Multiple sclerosis and non-dystrophic myotonias: do they share a common pathophysiology?

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Summary

Some patients with multiple sclerosis (MS) complain of symptoms, such as myokymia, myotonia, spasms, and stiffness, which have been demonstrated to be due to a concurrent non-dystrophic myotonia, i.e. myotonia congenita or paramyotonia congenita. Beyond the known casual association between MS and non-dystrophic myotonia, a channelopathy representing a primary trait of MS rather than an epiphenomenon of demyelization (i.e., an acquired channelopathy) may exist. Indeed, the finding of MS patients with no genetic evidence of non-dystrophic myotonia but showing a clinical picture resembling this condition would support this hypothesis.
Thirty patients with MS and no concurrent diagnosis of myotonia congenita or paramyotonia congenita were submitted to the Fournier protocol. Some of these MS patients presented abnormal muscle excitability with scarce myotonic discharges, but only a few of them had clinical features compatible with myotonia congenita or paramyotonia congenita syndromes.
Even though the low number of recruited patients did not allow a robust statistical analysis, our data seemed to indicate the presence of an ion channel dysfunction that is independent of the acquired channelopathies and likely represents a common pathophysiological mechanism underlying a unique channelopathy simultaneously involving the peripheral and the central nervous system in individuals with MS. Confirming the presence of such a primary channelopathy in MS patients is of non-negligible importance, since dysfunction of ion channels may represent a suitable therapeutic target in MS.

KEY WORDS: Fournier protocol, multiple sclerosis, myotonia congenita, paramyotonia congenital.

Introduction

Multiple sclerosis (MS) is an autoimmune disease that targets the myelin sheath in the brain and spinal cord (Kutzelnigg and Lassmann, 2014). Symptoms either occur during attacks (relapsing forms) or slowly accumulate over time (progressive forms). After an attack, symptoms may either resolve completely or leave permanent neurological deficits, especially in the advanced phases. Hence, MS is classified into different forms: relapsing-remitting, primary-progressive, secondary-progressive and progressive-relapsing (Lublin, 2014).
The pathophysiology of MS is fiercely debated. Initially regarded as a pure inflammatory demyelinating disorder of the central nervous system (CNS), it has since been interpreted as primary neuronal degeneration associated with demyelination, and more recently as coexistence of demyelination, neuronal degeneration and channelopathy (Meuth et al., 2009).
Channelopathies are disorders caused by ion channel dysfunction and they include a wide spectrum of neurological conditions, both with CNS involvement (e.g., generalized epilepsy with febrile seizures plus, type 2) and with peripheral nervous system (PNS) involvement (e.g., myotonia congenita and paramyotonia congenita, which belong to the family of the non-dystrophic myotonias). Specifically, myotonia congenita and paramyotonia congenita are muscle ion channelopathies caused by mutations in the genes for the chloride (CLCN-1) and sodium (SCN4A) channels, respectively (Matthews et al., 2010). These mutations result in the muscle hyperexcitability subtending myotonia and muscle stiffness. MS can also be considered an acquired channelopathy, given that ion channels can be maldistributed, dysfunctional or pathologically activated in CNS neurons and glia in MS (Waxman, 2001; Correale et al., 2017). In fact, the demyelination itself results in sodium channel redistribution, contributing to the impairment of nerve conduction (Correale et al., 2017). Moreover, dysfunctions of voltage-gated sodium channel subunits contribute to the pathophysiology of some neurological diseases, including MS (Wang et al., 2017). Finally, channels can also be targeted by autoantibodies (Brinkmeier et al., 1993).
Hence, dysfunction of voltage-gated ion channels (sodium, calcium and potassium) can be responsible for certain transient symptoms of MS (including paroxysmal attacks of migraine, epilepsy, weakness, numbness, myokymia, myotonia, spasms and stiffness) (Brinkmeier et al., 1993; Schattling et al., 2014), and thus play a role in the pathophysiology of the disease. In this regard, transient symptoms related to the PNS in patients with MS have been demonstrated, in a few reports, to be due to concurrent myotonia congenita or paramyotonia congenita (Weintraub et al., 1970; Portaro et al., 2013; Ashtari et al., 2014). Nonetheless, the fact that MS

patients may present with PNS symptoms compatible with myotonia congenita/paramyotonia congenita but no genetic evidence of these conditions may be considered to cast doubt on the casual nature of the association between MS and myotonia congenita/paramyotonia congenita (i.e., suggest that, instead, they share a specific underlying pathogenic mechanism) (Wang et al., 2017). In fact, it is possible to hypothesize the existence of a channelopathy that represents a primary trait of MS, as opposed to an epiphenomenon of demyelination (i.e., an acquired channelopathy) or a casual association with myotonia congenita or paramyotonia congenita.

To test this hypothesis, MS patients without a concurrent diagnosis of myotonia congenita or paramyotonia congenita were submitted to the Fournier protocol, which looks for muscle membrane hyperexcitability due to a muscle channelopathy (Fournier et al., 2004, 2006; Tan et al., 2011). Indeed, the presence of muscle hyperexcitability in patients not expected to show such a condition could indicate the existence of a primary channelopathy; in other words, there could be a common pathophysiological mechanism underlying a unique channelopathy involving, simultaneously, both the PNS (i.e. muscle) and the CNS. Despite some promising data (Shields et al., 2012; Schattling et al., 2014; Wang et al., 2017), clear neurophysiological evidence of channelopathy in MS is still lacking. The importance of establishing the presence of such a primary channelopathy in MS is not negligible, since dysfunctional ion channels may represent a suitable therapeutic target in patients with MS (Schattling et al., 2014).

Materials and methods

Subjects

Thirty patients attending the MS hub center of the IRCCS Centro Neurolesi Bonino Pulejo (Messina, Italy) were enrolled in the study. Clinical-demographic characteristics are summarized in Table I. Patients taking drugs acting on CNS excitability (including steroids, amantadine, antidepressants, antipsychotics and antiepileptic drugs) and with clinical, laboratory, and conventional electrophysiological evidence of PNS involvement were not included in the study. As control groups, we enrolled 20 healthy individuals without evidence of neuromuscular disease, and 18 patients with a clinical, electromyographic and genetic diagnosis of myotonia congenita/paramyotonia congenita (Table I). The local ethics committee approved the experimental procedure and all subjects also gave their written informed consent to it, in accordance with the requirements of the Declaration of Helsinki.

Experimental procedure

Patients and healthy individuals underwent a short exercise test at room temperature and after skin cooling, and a long exercise test, using a standardized protocol with minor modifications (McManis, 1986; Fournier et al., 2004, 2006), as well as needle electromyography of the biceps brachii (BB) and first dorsal interosseous (FDI) muscles.

Specifically, compound muscle action potentials (CMAPs) were evoked by supramaximal nerve stimulation (single square-wave stimuli of 0.3 ms duration, at an intensity 20-30% greater than that needed for maximal CMAP amplitude, delivered using a bipolar bar electrode) and recorded, using small disc-type skin electrodes, from the right FDI muscle after stimulation of the ulnar nerve at the wrist. A steady CMAP amplitude was obtained by collecting 20 CMAPs. Skin temperature was kept between 32 and 34°C throughout the session. The position of the upper limb was continuously checked to prevent articulation displacement. We performed, every 10 minutes, in a random order, the following steps: (i) the participant was invited to contract the relevant muscle as strongly as possible in isometric conditions for one minute. After completion of the exercise, the patient was instructed to completely relax the hand and CMAPs were measured every 10 seconds for 60 seconds, in accordance with the short exercise test described by Streib et al. (Streib et al., 1987). The trial was repeated three times. The presence of post-exercise myotonic potentials (PEMPs) was also checked; (ii) the participant was invited to contract the muscle as strongly as possible in isometric conditions for 5 seconds every 15 seconds (during which the hand was kept at rest) for 5 minutes. After completion of the exercise, the patient was instructed to completely relax the hand and CMAPs were measured every minute for 60 minutes, in accordance with the long exercise test described by McManis et al. (1986); (iii) neuromuscular transmission was tested by applying 3Hz repetitive nerve stimulation (RNS) (10 stimuli at 3Hz); (iv) the short exercise test was performed after cooling (20°C); (v) needle recording from the BB and FDI muscles was used to detect myotonic discharges, which were graded on a 0-3 scale (Streib, 1987); (vi) needle recording was performed after cooling.

Statistical analysis

Normal distribution, baseline differences, and homogeneity of variance of data were assessed using the Shapiro-Wilk and Levene tests. CMAP peak-to-peak amplitude was measured and expressed as a percentage of the baseline value. The reference range was defined as the mean±2SD.

Electrophysiological data (short and long exercise tests, RNS, Streib scores) were explored by using ANOVAs with the factors *time*, *group* (phenotype), and *condition* (i.e. repetition and temperature), where appropriate. Statistical significance was set at $p<0.05$. Post-hoc paired t-tests with Bonferroni correction were used.

Results

Clinical data

Patients with MS exhibited a variety of symptoms (e.g. weakness, sensory loss, paresthesia, blurred vision, nystagmus, ataxia, sphincter symptoms, diplopia, dysarthria), beyond those related to the PNS (which included transient weakness, transient myokymia, spasms, and stiffness) (Table I). Patients with myotonia congenita/paramyotonia congenita reported more marked muscle hyperexcitability-related symptoms (Table I). There were no demographic differences between the two groups (p=0.3) (Table I).

Table I - Clinical, demographic, and electrophysiological characteristics.

MS patients	Gender	Age (y)	Disease duration (y)	MS phenotype	Clinical features	Streib scale
FP_I (n=5)	M	43	7.0	PR	1 2 8	
	M	37	1.0	RR	2 7 8 9	1
	F	31	7.9	SP	3 5	
	F	34	9.4	SP	4 8 9	
	F	53	8.8	PR	1 3 7 8	
FP_II (n=4)	F	46	9.6	PP	5 6 8 9	
	F	30	5.3	PR	3 4 5	
	F	47	0.9	RR	4 5 8 9	
	M	40	5.7	PR	2 8 10	1
FP_III (n=3)	M	54	4.4	RR	2 9 10	1
	M	46	8.3	PR	2 4 10	1
	F	41	6.3	PP	1 4 6 10	1
No CMAP	F	55	6.7	PR	1 8 9	
changes	F	34	2.6	RR	2 3 5 7	
no EMG	F	36	1.1	RR	3 5	
sign s(n=18)	F	54	2.5	PR	5 6 10	
	F	47	9.2	PR	3 4 5 6	
	F	55	4.0	RR	1 3 10	
	F	32	1.6	PP	1 3 6 8	
	F	39	4.5	SP	4 8 9 10	
	F	37	1.8	PR	1 6 7	
	M	46	8.9	SP	1 2 5 9	
	F	40	3.1	RR	1 8 9	
	M	50	9.5	SP	5 7 9 10	
	F	32	3.0	SP	1 7 9 10	
	F	37	9.3	SP	3 5 6	
	F	40	3.9	RR	2 6 8	
	F	43	2.8	RR	1 3 4 8	
	M	54	1.8	RR	1 2 5 9	
	F	50	7.4	SP	5 8 9 10	
Mean (SD)	8M 22F	42 (7)	5 (3)	9 PR, 10 RR, 10 SP, 8 PR		1 (0)

NDM patients	Gender	Age (y)	Disease duration (y)	CRS score	MSS score	Streib scale score
FP_I(n=6)	M	28	7.7	1	0	2
	M	28	4.5	1	2	3
	F	23	6.0	2	2	2
	M	33	5.3	2	0	2
	F	29	4.6	1	2	3
	F	26	4.6	1	1	2
FP_II (n=2)	F	35	4.9	1	1	2
	M	28	7.7	1	2	3
FP_III (n=8)	F	31	5.1	2	1	2
	M	38	7.0	2	1	3
	M	37	6.0	1	0	2
	F	38	6.8	1	2	3
	M	37	5.3	1	2	3
	F	33	6.7	2	0	3
	M	34	5.9	1	0	2
	F	33	7.0	2	1	2
	8M 8F	31.9 (4.6)	6.7 (0.9)	1.4 (0.5)	1.1 (0.9)	2.4 (0.5)

Legend: 1 weakness, 2 sensory loss, 3 paresthesia, 4 blurred vision, 5 nystagmus, 6 ataxia, 7 sphincter symptoms, 8 diplopia, 9 dysarthria, 10 symptoms related to the peripheral nervous system (including transient myokymia, spasm, and stiffness). CRS=Clinical Rating Scale (a scale from 0 to 4 on which the presence of myotonia/paramyotonia, functional weakness and impairment is rated as follows: -0- absence of myotonia/paramyotonia; -1- presence of myotonia/paramyotonia and/or mild functional weakness without functional impairment; -2- moderate muscle weakness leading to some degree of functional impairment; -3- muscle weakness with severe functional impairment and in some cases resulting in the subjects being confined to a wheelchair; and -4- bedridden), MSS =Myotonia/Paramyotonia Severity Scale (a scale from 0 to 4 that rates the entity of myotonia/paramyotonia as follows: -0- absence of myotonia/paramyotonia, -1- minimal, -2- moderate, -3- severe, and -4- the worst myotonia/paramyotonia experienced); NDM=non-dystrophic myotonia. FP_I=Fournier pattern I, consisting of gradual and persistent reduction in CMAP enhanced by repetition, enhanced further by cooling; FP_II=Fournier pattern II, consisting of a little or no decrement in CMAP at room temperature, early decrement with rapid recovery and reduction with repetition may be seen; FP_III= Fournier pattern I, consisting of no CMAP changes but positive EMG.

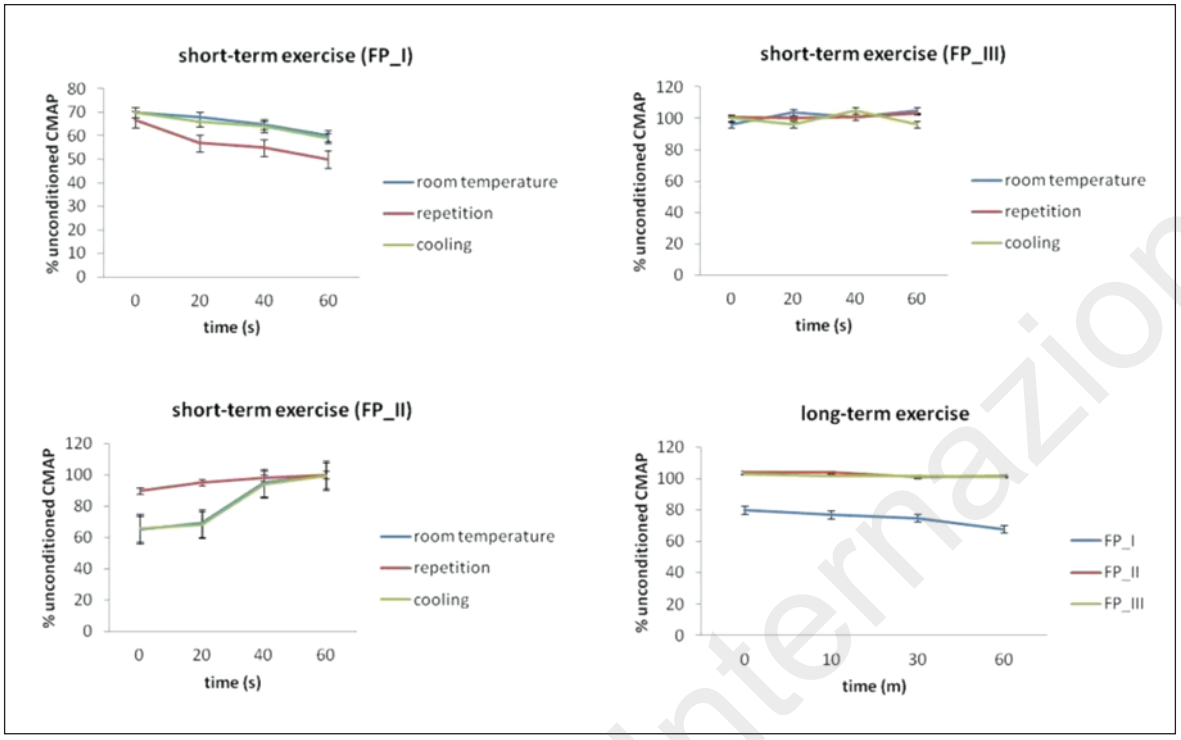

Figure 1. Percentage CMAP amplitudes changes (with SD) following short and long exercise test at room temperature, after repetition, and after skin cooling.

Short exercise test

There were no significant overall differences in short exercise test aftereffects (main interaction *time×group×condition* p=0.4). Even though patients with MS and those with non-dystrophic myotonia behaved very similarly (*time×group* p=0.4), the magnitude of the CMAP increment was significantly greater in the patients with MS (*group* p=0.001). Specifically, the patients with MS showed a non-significant *time×condition* interaction (p=0.3), given that five of them showed a gradual and persistent reduction in CMAP (*time* p<0.001), enhanced by repetition (p<0.001) (Table I, Figure 1), and four patients showed an early decrement in CMAP with rapid recovery (*time* p<0.001), disappearing with repetition (*time* p=0.1). Cooling had no effect in these patients (*time* p=0.1). The first of the above patterns, termed Fournier pattern I (FP_I), was also shown by six patients with paramyotonia congenita (*time×condition* p=0.01; *time* p<0.001), weakened by repetition (*time* p=0.005) and cooling (*time* p=0.001). The second pattern (FP_II) was also shown by two patients with recessive myotonia congenita (FP_II) (*time×condition* p=0.01; *time* p<0.001), weakened by repetition (*time* p=0.001), and without cooling effect (*time* p=0.1).

The remaining patients with MS showed no CMAP changes (*time* p=0.02), either at room temperature (*time* p=0.01) or after cooling (*time* p=0.01) (Table I; Figure 1). PEMPs were never detectable following the short exercise test.

We then investigated whether short exercise test aftereffects differed between MS phenotypes, and found no differences between the different MS phenotypes (main interaction *time×group×condition* p=0.3).

Healthy subjects showed a mild CMAP amplitude increase (*time×condition* p=0.01; *time* p=0.01), which disappeared with repetition (*time* p=0.3). Cooling had no effect in these subjects (*time* p=0.1).

Long exercise test

No significant overall differences were found in long exercise test aftereffects (*time×group* p=0.6). Even though patients with MS and those with non-dystrophic myotonia behaved very similarly, the magnitude of the CMAP increment was significantly greater in the patients with MS (*group* p=0.001). Specifically, the patients with MS showed a non-significant *time* effect (p=0.1), given that five of them showed a gradual and persistent reduction in CMAP (*time* p<0.001) (Table I, Figure 1), whereas the remaining patients showed no CMAP changes (*time* p=0.6). The first pattern (FP_I) was also shown by six patients with paramyotonia congenita (*time* p<0.001). Notably, the five MS patients were the same ones who showed FP_I after the short exercise test. Among the MS patients who did not show any long exercise test aftereffect, four individuals showed a FP_II after the short exercise test, thus matching the electrophysiological responses of two patients with recessive myotonia congenita.

We then examined whether long exercise test aftereffects differed between MS phenotypes. Again, no differences were found between the different MS phenotypes (*time×group* p=0.3).

No effect of the long exercise test was found in healthy individuals (*time* p=0.5).

RNS

3Hz-RNS showed no effect (*group* p=0.4).

Myotonic discharges with needle EMG

Significant differences were found between group and temperature effects on Streib grading (*group×temperature* p<0.001). In fact, rare myotonic discharges (Streib score 1) were detected in five patients with MS, without differences concerning the FP (Table I), whereas discrete or abundant myotonic discharges (Streib scores 2 and 3, respectively) were detected spontaneously and/or with percussion at needle EMG in all tested muscles of patients with myotonia congenita and paramyotonia congenita (*group* effect p<0.001) (Table I). Cooling had no effect on myotonic phenomenon in patients with MS and myotonia congenita (dominant and recessive), whereas it decreased myotonic discharges in patients with paramyotonia congenita (*group* p<0.001).

Discussion

To the best of our knowledge, this is the first study showing abnormal muscle excitability related to a channelopathy in patients with MS and without genetic evidence of myotonia congenita/paramyotonia congenita. Only 12 out of 30 patients with MS presented abnormal muscle excitability (without differences between MS phenotypes), and only 10 individuals complained of clinical features compatible with myotonia congenita or paramyotonia congenita syndromes (limited to transient weakness, transient myokymia, spasms, and stiffness). Nonetheless, only four patients with MS showed both myotonia/paramyotonia congenita-like symptomatology and a well-defined Fournier pattern (as well as myotonic discharges). Specifically, five patients showed a FP_I (gradual and persistent reduction in CMAP enhanced by repetition, enhanced further by cooling), four a FP_II (little or no decrement in CMAP at room temperature, early decrement with rapid recovery and reduction with repetition may be seen), and three a FP_III (no CMAP changes but positive EMG). The remaining patients showed neither CMAP changes nor positive EMG. Therefore we could not discern between normal pattern, chloride, or sodium channel myotonia.

However, the short/long exercise test and the Streib score in patients with MS were both significantly lower than in patients with myotonia congenita/paramyotonia congenita. Moreover, none of the MS patients was genetically positive for a channel mutation, and none reported a family history or clear clinical features compatible with a muscle channelopathy such as myotonia congenita/paramyotonia congenita. Therefore, we can exclude a concealed muscle channelopathy in our patients. Despite the lack of a clear association between symptomatology and the Fournier pattern shown, we can hypothesize that abnormal responses to the Fournier protocol might be due to an ion channel dysfunction within the PNS, which may be a primary trait of MS, at least in some cases.

We can postulate three possible scenarios. First, the Fournier pattern findings might, in some patients with MS, be due to abnormalities of voltage-gated ion channels other than those related to myotonia congenita/paramyotonia congenita (i.e. CLCN1 and SCN4A) (Kim, 2014). It is indeed conceivable that MS-related CNS abnormalities may induce the expression of abnormal muscle channels or unmask a covert channelopathy unrelated to myotonia congenita/paramyotonia congenita (Meuth et al., 2009).

Second, among the large repertoire of channelopathies in MS, a key role may be played by voltage-gated Na^+ channels other than SCN4A, which are also crucial for neuronal excitability (Wood and Baker, 2001; Yu et al., 2003,2005; Leterrier et al., 2010; Corry and Thomas, 2012) and may represent a suitable target of the Fournier protocol. Structurally, the voltage-gated Na^+ channel consists of 1-4 auxiliary β-subunits and a highly-glycosylated, pore-forming α-subunit, which form 10 different voltage-gated Na^+ channel subtypes, named $Na_v1.1$-$Na_v1.9$ and Na_vX (Goldin et al., 2000; Yu et al.,2005; Diss et al., 2004). To date, the $Na_v1.4$ Na^+ channel has been found only in muscles, whereas the expression of the other nine voltage-gated Na^+ channel subtypes has been generally detected in the CNS ($Na_v1.1$-1.3, 1.5-1.6) and PNS ($Na_v1.7$-1.9) (Candenas et al., 2006; Vacher et al., 2008; Pappalardo et al., 2016). It may be argued that the latter channels, owing to their location in the nodes of Ranvier, could mediate Fournier paradigm aftereffects (Craner et al., 2004, 2005). Moreover, there is now growing interest in the role of the other CNS and PNS voltage-gated Na^+ channel subtypes in MS pathophysiology, as they have been found to be significantly expressed in reactive astrocytes, and may therefore potentially contribute to the abnormal muscle hyperexcitability (Black et al., 2010).

Third, the postulated primary channelopathy in MS may represent a compensatory (to maintain the intracellular and extracellular ion homeostasis for Na^+/K^+-ATPase) but also maladaptive mechanism (involving chloride and sodium channels) to counteract the MS-related acquired channelopathy (Black et al., 2010). This hypothesis may also explain why we found a Fournier protocol-like response suggesting involvement of chloride channels, which should not be the case in MS. Given that the low number of recruited patients did not allow a robust statistical analysis to be performed, and the association between clinical and electrophysiological features was not significant, our data are not generalizable and larger sample studies are required to confirm our findings. Nonetheless, it is possible that there could exist a common pathophysiological mechanism underlying a unique channelopathy simultaneously involving the PNS (i.e. muscle) and the CNS in individuals with MS. Indeed, such a genetic basis needs to be clarified by looking for a possible new genotype related to voltage-gated ion channel dysfunction. Confirmation of such a pathophysiological entity could be helpful to guide patient-tailored treatment. In fact, it has been reported that voltage-gated ion channel blockers can reduce the expression of microglia and phagocytes, the release of IL-1 and TNF-α pre-inflammatory mediators (Bechtold et al., 2004; Black et al., 2007, 2008), and the degree of injury in cell axons in experimental autoimmune encephalomyelitis lesions (Black et al., 2010), and improve the clinical status of patients with MS (Bechtold et al., 2004; Black et al., 2007, 2008). Flecainide and mexiletine are the most used voltage-gated ion channel blockers to treat muscle channelopathies (Wang et al., 2003; Desaphy et al., 2004; Aoike et al., 2006; Hoffman and Kaminski, 2012). Moreover, other drugs, including carbamazepine and phenytoin, have shown a protective effect in channelopathies (Wang et al., 2003; Bechtold

et al., 2004; Kurihara, 2005; Black et al., 2007, 2008; Lossin and George, 2008).

In conclusion, we suggest that all patients complaining of PNS symptomatology compatible with myotonia congenita/paramyotonia congenita should undergo the Fournier protocol in order to identify a possible underlying channelopathy. This may be useful to better manage the pharmacological treatment of patients with MS, as the addition of voltage-gated ion channel blockers may help, at least in some cases, to relieve PNS and CNS symptomatology related to channel dysfunction.

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