MERRF Syndrome Presenting with Multiple Symmetric Lipomatosis in a Japanese Patient

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Abstract

Myoclonic epilepsy with ragged red fibers (MERRF), also called Fukuhara’s disease, is sometimes accompanied by the rare symptom of multiple symmetric lipomatosis (MSL). MSL associated with MERRF has been reported mainly in Caucasians; such cases have not been reported in Japanese patients. We report the case of a 59-year-old Japanese woman with MERRF syndrome associated with A→G substitution at nucleotide 8,344 of mtDNA. This case suggests that differences in lifestyle and gene polymorphism among races may be related to the prevalence of MSL due to mitochondrial abnormality, and that mitochondrial abnormalities should be considered as a cause of MSL even in Japanese patients.

Key words: myoclonic epilepsy with ragged red fibers (MERRF), multiple symmetric lipomatosis, mitochondria

Case Report

We describe the case of a 59-year-old Japanese woman with MERRF syndrome who presented with MSL. Over a period of 15 years, the patient had developed a tendency to fall, and 10 years previously cervical and axillary subcutaneous masses were found. The patient had no first-degree family history of mitochondrial disease and did not consume alcohol. Her physical examination revealed symmetric cervical and left axillary lipomas, characterized by soft, mobile, and ill-defined masses (Fig. 1). On neurologic examination, her oculomotor movements were neither restricted nor accompanied by nystagmus. She had sensorineural hearing loss, slurred speech, and moderate proximal muscle weakness that was more severe on the left side with the lower limbs more affected than the upper limbs. Her muscle tone was reduced and muscle bulk showed diffused atrophy. Deep tendon reflexes were absent and there were no pathologic reflexes. Hypermetria was also observed. She had a waddling and ataxic gait with difficulty in tandem walking, but the Romberg sign was absent. Although superficial sensation was fully preserved, deep sensation was slightly compromised. Her cognitive state was mildly impaired.
Figure 1. (A, B) Symmetric lipomas are seen around the neck.

Figure 2. (A, B) T2-weighted magnetic resonance images (A, coronary at the mid-chest level; B, axial at the level of axilla) show a poorly marginated fat-intense mass in the axilla. Arrows indicate the axillary lipoma.

Laboratory data showed a mildly elevated serum creatine kinase (260 IU/L; normal <180 IU/L). Other blood tests including complete blood cell count, tests for kidney, liver, and thyroid function, were normal. Blood and cerebrospinal fluid analysis showed slightly elevated levels of lactate and pyruvate. In particular, an aerobic exercise test using an ergometer at 15 watts for 15 minutes produced marked and protracted increases in serum lactate and pyruvate levels. Magnetic resonance imaging of the brain showed cerebellar atrophy, but the brainstem and cerebrum were preserved. Magnetic resonance imaging of the chest showed an unencapsulated fat-dense mass in the left axilla (Fig. 2). Electroencephalography under photostimulation showed background activity within the normal range with slow, diffuse delta bursts at intervals, and driving activity with transient sharp waves. Although motor nerve conduction studies were normal, sensory nerve conduction studies of the sural nerve demonstrated a low amplitude with normal distal latency. Needle electromyography indicated myopathic changes including an early recruitment pattern in the upper limbs, and showed neurogenic changes with a high-amplitude and low-interference pattern in the lower limbs without features of denervation at rest. The biceps brachii muscle biopsy demonstrated numerous fibers of varying size, fat replacement, ragged red fibers (Fig. 3A), decreased activity of cytochrome C oxidase (Fig. 3D), and few rimmed vacuoles (Fig. 3B). ATPase staining showed predominance of type 1 fibers (Fig. 3C). The diagnosis was confirmed by the Invader® DNA assay (8), which revealed a mitochondrial tRNA Lys gene mutation (position 8,344) in leukocytes.

Discussion

The present patient, a 59-year-old Japanese woman, was diagnosed as having MERRF syndrome with MSL. Berkovic et al were the first to demonstrate mitochondrial dysfunction in the skeletal muscle of patients with MSL (9), and consequently MSL has been regarded as one of the symptoms of mitochondrial disease, particularly those caused by point mutations associated with MERRF (10, 11). Although muscle biopsies in MERRF syndrome with MSL frequently show myogenic changes (7), the present patient had mixed myogenic and neurogenic changes, of which the latter were indicated by the characteristic predominance of type 1 fibers. We believe that the predominance of type 1 fibers should not be regarded as a specific feature but as a transient observation of chronic neurogenic changes accompanying reinnervation.

There are three possible reasons for the lack of reported cases of MSL resulting from mitochondrial abnormality in Japan. First, differences in lifestyle, including alcohol intake, may be related to the incidence rate of MSL (7). Second, the differences in mitochondrial gene polymorphisms between Caucasian and Japanese populations may be associated with differences in the incidence rate of MSL in MERRF patients, because it has been shown that in patients with MELAS related to mitochondrial point mutations at position 3,243, mitochondrial DNA polymorphism at position 12,308 can influence whether the patient develops stroke (12). Third, MSL that can be attributed to mitochondrial cytopathy often may be overlooked. In particular, in several previously reported cases of MSL associated with MERRF syndrome, simultaneous development of the tetrad of MERRF was not noted (6, 7). This was the case with our patient who developed myopathy and ataxia but not myoclonus and seizure. Although a given patient may not present all the core symptoms of MERRF syndrome, i.e., myo-
clonus, seizures, ataxia, and myopathy, we should be aware of mitochondrial abnormalities as a cause of MSL even in the Japanese population.

References