A Case of Marinesco-Sjögren Syndrome: MRI Observations of Skeletal Muscles, Bone Metabolism, and Treatment with Testosterone and Risedronate

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Abstract

Marinesco-Sjögren syndrome (MSS) is a rare autosomal recessive disorder characterized by cerebellar ataxia, congenital cataracts, mental retardation, primary hypogonadism, skeletal abnormalities and myopathy, and patients with MSS are considered to be at risk of falls and bone fractures. We report a patient with MSS who received testosterone replacement therapy and risedronate administration. Muscle strength and the MRI features of the skeletal muscles were not changed, but low bone mass was improved by these treatments, and improvement has continued after risedronate treatment alone. This case suggests that treatment of MSS-related low bone mass using bisphosphonates is likely beneficial.

Key words: Marinesco-Sjögren syndrome, muscle MRI, testosterone, low bone mass, risedronate, bisphosphonate


Introduction

Marinesco-Sjögren syndrome (MSS) is a rare autosomal recessive disorder characterized by cerebellar ataxia, congenital cataracts, mental retardation, primary hypogonadism, skeletal abnormalities and myopathy. In 1931 Marinesco et al (1) described four affected siblings in a Romanian family, and in 1950 Sjögren (2) also described 14 cases in 6 Swedish families. Recently, mutations of the SIL1 gene on chromosome 5q31 have been found in MSS patients (3-6).

In MSS, myopathy leads to loss of ambulation in adulthood, when cerebellar ataxia becomes less noticeable (7). Skeletal changes associated with MSS include a small posterior fossa, kyphoscoliosis, gracile bones, short metatarsals and metacarpals (8, 9), but measurement of bone metabolism has not been reported and the patients with MSS are considered to be at risk of falls and bone fractures.

Here, we report a Japanese patient with MSS, in whom a new homozygous frameshift insertion mutation in the SIL1 gene was identified (10), together with MRI observations of the skeletal muscles and the result of testosterone therapy. We also describe details of the bone metabolism in this patient, and the result of treatment with testosterone and risedronate.

Case Report

The present male patient had been born after a normal pregnancy and delivery. His parents were Japanese with no consanguinity, and neither they, nor his brother or uncles, had any neurological symptoms. The patient showed developmental delay at the age of 3-4 months. He became able to control his head movements at the age of 8 months, and sit at the age of 2 years. The visual acuity of both eyes was poor, and he was diagnosed as having congenital cataracts, for which he underwent operations at the age of 3, 7, and 11 years. He started to walk with the aid of bilateral axillary crutches at the age of 6 years. He had mild mental retardation, but no problems at school or later at work in a facility
for the handicapped.

After age 30, his ataxic gait worsened and he sometimes fell backward. He sustained fractures of the right tibial and peroneal bones, and he was admitted to our hospital to undergo surgical reduction. At the age of 31 years, he was readmitted to our hospital because of displacement of a fixation nail, and transferred to the neurology section for evaluation.

At this time, he was 157 cm in height and 52.8 kg in weight. Bilateral cataracts had been removed surgically. His visual acuity was blind OD, and 0.01 OS. His right big toe was slightly short and the bilateral third toes were also short. He had mild mental retardation but was capable of daily conversation and was very friendly. He had mild cerebellar speech. His ocular movement in the right eye was fair in all directions. Rotatory nystagmus was evident in the horizontal gaze. Muscle strength of the \textit{M. orbicularis oculi} was 4 by manual muscle testing (MMT), and that of the \textit{M. orbicularis oris} was 5. He had no dysphagia, or fasciculation of the tongue. Mild muscle atrophy, without fasciculation, was evident in the bilateral lower extremities. Muscle tendon was flaccid in the four extremities. Hand grip was 10.5 kg on the right and 6 kg on the left. Muscle power was 4 in the upper limbs, 3- in the proximal lower limbs, and 4 in the distal limbs. Cerebellar ataxia was evident in all four extremities, and the gait was ataxic with bilateral Lofstrand crutches. Daily life was spent in a wheelchair. Deep tendon reflexes were normal in the upper extremities; PTR was slightly increased, and ATR was normal. Babinski reflex was negative. His penis and testicles were small, and he had incomplete development of secondary sex characteristics.

Laboratory studies yielded normal results for blood cell counts, ESR, blood sugar, and renal function. The serum creatine kinase level was 490 IU/L (normal 0-200), AST 30 IU/L (0-35), and ALT 70 IU/L (0-30). Serum Ca and P levels were normal. The serum LH level was 15.8 mIU/mL (1.8-9.2), FSH 31.8 mIU/mL (1.6-10.6), and testosterone 0.93 ng/mL (2.0-10.7). Lactate and pyruvate levels in the serum and CSF were normal. No chromosomal anomaly was evident.

Skeletal x-rays demonstrated coxa valga, right first and bilateral fourth metatarsal shortening, and gracile long bones and vertebral bodies. Motor and sensory nerve conduction studies of both the upper and lower limbs yielded normal findings, except for reduced compound muscle action potential of the tibial nerves. An EMG study using a concentric needle showed short-duration and low-amplitude motor unit potentials, indicating myopathic change.

MRI of the brain demonstrated marked atrophy of the cerebellum, especially the vermis. The pons was slightly atrophic and the fourth ventricle was enlarged (Fig. 1).

Skeletal muscle MRI findings in the lower extremities included severe fatty replacement of the muscles, predominantly the quadriceps femoris, gracilis, and semitendinosus muscles in the proximal areas and the peroneus and gastrocnemius muscles in the distal areas (Fig. 2).

The patient had been diagnosed as having MSS. He suffered repeated falls thereafter due to visual disturbance, ataxia, and muscle weakness, and was considered to be at risk of further bone fracture. His bone metabolism was examined at the age of 35 years, and low bone mass was diagnosed on the basis of a low bone mineral density (BMD) of 0.758 g/cm² (t score 64%, z score 68%) in the lumbar spine and a high levels of urinary N-terminal telopeptide type I (NTX) at 72.8 nMBCE/m (0.0-35.3). Examination of the testicular tissue by ultrasonography (US) demonstrated primary hypogonadism, which was confirmed by high serum levels of FSH and LH, and low levels of testosterone. We considered that his muscle weakness and low bone mass were partly associated with hypogonadism, although the gene mutation in this syndrome may cause a change of body composition. After obtaining informed consent from the patient and his family, we started testosterone replacement therapy (methyltestosterone 25 mg per os per every alternate day) for three years and risedronate administration (2.5 mg per os daily) for three years. We changed methyltestosterone to testosterone enanthate 125 mg, i.m., monthly for two months, but withdrew the latter because of appetite loss. We then administered methyltestosterone again for two months.

These therapies resulted in no improvement of muscle strength, and follow-up MRI studies of the lower extremity muscles demonstrated no change. Bone metabolism was significantly improved after treatment for three years; BMD was increased from 0.758 to 0.805 g/cm² (+ 6.2%) and the level of urinary NTX decreased from 72.8 to 43.5 nMBCE/m. Episodes of falls became less frequent, and no serious bone fractures occurred after these treatments. Although the low serum testosterone level was unchanged, the level of LH was decreased from 15.8 to 5.24 mIU/mL and that of FSH also decreased from 31.8 to 13.7 mIU/mL. As an adverse effect, the serum levels of AST and ALT were slightly elevated, and therefore we discontinued methyltestosterone therapy, which led to improvement of these parameters. There were no adverse effects associated with risedronate, and the improvement of low bone mass has continued for three years with risedronate treatment alone. The patient’s voice and sexual organs remained unchanged. Recently, we found a gene mutation in this case, revealed to be a new homozygous frameshift insertion mutation, 936_937insG, in exon 9 of the SIL1 gene (10).

\textbf{Discussion}

The present patient with MSS underwent replacement therapy with testosterone and risedronate administration. He had congenital cataracts, ataxia, mental retardation and muscle weakness, which were consistent with MSS (1, 2, 9). The findings of brain CT or MRI were also typical for MSS (11, 12). Follow-up MRI study of the brain showed no obvious change over an 8-year period. Myopathy, which was reported as a pathologic feature of MSS by Komiyama et al (7) and Sasaki et al (13), was apparent upon clinical
Figure 1. (A) Sagittal midline T1-weighted MRI of the brain, and (B) axial T1-weighted image at the level of the pons, showing marked atrophy of the cerebellum, especially the vermis. The pons is slightly atrophic and the fourth ventricle is enlarged. The anterior and posterior regions of the pituitary gland are normal. (C) Axial T2-weighted image at the level of the basal ganglia shows a normal cerebral cortex and white matter. The corpus callosum is also normal.

examination and muscle MRI. However, reports of MSS including details of muscle CT or MRI have been rare. Higuchi et al (14) and Mahjneh et al (15) reported findings of muscle CT in MSS. The cases reported by Higuchi et al (14) involved the quadriceps femoris, semitendinosus, gastrocnemius and soleus muscles. Mahjneh et al (15) reported that in relatively severe and moderate cases almost all thigh muscles and peronei and posterior compartment muscles of the leg were involved. The present findings were similar. Primary hypogonadism in MSS has also been reported (9, 16), and in the present patient this was diagnosed by US and measurement of LH, FSH, and testosterone levels. Our follow-up MRI study of muscles during testosterone therapy showed no change in muscle structure or fatty replacement. There was also no change in muscle strength. Previous reports have documented that testosterone increases fat-free muscle mass and size in hypogonadal men (17), increases muscle size in healthy young men (18), or increases muscle mass and strength in young men with chronic HIV infection or in relatively healthy older men (19). The failure to increase muscle mass and strength in the present patient may have been attributable to inadequate oral testosterone administration. Several reports have described hepatic side effects of methyltestosterone, including cholestatic jaundice, peliosis hepatis, and liver tumours (20). We treated this patient carefully, with close monitoring of hepatic function and abdominal CT, and these side effects did not appear. Although our patient did show a side effect when treated with i.m. testosterone enanthate, it seems that testosterone therapy by the i.m. or transdermal route will be appropriate in the future.

Skeletal abnormalities in MSS have been reported in detail by Brogdon et al (8) and others, but measurement of bone metabolism in MSS has not been reported. We confirmed the presence of low bone mass in this MSS patient. Risedronate is a bisphosphonate reported to be effective in male patients with primary osteoporosis (21). Risedronate and testosterone treatments improved the low bone mass in
our patient, which was apparent by measurement of BMP and urinary NTX. Episodes of falls became less frequent, and no serious bone fractures occurred after these treatments. This may have been due to the improvement of strength for body support, which had not been apparent in our previous evaluations. Thereafter, alfacalcidol therapy was added, but this had to be discontinued because of incipient calcification of the patient’s cornea. As there were no adverse effects associated with risedronate, and the improvement of low bone mass continued for three years under treatment with risedronate alone, this case suggests that treatment of MSS-related low bone mass using bisphosphonate is probably effective. In patients for whom testosterone can be used without side effects, the effect of testosterone treatment alone on low bone mass should be clarified.

In this patient, a new SIL1 gene mutation was identified (10). This gene is associated with the function of the endoplasmic reticulum (3-6). Studies by Anttonen et al (3) and Senderek et al (4) have convincingly demonstrated that MSS is caused by the loss-of-function mutations in the SIL1 gene (5). Loss of function was demonstrated by lack of immunostaining for SIL1 in biopsy samples of skeletal muscle from MSS patients (3). The resulting dysfunction of the endoplasmic reticulum would be associated with not only muscle metabolism but also bone metabolism and physiological parameters.

Future studies may help to clarify the mechanism of, and associations between the dysfunction of the endoplasmic reticulum and cerebellar, muscular, and osseous damage, thereby facilitating development of improved basic treatment.

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

References


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