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Case report

# Stiffness as a presenting symptom of an odd clinical condition caused by multiple sclerosis and myotonia congenita

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**Abstract**

A 24-year-old woman complained of a 4-year history of muscle cramps, stiffness of the right lower limb and walking difficulties. After clinical and laboratory investigations, a diagnosis of multiple sclerosis was made. However, her family history revealed that her father and an older sister had lifelong symptoms of impaired muscle relaxation following contraction, improving with physical exercise. Molecular genetic studies in both sisters confirmed the diagnosis of myotonia congenita, due to a c.568GG>TC (Gly190Ser) pathogenic mutation in CLCN1 gene. Occurrence of two different neurological conditions in the same patient, both manifesting with stiffness, is quite unusual and suggests the opportunity of an accurate differential diagnosis.


*Keywords:* Multiple sclerosis; Myotonia congenita; Muscle disorders; Stiffness

## 1. Introduction

Multiple sclerosis (MS) is an autoimmune disease where immune cells attack and destroy the myelin sheath that insulates neurons in the brain and spinal cord. This disease may manifest with a large variety of symptoms depending on demyelination sites. Symptoms occur either during attacks (relapsing forms) or slowly accumulate over time (progressive forms). Between attacks, symptoms may resolve completely, but permanent neurological deficits often occur, especially as the disease advances. Among the symptoms encountered in MS, muscle spasticity (muscle stiffness as a result of an increased pyramidal tone) and cramps occur in up to 90% of patients. These symptoms often lead to considerable distress because of pain, reduced mobility and interference with daily living activities [1].

Myotonia congenita (MC) is the most common inherited skeletal muscle channelopathy. This disorder may manifest either with a dominant (Thomsen disease) or recessive inheritance (Becker disease) pattern and it is caused by mutations in the skeletal muscle chloride channel gene CLCN1 [2,3]. In both forms, muscle stiffness is most pronounced, during rapid voluntary movements, following a period of rest but improves with repeated muscle activity – the so-called 'warm-up' phenomenon [4]. Some clinical findings are more recurrent in the recessive than in the dominant form. In fact, recessive MC tends to be more severe: patients may show muscle hypertrophy and depressed tendon reflexes [2], and they typically complain of transient weakness on initiating a movement that is rarely seen in the dominant form [3].

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## 2. Case report

A 24-year-old woman of European ancestry was referred to our clinic for the evaluation of onset of progressive stiffness and hypoesthesia of the right lower limb; two months later, she experienced right facial paresthesias.

She underwent several investigations, such as evoked potentials, lumbar puncture, brain and spinal cord MRI. Somatosensory, visual and auditory brainstem evoked potentials were normal, but MRI on T2-weighted images and fluid-attenuated inversion-recovery (FLAIR), showed the presence of several white matter hyperintense lesions involving periventricular white matter in the corpus callosum, juxtacortical and left cerebellum areas of the brain (Fig. 1) and a hyperintense lesion at C7 level of the spinal cord, all strongly suggestive of a demyelinating disease. Some of those lesions showed an enhancement after gadolinium injection; in addition, there was a Chiari type I anomaly. Cerebrospinal fluid examination revealed the presence of intrathecal IgG-oligoclonal bands. According to the McDonald criteria [5], the patient was diagnosed as having a relapsing-remitting MS. She was treated with glatiramer acetate withdrawn a year later because of diffuse allergic phenomena. During that period, no clinical disease progression was observed. A neuroradiological assessment was made every six months, showing an increasing lesion load in brain as additional signs of disease activity, even in the absence of new symptoms. Despite the clinical progression, she refused to take other medications. She also revealed that, since childhood, she had mild persistent difficulties, worsened by cold temperatures, in initiating gait, opening eyes and fists, after strong muscle contractions, and in speech and chewing because of facial muscle stiffness. She also manifested with muscle cramps in her lower limbs that improved after physical exercise. Neurological examination showed mild increased muscle tone and hypoesthesia in the right lower limb, increased deep tendon reflexes in the upper and lower limbs, and handgrip, eyelid and jaw prolonged contraction with hypertrophic calves. In addition, her parents were first degree cousins; she also revealed a positive family history for neuromuscular disorders because, since many years, her father and her older sister showed similar muscle symptoms. In fact, when examined, her father presented with a pronounced eyelid myotonia whereas her sister revealed the presence of eyelid, jaw, and handgrip myotonia and hypertrophic calves.

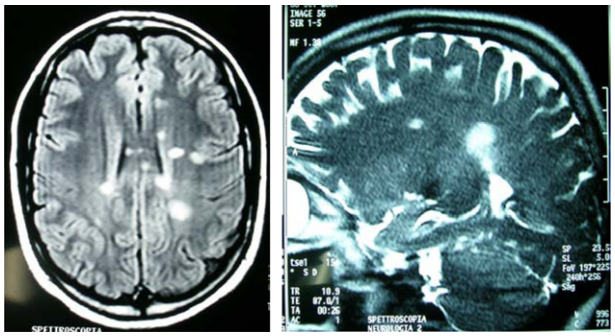

Fig. 1. Brain MRI – T2-weighted images and FLAIR – Presence of several white matter hyperintense lesions involving periventricular white matter in the corpus callosum, juxtacortical and left cerebellum areas.

In order to better define her muscle symptoms, the patient underwent extensive neurophysiological investigations including the Fournier protocol [6]. Diffuse myotonic discharges were detected spontaneously with needle EMG in all tested muscles (Fig. 2); short and long exercise tests did not induce a significant decrease of compound motor action potential (CMAP) amplitudes in the abductor digiti minimi (ADM) muscles. As a result, a Fournier pattern II was recognized in agreement with the neurophysiological guidelines for myotonia congenita [6].

Thyroid, liver, kidney and heart assessment were normal.

Genetic testing for MC, included bidirectional sequencing of the coding region of CLCN1 and dosage analysis of the coding exons using Multiple Ligation dependent Probe Amplification (MLPA) analysis. This analysis revealed the presence of a homozygous pathogenic mutation c.568GG>TC; p.Gly190Ser in exon 5. Furthermore, on testing her sister, the same CLCN1 gene mutation was detected in the heterozygous state, her parents refused to be screened for the mutation.

## 3. Discussion

In the case, herein reported, we describe a patient who came to our center because of the presence of muscle cramps, stiffness, limb hypoesthesia and facial paresthesias; her clinical history and the results of specific investigations confirmed a diagnosis of relapsing-remitting MS. In addition, other clinical findings in association with family data, neurophysiological examination and molecular-genetic studies, demonstrated a concurrent diagnosis of MC.

Stiffness is a very common symptom of CNS disorders involving the pyramidal tract, such as MS, but it also could be the main feature of some muscle channelopathies, such as MC, either in the dominant or in the recessive form.

Association between MS and neuromuscular disorders has rarely been described. In particular, there are a few reports of MS associated with pure muscle disorders such as centronuclear myopathy [7], facio-scapulo-humeral muscular dystrophy [8], mitochondrial myopathy [9], Pompe disease [10], myotonic dystrophy [11] and paramyotonia congenita [12]. Among those cases, myotonic dystrophy and paramyotonia congenita were characterized by the presence of myotonia as an additional cause of muscle stiffness.

It is worthwhile to outline that in the case with MS and paramyotonia congenita [12], stiffness was present, but myotonia worsened after a repeated physical exercise ("paradoxical myotonia"), whereas, generally, in MC it improves after repeated muscle contractions ("warm-up phenomenon") [4].