems such as muscle weakness.[28] The summary of clinical presentations of m.T14709C is listed in Table 1. Our patient's clinical manifestation showed muscle weakness, cerebellar ataxia, and scoliosis, which have been reported related to m.T14709C mutation, but seizures and myoclonus were not previously related to m.T14709C. Besides, there is no evidence of other m.T14709C associated symptoms such as diabetes, deafness, dementia, or ophthalmoplegia. The reason of this clinical variety is unknown to us, is it just hazard or environmental factors or some undetected nuclear genes? Although targeted NGS (nuclear genes associated with mitochondrial as well as other neuromuscular disorders) is negative, we suggest a further whole-exome sequencing.

However, association of m.T14709C and classic MERRF was not retrieved before. Our patient shows a new presentation, namely MERRF, indicating that there might be MERRF-related factors which play a role in the

Table 1: Summary of clinical presentations of m.T14709C

Number	Age	Age of onset	Gender	Clinical presentation	Family history	Description	RRF	References
1	29 y	27 y	Male	Myopathy and diabetes mellitus	–		+	[27]
2	6 w	Congenital	Female	Hydrops fetalis, hypertrophic cardiomyopathy with secondary dysrythmia	+		/	[28]
3	/	Congenital	Female	Axial hypotonia, intermittent hyperlactatemia, mild psychomotor retardation	+	Sister of P19	+	[28]
4	28 y	Congenital	Male	Congenital myopathy, mental retardation, cerebellar ataxia, lumbar scoliosis, pectus carinatum, bilateral pes cavus	+	Brother of P5	+	[29]
5	25 y	Congenital	Female	Congenital myopathy, mental retardation, cerebellar ataxia, primary pulmonary hypertension, bilateral pes cavus	+	Sister of P4	+	[29]
6	21 m	Childhood	Male	Respiratory distress, hypotonia, muscle weakness, gastroesophageal reflux	+		+	[30]
7	55 y	Childhood	Male	Muscle weakness, diabetes	+	Brother of P3	+	[30]
8	51 y	35 y	Female	Gestational diabetes, exercise intolerance	+	Sister of P2	+	[30]
9	/	30 y	Male	Diabetes, hearing loss, pigmentary epithelium of retina, myopathy	/		+	[31]
10	/	Congenital	Male	Myopathy and diabetes mellitus	+	Son of P9		[32]
11	/	Teens	Female	Myopathy and diabetes mellitus, peripheral neuropathy	+	Mother of P8	+	[32]
12	55 y	14 y	Male	Proximal myopathy, orb oculi weakness, diabetes mellitus, ataxia and dysarthria, peripheral neuropathy, cerebral atrophy, peripheral vascular disease	+		+	[33]
13	60 y		Female	Proximal myopathy, orb oculi weakness, left hemiparesis, nystagmus and ataxia	+		/	[33]
14			Male	Proximal myopathy	+		+	[33]
15	17 y	6 y	Female	Proximal myopathy, orb oculi weakness, diabetes mellitus/DKA breathlessness	+		+	[33]
16		27 y	Female	Diabetes	+	Sister of P15 and P16	/	[34]
17		28 y	Female	Diabetes and retinitis pigmentosa	+	Sister of P14 and P16	/	[34]
18		35 y	Female	Diabetes	+	Sister of P14 and P15	/	[34]
19		14 y	Female	Diabetes	+	Daughter of P16	/	[34]
20		50 y	Female	Diabetes, high blood pressure	–		/	[34]

RRF: Ragged red fibers; y: years; w: weeks; m: months; +: Positive; -: Negative; /: No materials shown.

functional consequences of the m.T14709C mutation. The mutation of m.T14709C affects a highly conserved and functionally important nucleotide flanking the anticodon of the mt-tRNA^{Glu} and directly affects the functions of the tRNA^{Glu} by altering the secondary structure of this tRNA, which would disrupt mitochondrial protein synthesis.[34] This is also proved by McFarland *et al*. that there is a striking reduction in steady-state levels of mt-tRNA^{Glu} in fibroblasts and skeletal muscle from patients carrying the mutation, and a posttranscriptional pathogenic mechanism causing a reduced rate of overall protein synthesis has been described.[33] The biggest regret for this study is that we did not get any samples from the patient's mother, so we cannot figure out the segregation study.

To conclude, this is a patient report of a sporadic case of the m.T14709C mutation presenting as a typical MEERF; it is not yet known how the clinical diversity can be explained by the mutation of m.T14709C. Further studies of the functional outcome of the m.T14709C mutation should be carried out.

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Conflicts of interest

There are no conflicts of interest.

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一例中国肌阵挛性癫痫伴碎红纤维（MERRF）患者的新发线粒体基因T14709C 点突变

摘要

背景：肌阵挛性癫痫伴碎红纤维（MERRF）综合征以肌阵挛、癫痫发作、小脑共济失调和肌活检发现破碎红纤维为主要特征。线粒体tRNA^{Glu}基因14709位碱基的T到C突变（m.T14709C）此前报道与母系遗传性糖尿病与耳聋（MIDD）有关。但MERRF与线粒体基因14709位碱基（m.T14709C）突变相关性未见报道。

方法：收集患者临床表现、肌活检表现和二代测序（全线粒体基因组和神经肌肉病靶向芯片）结果，并用Sanger测序来y验证点突变。

结果：患者表现为典型的MERRF表型，即肌无力、癫痫发作、肌阵挛、小脑共济失调伴有脊柱侧弯。肌活检可见破碎红纤维（RRF），提示线粒体功能异常。线粒体全基因组二代测序检出m.T14709C点突变，并由Sanger测序验证。

结论：报道一例典型MERRF表现的患者携带m.T14709C点突变，从而扩展了m.T14709C的临床表现谱系。