

Clinical background of the multifocal motor neuropathy: the Lausanne experience

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Summary

Kuntzer T, Radziwill AJ, Botez SA. Clinical background of the multifocal motor neuropathy: the Lausanne experience. Schweiz Arch Neurol Psychiatr. 2007;158:57–64.

In this review we describe patients examined in Lausanne in whom a diagnosis of multifocal motor neuropathy (MMN) with conduction block (CB) was made, the basis of a discussion of the literature.

Thirteen patients are described with their clinical features and the results of their laboratory and neuroimaging characteristics. There were 3 women and 10 men followed over a mean period of 7.3 years. Diagnosis was established after a mean period of 1.9 years. The location of the blocked nerve was predominantly observed in the upper limbs. Thirty per cent of the patients were considered as non-responders to treatment, including infusions of immunoglobulins (IVIg), cyclophosphamide or mycophenolate mofetil, and 70% of the patients were responders to IVIg infusions given repetitively. IVIg response was maintained during a mean period of time of 4.7 years in 8 patients. Only one patient is considered as cured following the associated treatment after 10 IVIg monthly courses associated with interferon alpha given subcutaneously over 16 months.

The natural history of multifocal motor neuropathy is of a slowly progressive motor neuropathic process. Most patients have progression over many years, with treatment having persistent effects in the responders, but not curing the disease. The predilection for the upper limbs and in particular the handy muscles results in neurologic disability in the majority of the patients. Some patients are disabled by fatigue. The aetiology and pathogene-

sis of multifocal motor neuropathy remain unresolved, in part because the neuropathy runs an indolent course rarely justifying motor nerve biopsy and because there are no animal models of the disease. Nevertheless, it is widely believed that multifocal motor neuropathy is an autoimmune disorder. Recent excitability measurements of the nerves showed that there is axonal hyperpolarisation adjacent to sites with conduction block secondary to intraaxonal sodium accumulation.

In conclusion, multifocal motor neuropathy is a disease that is slowly progressive but not benign, nerves showing conduction block develop axonal changes, and markers for this disease are needed. There are therefore open questions in this peripheral nerve disorder, the two most crucial being lack of real knowledge of the pathophysiological mechanisms of this peripheral nerve channelopathy and need of alternative treatments to IVIg infusions to cure this disease.

Keywords: motor neuropathy; clinical background; multifocal motor neuropathy

Introduction

Patients with a pure motor asymmetric neuropathy with multifocal conduction blocks (CBs) have been reported from 1986 onwards by several groups, from Geneva [1], San Francisco [2] and Philadelphia [3], under different names such as motor neuropathy, multifocal neuropathy, multifocal motor neuropathy with conduction blocks and lower motor neuron syndrome with anti-GM1 antibodies. Pestronk and colleagues [4] from Baltimore first introduced the term ‘multifocal motor neuropathy’ (MMN), highlighted the association with immunoglobulin M anti-ganglioside GM1 antibodies and gave support to an immune-suppressive therapy. Kaji et al. [5] from Kyoto suggested that infusions of intravenous immunoglobulins (IVIg) can be a choice of therapy for this neuropathy.

Several diagnostic criteria for multifocal motor neuropathy have been proposed [6–8], and recent

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guidelines have been published by a joint task force of the European Federation of Neurological Societies/Peripheral Nerve Society [9]. These criteria share the following clinical features: slowly progressive, asymmetric, predominantly distal weakness without objective loss of sensation in the distribution of two or more individual peripheral nerves, and absence of upper motor neuron signs. The hallmark of the disease is the presence of multifocal conduction blocks on electrophysiological (EDX) testing outside the usual sites of nerve compression. Conduction block is a reduction in the amplitude and area of the compound muscle action potential (CMAP) obtained by proximal versus distal stimulation of motor nerves in the absence of abnormal temporal dispersion.

The aims of this review are to describe the clinical features, the laboratory and neuroimaging characteristics of this neuropathy in order to discuss the differential diagnosis and the natural course of multifocal motor neuropathy in the light of the personal experience of the authors.

Patients and methods

During a 12-year period (1994 to 2005) 13 patients were treated and followed in our out-patient clinic, and all had signs of an asymmetric and distal weakness in the distribution of two or more individual peripheral nerves and presence of multifocal conduction blocks on electrophysiological testing outside the usual sites of nerve compression.

Results

The demographic, clinical features and main results of the patients are given in table 1.

There were 3 women and 10 men followed over a mean period of 7.3 years. Diagnosis was established after a mean period of 1.9 years. Location of the blocked nerve is also described in table 1. Very high titres of anti-GM1 antibodies were only found in 2/13 patients. Four of 13 patients (30%) were considered as non-responders to IVIg following at least 2 courses of IVIg at the dosage of 2 g/kg/course, and among these patients, 4 were considered as non-responders to cyclophosphamide, 3 to mycophenolate mofetil (2 g/day for 6 months) and in one muscle weakness was worsened by taking carbamazepine 200 mg/day. Nine of 13 patients were considered as responders to IVIg infusions given repetitively at regular periods of time that depended on each patient, between 2 and 8 weeks. IVIg response was maintained during a

mean period of time of 4.7 years in 8 patients. In 3 of these responders prednisone was initially prescribed at 1 mg/kg/day and in all 3 a rapid worsening was seen, needing to stop the treatment within a few days. One patient is considered as cured following the associated treatment after 10 IVIg monthly courses associated with interferon alpha given subcutaneously over 16 months.

Clinical vignette 1 (JO, a responder): During summer 1996 a 32-year-old active sales supervisor developed progressive heaviness of his right arm and had intermittent neck pain. As a progressive muscle weakness was reported, he was examined in autumn 1998 with the question of a C5 radiculopathy. No amyotrophy was observed, but the examination showed a right-arm non-homogeneous muscle weakness (M3 MRC for the biceps brachii and deltoid muscles; M4+ for extensor digitorum communis, interossei and abductor digiti minimi muscle), as well as fasciculations in biceps brachii and deltoid muscles, absent biceps brachii reflex and an increased muscle contraction of the right biceps brachii in response to direct muscle percussion. Blood testing, including complete blood count, chemistry and a dysimmune work-up were within normal values. EDX study demonstrated normal shape and amplitude of the sensory nerve action potentials (SNAPs) and the compound muscle action potentials (CMAPs) from distal stimulations of the following nerves: median, ulnar, radial and musculocutaneous. An almost complete absence of CMAP (or conduction block) was observed secondary to Erb's point stimulation of the musculocutaneous, with a partial conduction block of the ulnar and radial nerves (fig. 1A). Brain and cervical magnetic resonance imaging (MRI) were normal, but brachial plexus MRI showed thickening and high signal intensity on T₂-weighted images of different parts of the plexus (fig. 1C). Four days after his first IVIg infusion (2 g/kg over 5 days), muscle strength normalised together with a transient clear increase of frequency of fasciculation in the biceps brachii and deltoid muscles. The improvement lasted about 5 weeks, but IVIg infusion was then resumed due to the progressive reappearance of weakness with the inability to bend the right elbow. IVIg infusion was given initially at 2 g/kg once every 6 weeks and then at 1 g/kg once a month. After 6 infusions prednisone was given at 1 g/day during 4 days but had to be stopped abruptly due to the appearance of an asymmetrical but generalised muscle weakness of the four extremities including difficulties in walking. The improvement was then progressive and within 4 weeks the deficits were again limited to the right arm. Eight years later, muscle weakness could

still be improved following IVIg via a permanent venous catheter that allowed 80 IVIg infusions; progressively, the deficits were also found in the left foot extensors, but the weakness was improved by the recurrent IVIg infusions.

Comments: Conduction block, the failure of a nerve impulse to propagate through a structurally intact axon, is the electrophysiological hallmark of multifocal motor neuropathy in motor EDX studies and is discussed by M. R. Magistris (in the same issue).

As observed in our patients, results of routine analysis of blood and urine are unremarkable in patients with multifocal motor neuropathy, despite slightly to moderately high serum creatine-kinase activity, consistent with slowly progressive axonal degeneration, in up to two-thirds of patients. The

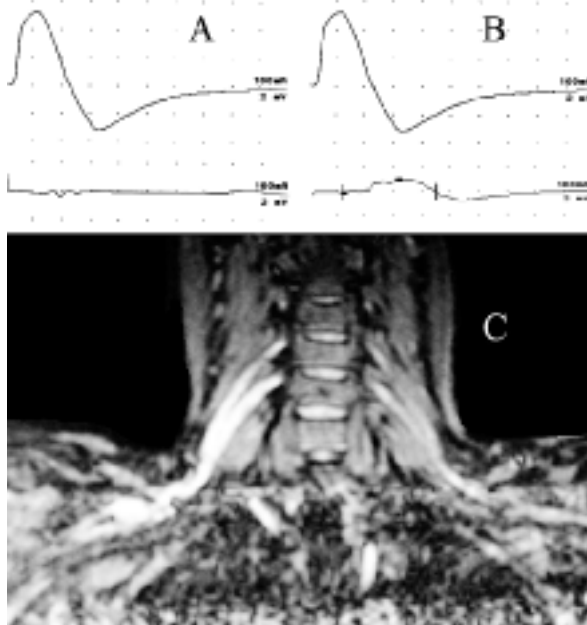
number of patients with a creatine-kinase level greater than 180 U/L were significantly lower in responders than non-responders in one study [10]. In multifocal motor neuropathy oligoclonal bands are not found in the CSF and the IgG index is normal [11, 12]. Immunofixation electrophoresis is typically normal in multifocal motor neuropathy; if a monoclonal spike is seen, the disease should be differentiated from polyneuropathy associated with monoclonal gammopathy of unknown significance. Serum immunoglobulin concentrations are high in some patients, but they are polyclonal [11].

Initial reports of increased antibodies to GM1 ganglioside in patients with a pure muscle weakness and conduction block in EDX studies raised hopes for a diagnostic marker for multifocal motor neuropathy [4, 13–16]. Positive findings for poly-

Table 1 Demographic data, results of electrophysiological and laboratory tests of the 13 patients encountered in Lausanne. Distal CMAPs must be >5 mV (normal value), ↓ describes low amplitude (between 2 to 5 mV), and ↓↓ very low amplitude (2 mV). N: normal; R: right; L: left; ↑ denotes a moderate increase above the normal upper range, and ↑↑ denotes a great increase above the normal upper range.

patient (sex), age at onset	weakness at onset	EDX		brachial plexus MRI	CSF proteins (oligoclonal bands)	serum			follow-up
		distal CMAPs	location of conduction blocks (# nerves blocked)			CK	immuno-fixation electrophoresis	anti-GM1 antibodies	
AP (♂), 51	R hand grip & arm flexion	↓↓	ulnar median musculocutaneous (3)	N	N (+)	N	IgM gammopathy	N	IVIg + IFN α , responder
BC (♂), 36	L hand grip, foot drop	N	ulnar peroneal (2)	N	N (-)	N	N	N	IVIg responder
BM (♂), 65	R hand grip	↓	median ulnar (2)	N	N (-)	N	N	N	IVIg responder
DD (♂), 42	R hand grip	↓	median ulnar (2)	N	N (+)	N	α -2 ↓, β/γ ↑	N	IVIg responder
DY (♂), 51	R hand grip	↓	ulnar radial (2)	N	N (-)	N	N	N	non-responder
HD (♂), 48	R hand grip	↓	radial ulnar (2)	N	N (-)	N	N	N	non-responder
JO (♂), 32	R arm flexion & hand grip	N	ulnar median musculocutaneous (3)	brachial plexus and roots hypertrophy	N (-)	N	N	N	IVIg responder
ME (♂), 26	R & L hand grip	↓	median ulnar (4)	N	N (-)	↑(5 ×)	N	N	IVIg responder
RM (♀), 61	R & L hand grip	↓	median ulnar (4)	N	N (-)	N	N	↑↑(15 ×)	non-responder
RA (♂), 53	L hand grip	↓	radial ulnar (2)	N	N (+)	N	N	N	non-responder
TJ (♀), 60	L hand grip & arm flexion	N	median radial musculocutaneous (3)	N	N (-)	N	N	↑↑(20 ×)	IVIg responder
WJ (♂), 38	R & L arm flexion, L hand grip	N	ulnar median musculocutaneous (5)	N	N (-)	↑(3 ×)	N	N	IVIg responder
DS (♀), 30	R hand grip	N	ulnar median (2)	N	N (-)	N	N	↑(3 ×)	IVIg responder

Figure 1 Patient JO. Results of the EDX study (musculocutaneous nerve, stimulation near the motor point of the biceps brachialis muscle, upper traces and at Erb's point, lower traces) at the time of diagnosis (A) and 7 days after the first infusion of IVIg (B). There is a complete proximal conduction block at Erb's point (with a M3 MRC biceps brachialis muscle weakness), followed by the reappearance of a partial proximal response one week later, with normalisation of muscle strength. In C, swelling and increased intensity of the right cervical roots and of the brachial plexus on fat-suppressed, T₂-weighted, fast spin-echo MRI of the brachial plexus, these changes being still present after the infusion of IVIg.



clonal anti-GM1 in about half of the patients with multifocal motor neuropathy (range 22–85%), as well as in patients with lower motor neuron disorders (MND), amyotrophic lateral sclerosis (ALS), Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP), and even in healthy people, suggested that the sensitivity and specificity of antibody testing are limited [11, 17, 18], as exemplified in our cases (table 1). However, in healthy people and patients with disorders other than multifocal motor neuropathy, the titres of anti-GM1 are typically much lower than in multifocal motor neuropathy. A meta-analysis on the diagnostic value of IgM anti-GM1 in multifocal motor neuropathy showed that probabilities before the test between 20 and 60% for having multifocal motor neuropathy on the basis of clinical characteristics changed to probabilities between 50 and 85% when IgM anti-GM1 was found [19]. Overall, these studies show that a positive test in a patient with a MND syndrome is supportive of a diagnosis of multifocal motor neuropathy and should prompt extensive electrophysiological assessment, whereas a negative test has no diagnostic value.

In about 40–50% of patients with multifocal motor neuropathy signal intensity on T₂-weighted images of the brachial plexus is asymmetrical and high, as shown in figure 1C, corresponding with the distribution of symptoms [10, 20–23]. Recently, using ultrasonography multiple sites with nerve enlargement have been found in one study, enlargement without clinical or electrophysiologic abnormalities along the course of the brachial plexus, median, ulnar and radial nerves [24].

Clinical vignette 2 (RM, a non-responder): In Winter 1994 a 61-year-old former nurse developed insidious weakness of her left upper limb. She had been treated for an acute left 6th cranial nerve neuropathy of undetermined cause 16 years previously. In summer 1995 weakness and amyotrophy were evident and she was referred to our unit with a question of a motoneuron disease: on examination an M3 MRC intrinsic muscle weakness of the hand was observed together with an M4 MRC weakness of the flexors and extensors muscles of the wrist and fingers. Muscles were wasted with amyotrophy of the whole intrinsic hand muscle, but there was no sensory loss. Fasciculations could be seen in biceps brachii and deltoid muscles, and the left biceps and triceps reflexes were absent. An EDX study showed reduced radial, ulnar and median CMAPs amplitudes (to about 50% of the expected normal value) and complete absence of the responses when the stimulations were performed at the Erb's point. Radial, ulnar and median SNAPs amplitudes and shape were normal. Results of routine analysis of blood and urine was unremarkable despite high titres of antibodies to GM1 ganglioside (>15 000 U, n <200). Brain, spinal and brachial MRIs were normal. A progressive proximal extension of the weakness of the left arm was observed despite 4 infusions of IVIg (2 g/kg once a month), followed by 6-monthly infusions of cyclophosphamide and then mycophenolate mofetil (2 g/day during 6 months). Permanent fasciculations were seen over left trapezius and other periscapular muscles.

Episodes of paroxysmal spasmodic dysphonia with paroxysms of coughing, inspiratory stridor and four episodes of complete upper-airway occlusion were then reported. These episodes were thought to be motor positive signs of a recurrent laryngeal nerve dysfunction. Rituximab was started in summer 2006 and in December the deficits were persistent, but no more paroxysmal spasmodic episodes of dysphonia were reported.

Comments: As observed in the Lausanne patients (see table 1), multifocal motor neuropathy is typically characterised by slowly progressive weakness that develops gradually over years

Figure 2 Demonstration of the progressive motor neuropathic process with predilection for the upper limbs and in particular the handy muscles results in neurological disability in A and B patients in whom the progression was described over 5 and 10 years, respectively. This progressive severe weakness is attributed to the evolution of axonal loss. In C (patient HD, non-responder) there is a progressive loss of function of supination of the right arm over the 3 years of follow-up.



[11–13, 21, 25, 26]. More men than women are affected, at a ratio of 2.6. The most common initial symptoms are wrist drop, grip weakness and foot drop. Weakness develops asymmetrically and is more prominent in the arms than in the legs, as in most patients with onset in the legs, the abnormalities also eventually affect the arms. Symptoms and signs in the distal muscles prevail for a long time, but eventually weakness in proximal muscle groups of the arms may develop as happened in our patient 2. Weakness is typically more pronounced than the degree of atrophy suggests, nevertheless, atrophy of affected muscles can be evident in patients with long disease duration (fig. 2). Other motor symptoms include muscle cramps and fasciculations in about two-thirds of patients. Tendon reflexes are commonly reduced in affected regions, but an increased muscle contraction of the right biceps brachii in response to direct muscle percussion could be seen in patients with conduction block [27]. Some patients report feelings of paraesthesia or numbness but sensory loss on objective neurological or neurophysiological assessment should not be found. Atypical evolution with cra-

nial-nerve involvement may be encountered, as in our patient 2 [5, 28], and in 3 cases there was involvement of the phrenic nerve, with respiratory failure [29–31].

The differential diagnosis of multifocal motor neuropathy includes motor neuron disorders and demyelinating neuropathies. The first signs and symptoms in multifocal motor neuropathy can be similar to those in motor neuron disorders, and some patients are initially diagnosed as having amyotrophic lateral sclerosis or monomelic motor neuron disorders. The slowly progressive disease course, the absence of upper-motor neuron or bulbar signs and the presence of demyelinating features and conduction blocks on EDX studies will eventually differentiate multifocal motor neuropathy from amyotrophic lateral sclerosis. Differentiation of multifocal motor neuropathy from other motor neuron diseases may be more complicated [32], but the finding of persistent motor conduction block on EDX studies outside nerve compression sites, a positive titre of anti-GM1 or high signal intensity on T₂-weighted MRI of the brachial plexus have the potential to aid in the diagnosis. Within the demyelinating neuropathies the disorders from which multifocal motor neuropathy must be differentiated are: hereditary neuropathy with liability to pressure palsy [33], the pure motor form of CIDP and the Lewis-Sumner syndrome [34–36]. In patients with CIDP proximal symmetrical weakness and general areflexia are common, whereas weakness in multifocal motor neuropathy is asymmetrical and distal, and reflexes are only poor or absent in affected limbs. A remitting and relapsing course or a progression of symptoms in weeks is common in CIDP but not in multifocal motor neuropathy. The CSF protein concentration in multifocal motor neuropathy is normal or slightly increased but rarely higher than 1 g/L, unlike in CIDP, and can therefore help to differentiate between the two. Sensory signs and symptoms also differ for multifocal motor neuropathy and CIDP. On EDX studies motor conduction block is found in both disorders, but other features of demyelination are more prominent in CIDP, such as slowed conduction velocities and prolonged distal latencies. Patients with the Lewis-Sumner syndrome have an asymmetrical sensory or sensorimotor demyelinating neuropathy that can be localised to one arm or leg for several years, sometimes associated with neuropathic pain or focal nerve tenderness. Patients with this syndrome can benefit from treatment with corticosteroids, whereas those with multifocal motor neuropathy do not and can even deteriorate, as in the 2 patients discussed in the vignettes [5, 37–39].

Table 2 Clinical criteria for multifocal motor neuropathy (MMN), from [9].

<i>core criteria (both must be present)</i>	
(1)	slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least 2 nerves, for more than 1 month*
(2)	no objective sensory abnormalities except for minor vibration-sense abnormalities in the lower limbs
<i>supportive clinical criteria</i>	
(3)	predominant upper limb involvement **
(4)	decreased or absent tendon reflexes in the affected limb ***
(5)	absence of cranial nerve involvement ****
(6)	cramps and fasciculations in the affected limb
<i>exclusion criteria</i>	
(7)	upper motor neuron signs
(8)	marked bulbar involvement
(9)	sensory impairment more marked than minor vibration loss in the lower limbs
(10)	diffuse symmetric weakness during the initial weeks
(11)	laboratory: cerebrospinal fluid protein >1 g/L
*	usually more than 6 months
**	at onset predominant lower limb involvement accounts for nearly 10% of the cases
***	slightly increased tendon reflexes, in particular in the affected arm, have been reported and do not exclude the diagnosis of multifocal motor neuropathy, provided criterion 7 is met
****	12th nerve palsy has been reported

The natural history of multifocal motor neuropathy is of a slowly progressive motor neuropathic process. Patients are expected to have a normal lifespan except if there is a phrenic nerve dysfunction, death after several years with the disease has been reported in only one patient [29]. Most patients have progression over many years, with treatment having persistent effects in the responders, but not curing the disease [13, 21, 40]. The predilection for the upper limbs and in particular the hands results in neurologic disability in the majority of the patients. Some patients are disabled by fatigue [41]; in our opinion this symptom has been underestimated in patients with multifocal motor neuropathy and needs further studies.

The progressively more severe weakness is attributed to the evolution of axonal loss (i.e. loss of distal CMAP amplitudes). Motor nerves develop low distal CMAP amplitude in one of two ways: multifocal conduction block in different segments, a process that can be caused by random foci of conduction block in the long nerves eventually causing loss of amplitude, and conduction block outside of standard stimulation sites with distal axonal loss (i.e. distal to the most distal site of

stimulation or proximal to the most proximal site of stimulation), as observed in a patient with multifocal motor neuropathy who had annual clinical and physiological examinations for 18 years but declined treatment for personal reasons [42].

Discussion

Many clinical and electrophysiological studies have improved our understanding of multifocal motor neuropathy in the past 20 years, but the disease mechanisms underlying weakness in multifocal motor neuropathy are poorly understood. As multifocal motor neuropathy is a potentially treatable disorder (see J. M. Léger, this issue, and L. van den Berg, this issue), a guideline of a joint task force of the European Federation of Neurological Societies/Peripheral Nerve Society prepared consensus guidelines for multifocal motor neuropathy [9] and these are listed in table 2. The main clinical features are weakness without objective sensory loss, slowly progressive or stepwise progressive course, asymmetric involvement of two or more nerves and absence of upper motor neuron signs. Additional clinical criteria have also been proposed: not more than seven of eight affected limb regions, predominance of weakness in the upper limbs, decreased or absent tendon reflexes and age of onset between 20 and 65 years. The task force decided not to include an age limit in the criteria. The presence of conduction block in motor nerve fibres is the hallmark of the disease (see M. R. Magistris, this issue; A. Priori, this issue; and L. H. van den Berg, this issue).

On the basis of consensus expert opinion [9], consideration of multifocal motor neuropathy should enter the differential diagnosis of any patient with a slowly or stepwise progressive asymmetrical limb weakness without objective sensory abnormalities and upper motor neuron or bulbar signs or symptoms. Clinical examination and EDX tests are mandatory. A family history should be obtained in order to diagnose hereditary liability to pressure palsy. Other tests that can support the diagnosis of multifocal motor neuropathy are CSF protein <1 g/L, anti-ganglioside GM1 antibody testing and increased signal intensity on T₂-weighted MRI scans of the brachial plexus. Nerve biopsies are not routinely performed in multifocal motor neuropathy, where segmental demyelination or onion bulb formation were not observed [43] but can be useful in detecting an alternative cause [12]. Needle EMG, serum and urine paraprotein detection by immunofixation, thyroid function test, CK test and measurement

of CSF cell count and protein level are investigations which can be helpful to discover concomitant disease or exclude other possible causes.

The aetiology and pathogenesis of multifocal motor neuropathy have been addressed in some studies published over the last years but remain unresolved, in part because the neuropathy runs an indolent course rarely justifying motor nerve biopsy, and that there are no animal models of the disease. Nevertheless, it is widely believed that multifocal motor neuropathy is an autoimmune disorder. The association between axon loss and conduction block could suggest that an axon will eventually degenerate if a process resulting in conduction block affects it. This mechanism is supported by excitability measurements that showed axonal hyperpolarisation adjacent to sites with conduction block. Hyperpolarisation was thought to be secondary to intraaxonal sodium accumulation at the site with conduction block, caused by low activity of the sodium/potassium pump (see R. Kaji, this issue; and A. Priori, this issue).

There are therefore open questions in this disorder, the two most crucial being lack of real knowledge of the pathophysiological mechanisms of what could be considered as a peripheral nerve channelopathy that usually does not respond to prednisone or plasmapheresis and need of alternative treatments to IVIg infusions to cure this disorder.

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