CASE REPORT

Falling after Starting Running in a Case of Myoclonus Epilepsy Associated with Ragged-red Fibers with a 8344A>G mtDNA Mutation

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Abstract:
Myoclonus epilepsy associated with ragged-red fibers (MERRF) is traditionally characterized by myoclonus, generalized epilepsy and ragged-red fibers. We herein report a 42-year-old man who complained of falling after starting running, symptoms resembling those of paroxysmal kinesigenic dyskinesia. He showed only slight muscle weakness of the right quadriceps femoris. Muscle pathology and a genetic analysis identified him as having MERRF with a 8344A>G mtDNA mutation. We diagnosed his symptoms as having been caused by slight quadriceps femoris muscle weakness and exercise intolerance. This case suggests that mitochondrial myopathy should be considered in cases with strong muscle symptoms for muscle weakness.

Key words: MERRF, mitochondrial myopathy, paroxysmal kinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.1210-18)

Introduction

Myoclonus epilepsy associated with ragged-red fibers (MERRF) is a very rare mitochondrial syndrome characterized by myoclonus, generalized epilepsy, cerebellar ataxia and ragged-red fibers (RRF) on a muscle biopsy (1). MERRF is a maternally inherited disease and associated with various mitochondrial DNA (mtDNA) point mutations, the most frequent of which is the A to G transition at nucleotide pair 8344 of the MTTK gene (8344A>G mtDNA). This mutation accounts for approximately 80%-90% of MERRF cases (2) and approximately 4% of all pathogenic mtDNA mutation (3) and was reported to occur with a prevalence of 0.7 in 100,000 individuals in a large population study (4). Furthermore, the clinical features vary among affected individuals carrying the same 8344A>G mtDNA mutation (5) and was reported to occur with a prevalence of 0.7 in 100,000 individuals in a large population study (4). In addition, the clinical features vary among affected individuals carrying the same 8344A>G mtDNA mutation (5), and in addition to the MERRF symptoms, the 8344A>G mtDNA mutation can be associated with other clinical phenotypes, such as Leigh disease (6) and multiple lipomas (7).

We herein report the case of a 42-year-old man with a 8344A>G mtDNA mutation whose chief complaint was falling after starting running.

Case Report

A 42-year-old man, who played volleyball once a week reported sometimes falling down when jogging for a long time during the last 2 years. In addition, in the previous 6 months, he had also begun to fall after starting running in volleyball games. He had no significant medical history or family history. On a neurological examination, he showed only slight muscle weakness of the right quadriceps femoris and slight left limb dominant ataxia without truncal ataxia. When we observed his running on the ground, he fell within the first few steps after starting running.

Blood test findings revealed mild elevation of creatine kinase (600-900 U/L, normal <225) and slight elevation of lactic acid (21.3 mg/dL, normal <17). Serum anti-acetylcholine receptor antibody, antinuclear antibody and myositis-specific antibodies were negative. A nerve conduc-
tion study, electromyography and electroencephalography findings were normal. Brain magnetic resonance imaging demonstrated slight cerebral atrophy for his age and mild left dominant cerebellar hemisphere atrophy (Fig. 1A). Cerebrospinal fluid (CSF) findings showed elevation of lactate (26.9 mg/dL, normal <17) and pyruvate concentrations (1.32 mg/dL, normal <0.94). An aerobic exercise test using a cycle ergometer induced a marked increase in the serum lactate levels (24 mg/dL at rest and 54.3 mg/dL at peak) (Fig. 2). These inspection results indicated mitochondrial dysfunction in the patient.

Computed tomography (CT) of the extremities and truncal muscles revealed slight atrophy of the right quadriceps femoris muscle (Fig. 1B), so we performed a muscle biopsy. The pathological findings of the muscle demonstrated some RRF with Gomori trichrome stain and ragged blue fibers with succinate dehydrogenase (SDH) stain, both of which indicated a decrement in the cytochrome c oxidase activity (COX) (Fig. 3). Genetic testing revealed the 8344A>G mtDNA mutation in his skeletal muscle (94% mutation load using next-generation sequencing) and blood (80% using Sanger sequencing). We diagnosed him with MERRF based on these pathological and genetic results and his clinical symptoms.

**Discussion**

To our knowledge, this is the first report of a patient with a MERRF mutation falling after starting running. The MERRF acronym implies the presence of myoclonus epilepsy and RRF, which are the major features of MERRF. Indeed RRF on a muscle biopsy are found in almost all MERRF cases (8); however, either or both can be absent in some MERRF cases. Indeed, the present case showed neither myoclonus nor epilepsy, even on electroencephalography. In addition, the patient showed none of the clinical symptoms often seen in cases with mitochondrial disorders, including diabetes, hearing loss, and migraine. The clinical features of MERRF are various, and the diagnosis is often difficult without a muscle biopsy and genetic testing. A previous report found that the most frequently occurring symptom was muscle weakness (9), and cerebellar ataxia was also observed more frequently than myoclonus in MERRF cases with 8344A>G mtDNA mutation (5). The serum lactate level was elevated in approximately half of MERRF cases. Mitochondriopathy patients with normal serum lactate
levels at rest often turn out to have markedly increased levels on the lactate stress test using a cycle ergometer (10). Indeed, the present case showed slightly increased serum lactate levels at rest but marked elevation on the lactate stress test.

The present patient’s chief complaint of falling after starting running was considered similar to the symptoms of paroxysmal kinesigenic dyskinesia (PKD). PKD is a rare condi-
tion characterized by abnormal involuntary movements, comprising dystonia, chorea, athetosis, or ballism, and is triggered by the initiation of voluntary movements, such as getting up quickly, walking, or running (11). PKD is estimated to occur in 1 in 150,000 individuals (12), and men are more commonly affected than women. The onset age in PKD is usually between 7 and 15 years (13). Most PKD cases have a family history of a similar disorder with an autosomal dominant inheritance and are associated with a PRRT2 mutation (14). PKD attacks often respond well to carbamazepine (15). However, the present case had no family history of symptoms of PKD, and the onset age was different from typical PKD cases. Carbamazepine was prescribed but had no effect. Based on the involuntary movement associated with exercise, paroxysmal exercise-induced dyskinesia (PED) was also considered. PED is characterized by attacks of dystonia or choreoathetosis triggered by several minutes of exercise such as walking or running, typically lasting for 5 to 30 minutes (16, 17). However, the present patient fell within the first few steps of running and was able to stand up a few seconds later, which did not fit the typical symptoms of PED.

The patient’s clinical neurological examination findings showed only slight muscle weakness of the right quadriceps femoris, and muscle CT demonstrated slight atrophy. In addition to the muscle weakness and atrophy, fatigue and exercise intolerance are often observed in MERRF cases with 8344A>G mtDNA mutation (9). Exercise intolerance is characterized by a failure to maintain an expected level of force during sustained or repeated muscle contraction (18). To evaluate the patient’s fatigue and exercise intolerance, we had him walk up stairs rapidly and jump on one leg. He performed these exercises without problem on the left side, but it was difficult to continue the exercises on the right side. These results suggested that the slight weakness in his right quadriceps femoris muscle made him unable to tolerate continuous high exercise loads, such as going up stairs rapidly and jumping. His complaint of falling down within the first few steps of running was presumed to occur due to the same reason.

Quadriceps femoris muscle weakness is associated with an increased risk of falling (19). In general, patients who show muscle atrophy of lower limbs usually complain of muscle weakness or fatigue, not falling, and adults have a tendency to run less frequently than children. In contrast, the present patient played volleyball regularly, so his slight muscle weakness appeared to be a symptom similar to those seen in PKD cases. In addition, his quadriceps femoris muscle showed right dominant atrophy. Most mtDNA mutations are heteroplasmic, with both mutated and wild-type mtDNA co-existing in affected individuals (20). The ratio of wild-type to mutated mtDNA determines the onset of clinical symptoms, and the threshold level differs amongst tissues (21). A previous report described a case of mitochondrial myopathy with chronic asymmetric progressive external ophthalmoplegia and facial weakness (22), so asymmetric muscle atrophy may be included as a clinical feature of mitochondrial myopathy.

In conclusion, we herein report a patient with a 8344A>G mtDNA mutation whose complaints resembled the symptoms of PKD. Slight quadriceps femoris muscle weakness and exercise intolerance caused him to fall after starting running. Strong muscle symptoms for muscle weakness could therefore lead to the onset of mitochondrial myopathy, such as in individuals carrying a 8344A>G mtDNA mutation.

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

References
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