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Multiple symmetric lipomatosis and MERRF: A case from Turkey

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Abstract

The association of multiple symmetric lipomatosis (MSL) and mitochondrial disorders is not frequent. We report a male patient with multiple lipomas, hearing loss, progressive limb-girdle muscle weakness, neuropathy and myoclonia. Serum creatinine kinase was mildly elevated. Electromyography revealed sensory axonal polyneuropathy and myopathy with sparse denervation. A muscle biopsy showed ragged-red fibers. Next-generation DNA sequencing revealed a heteroplasmic m.8344A>G mutation in the MT-TK gene. To the best of our knowledge, this is the first patient to be reported from Turkey with a diagnosis of MSL and myoclonic epilepsy with ragged red fibers (MERRF).

Keywords: lipomatosis, MERRF, mitochondrial disorder, myopathy, MT-TK

INTRODUCTION

Multiple symmetric lipomatosis (MSL) is a rare disorder of middle-aged adults characterised by large nonencapsulated lipomas around the neck, shoulders and other axial regions. Alcoholism is frequently associated with MSL. Peripheral neuropathy is considered a part of MSL.[1] However, the association between MSL and mitochondrial disorders is not frequent. Herein, we present a patient with MSL who presented with proximal muscle weakness and was diagnosed as having myoclonic epilepsy with ragged red fibers (MERRF) with typical findings in a muscle biopsy and a heteroplasmic m.8344A>G mutation in the MT-TK gene.

CASE REPORT

A 60-year-old male with a history of hearing loss and hypertension noted the first symptoms of slowly progressive weakness of limb girdles at the age of 47 years. No alcohol consumption was noted. His family history revealed a brother with a similar shoulder girdle weakness who died of lung cancer without receiving any neurologic diagnosis. Upon examination, our patient had multiple lipomas on his neck, shoulder girdles, and arms (Figure 1). A neurologic examination revealed symmetrical proximal weakness of both upper and lower extremities (MRC 4/5) with positive Gower's sign, reduced deep tendon reflexes and stocking-and-glove distribution hypoesthesia. He had mild weakness of the orbicularis oculi without any ptosis or restriction of eye movements. He had a waddling and ataxic gait with difficulty in tandem walking. The serum creatine kinase (CK) level was 1130 U/L.

Electromyography (EMG) revealed a sensory axonal polyneuropathy with decreased sensory nerve action potential amplitudes (Table 1) and myopathic involvement in proximally located muscles, motor unit potentials with small amplitude, short duration, polyphasia, and increased interference pattern. Needle insertion activity was increased with sparse fibrillation potentials and positive spike trains. Cranial magnetic resonance imaging (MRI) showed mild cortical atrophy. The cervical MRI was normal. Electrocardiography and echocardiography were normal.

The serum lactate level was 43 (range 4.5-19.8) mg/dL. The serum pyruvate level was 0.23 (range 0.3-0.7) mg/dL. His lipid profile was normal. In an otorhinolaryngology consultation, bilateral sensorineural hearing loss was noted. In an ophthalmology consultation, cataract formation

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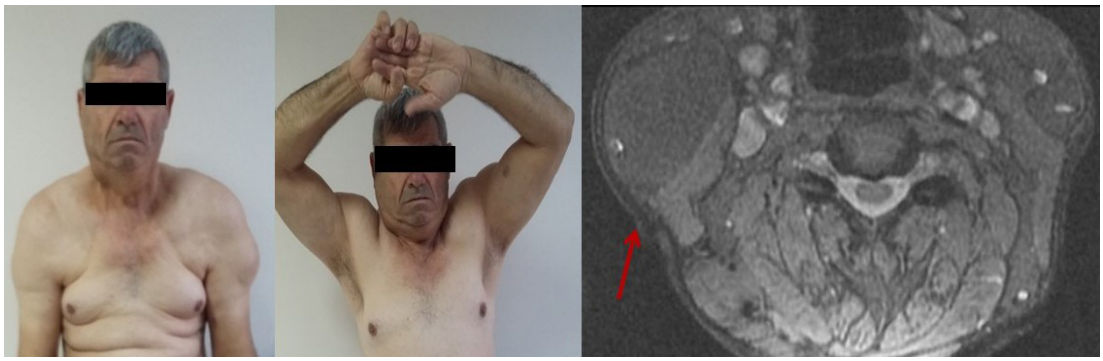

Figure 1. Multiple lipomas on the neck, shoulder girdles, and arms, with limb girdle weakness. Note the lipoma seen in the cervical MRI (red arrow).

on his left eye was noted. A cerebrospinal fluid (CSF) direct examination was acellular, with normal protein levels and biochemistry. The CSF pyruvate level was normal (0.65, range 0.5-1.7). Serologic, vasculitic, and tumor markers were negative. Protein electrophoresis and immunofixation were normal. Chest X-ray and abdominal ultrasonography were normal. A

Table 1: Sensory and motor nerve conduction studies

A. Sensory Nerve Conduction Studies				
Nerve/stimulation site	Recording site	Peak Latency (ms)	Amplitude (μV)	Velocity (m/s)
Median (R)/2nd digit	Wrist	3.02	8.8	52.4
Ulnar (R)/5th digit	Wrist	2.60	5.0	50.3
Sup Peroneal (R)/cruris	Ankle	2.19	3.9	61.9
Sural (R)/cruris	Lat malleol.	2.45	6.4	57.1
Sural (L)/cruris	Lat malleol.	3.13	7.2	48.0

A. Motor Nerve Conduction Studies				
Nerve/Stimulation site	Recording site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Median (R)/				
Wrist	APB	3.28	8.4	51
Elbow	APB	8.23	8.0	
Ulnar (R)/				
Wrist	ADM	3.07	9.4	52
Below elbow	ADM	7.08	8.9	55
Above elbow	ADM	9.43	8.8	
Peroneal (R)/				
Ankle	EDB	5.78	5.0	41
Head of fibula	EDB	12.55	4.5	43
Knee	EDB	14.90	3.6	
Tibial (R)/				
Ankle	AH	5.78	5.5	43
Knee	AH	15.78	3.7	

APB: abductor pollicis brevis, ADM: abductor digiti minimi, EDB: extansor digitorum brevis, AH: abductor hallucis

paraneoplastic panel involving anti-amphiphysin, anti-CV2-1, anti-Ma2/Ta, anti-Ri, anti-Yo, and anti-Hu was negative. During his clinical follow-up, myoclonic jerks were observed in his arms and legs. The patient was referred to the electroencephalography (EEG) laboratory and generalized spike and waves, and multi-spike and waves with normal baseline activity were recorded. Levetiracetam treatment was initiated.

A muscle biopsy was performed and stained with Gomori's trichrome, and varying sizes of muscle fibers and characteristic ragged-red fibers were visible histologically. This appearance is due to the accumulation of abnormal mitochondria below the plasma membrane of muscle fibers. Fibers with mitochondrial accumulation were stained dark with SDH, and COX staining of these fibers was reduced or absent. Cellular components of glycogen, neutral lipid, and myophosphorylase were normal (Figure 2). MHC-1 immunohistochemistry reaction was negative. Next-generation DNA sequencing revealed a heteroplasmic m.8344A>G mutation in the MT-TK gene.

The patient was diagnosed as having a mitochondrial disorder, MERRF associated with MSL, and treated with levetiracetam, L-carnitine, coenzyme Q10, vitamin C, vitamin E, and folic acid. When last assessed at the neuromuscular disorders outpatient clinic, his weakness and sensory neuropathy were stable, the myoclonic jerks were under control with levetiracetam, and he was still ambulatory without aids.

DISCUSSION

MSL was first described in the 19th century and since the first description, it has been named differently according to the scientists who described its clinical features: Brodie syndrome, Madelung's disease, or Launois-Bensaude disease.[1-4] MSL involves adipose tissue and is characterized by the development of non-encapsulated lipomas. The lipomas are usually benign and superficial but may rarely cause serious complications such as respiratory airway obstruction if located viscerally.[5] The pathogenesis of lipoma formation is unclear but observations link MSL with mitochondrial dysfunction.[6]

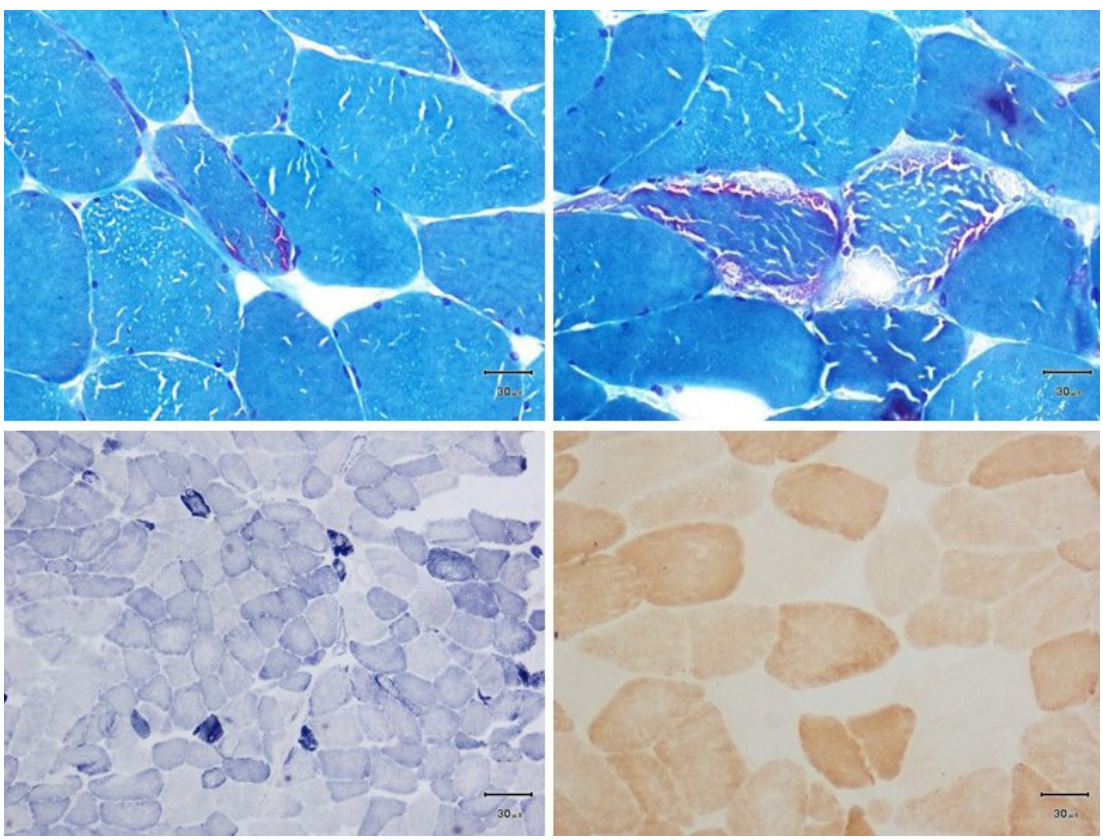

Figure 2. Muscle fibers of varying size and ragged red fibers. Some fibers with excessive SDH staining have reduced or absent COX staining.

The lipomatous masses in MSL are located in the axial and mainly cervical region where brown adipose tissue is normally present in newborns. Brown adipose tissue is different from white adipose tissue in that it is responsible for thermoregulation and depends on uncoupling carrier protein 1 (UCP1) in the mitochondrial oxidative phosphorylation pathway. Dysfunction of the mitochondrial phosphorylation pathway leads to decreased lipolysis in brown fat, which may lead to lipid accumulation and lipoma formation.[7,8] This hypothesis may explain the association between the pathophysiology of MSL and the mitochondrial disorder. The patient presented here had multiple symmetric lipomas in axial cervical regions, the neck, shoulder girdles, and arms, probably with high brown adipose tissue amount.

Mitochondrial disorders present with a wide range of clinical expressions. Systems relying mostly on aerobic metabolism are preferentially affected. With an estimated birth prevalence of 13.1:100,000[9], primary mitochondrial disorders are the most common inherited disorders of metabolism.[10] MERRF is a rare mitochondrial disorder with canonical features including myoclonus, generalized epilepsy, ataxia, and ragged-red fiber myopathy. The prevalence of MERRF syndrome is 0.9:100,000 in Europe.[11] Besides the canonical features, dementia, optic atrophy, bilateral deafness, peripheral neuropathy, spasticity, and multiple lipomas can also be seen.[12] The onset of clinical features can occur in infancy, childhood, or adolescence. More than 80% of patients with MERRF harbor an A to G mutation at nucleotide 8344 in the mitochondrial MT-TK gene encoding tRNA (lysine).[13,14] The patient presented here showed typical features of lipomatosis and mitochondrial multisystem expression, including myopathy, neuropathy, myoclonic epilepsy, and cortical atrophy. The mitochondrial disorder was compatible with the clinical syndrome, electrophysiologic findings, supported by both muscle biopsy and genetic results.

The association of MSL and MERRF has been described occasionally. In literature, there are single or small series of cases/families and a few cohorts. Mancuso *et al*. reported lipomatosis in two out of 24 patients with MERRF (8.3%), among whom only eight were carrying a heteroplasmic m.8344A>G mutation.[15] Chinnery *et al*. reported the frequency of lipomatosis as 8% among 55 subjects associated with an A8344G mutation.[16] Some other studies revealed a higher association between lipomatosis and the m.8244A>G mutation. A retrospective study presented 42 8344 A>G carriers in an Italian nationwide database of patients with mitochondrial disorders and reported the frequency of multiple lipomatosis as 30%.[17] Altmann *et al*. reported lipoma in four out of 24 patients with an m.8344A>G mutation (17%).[18] Catteruccia showed lipomas in three out of 15 patients with an m.8344A>G mutation (20%).[19] Also, mitochondrial changes such as ragged-red fibers and COX-negative fibers in muscle biopsies were reported in 28% of patients with MSL.[20] Mitochondrial DNA mutations have been diagnosed in nearly 16% of tested patients with MSL.[21] To the best of our knowledge, this association of the two rare disorders MSL and MERRF has not been reported before from our country and the presented case is the first patient with MSL and MERRF from Turkey. Only a patient with a demyelinating disease of the central and peripheral nervous system associated with a A8344G mutation in the mitochondrial lysine gene was reported from Turkey before.[22]

In summary, we report a patient with MSL who presented with progressive weakness of limb girdle muscles, neuropathy, myoclonus, and hearing loss and was diagnosed as having MERRF with typical findings in muscle biopsy and a heteroplasmic m.8344A>G mutation in the MT-TK gene. Remembering the association between lipomatosis and mitochondrial disorders, especially MERRF, is important in clinical practice because MSL can be a red flag for mitochondrial disorders.

DISCLOSURE

Conflict of interest: None.

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