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Case report

Impaired conduction of Ia sensory fibers in multifocal motor neuropathy: An electrophysiological demonstration

Eglė Sukockienė [a,b,*], Michel R. Magistris [c], Ruxandra Iancu Ferfoglia [a], Agustina M. Lascano [a], André Truffert [a]

[a] Division of Neurology, Department of Clinical Neurosciences, Geneva University Hospitals, Geneva, Switzerland
[b] Department of Neurology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania
[c] Faculty of Medicine, Geneva University, Geneva, Switzerland

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ABSTRACT

Objectives: To report the clinical and electrophysiological findings in two patients with multifocal motor neuropathy (MMN) and bilateral absent patellar and Achilles tendon reflexes despite normal strength of quadriceps and calf muscles.
Methods: The medical history and clinical evaluation were completed by electrophysiological tests: sensory and motor nerve conduction studies, needle electromyography, motor-evoked potentials (MEPs) after transcranial magnetic stimulation, patellar T (tendon) responses, quadriceps and soleus H (Hoffman) reflex recordings.
Results: In the two patients, history, clinical evaluation, nerve conduction studies, favorable response to intravenous immunoglobulins, and positive anti-GM1 antibodies fulfilled the diagnosis of MMN. The lower limbs were asymptomatic, except for a unilateral weakness of foot dorsiflexion. The patellar and Achilles tendon reflexes disappeared during the course of the disease. The sensory nerve conduction studies were normal or minimally modified, M-wave and MEP/M amplitude ratio to the quadriceps were normal, patellar T (tendon) responses were virtually absent, and H-reflex to the quadriceps and soleus muscles were absent.
Conclusions: These observations, which show the interruption of the reflex afferent pathway, raise the question of Ia afferent involvement in the lower limbs of these two patients with MMN. Further investigations should determine the frequency and significance of these findings in this disorder.

1. Introduction

Multifocal motor neuropathy (MMN) is an immune-mediated disorder of peripheral motor nerve fibers, originally described in the 1980s (Chad et al., 1986; Roth et al., 1986; Parry and Clarke, 1988). The clinical features include slowly progressive, focal, asymmetric limb weakness in the motor territory of at least two nerves for >1 month with no or only minor sensory signs (Joint Task Force of the EFNS and the PNS, 2010). The electrophysiological hallmarks are multifocal persistent motor conduction blocks (CB) that are not located at usual nerve entrapment sites and are primarily proximal. In approximately half of the patients, GM1-specific immunoglobulin M (IgM) antibodies are identified (Cats et al., 2010).

MMN is a distinct condition among dysimmune peripheral nerve disorders in that it affects exclusively or mainly motor axons. Minor involvement of sensory fibers has been much debated. Decreased or absent tendon reflexes were reported since the first descriptions and may be explained by the presence of CB on motor axons, but a precise correlation between the severity of hyporeflexia and that of weakness of the muscle responsible for the reflex has not been reported. Here, we describe two patients with MMN who presented with the unusual condition of a bilateral patellar and Achilles tendon areflexia despite normal quadriceps and calf muscle strength and normal or minimally modified sensory examination.

Abbreviations: CB, conduction block; IV Ig, intravenous immunoglobulins; MEP, motor evoked potential; MMN, multifocal motor neuropathy; QCT, quadriceps combined technique.

* Corresponding author at: Department of Neurology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50161 Kaunas, Lithuania.
E-mail address: egle.sukockiene@kaunoklinikos.lt.

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2. Patients and method

2.1. Patient 1

This patient (man, right handed, and height 168 cm) was 26 years old in 2005, when he noticed a gradual weakness and tremor of his left hand as well as twitchings of his left forearm muscles. At that time, apart from the observation of the tremor (with recording of discharges firing at circa 7 Hz from the left extensor digitorum communis muscle), two clinical neurological examinations and an electroneuromyography of the left distal upper arm were normal.

In 2018, weakness and tremor progressed to the right upper extremity. A moderate atrophy was observed in the left dorsal interossei. Postural and kinetic distal predominant low amplitude tremor concerned both upper extremities. Sensory examination was normal. Muscle force using the Medical Research Council scale grading was as follows: fingers and wrist extension on the left was 4/5, right intrinsic hand muscles was 4/5, and other muscle groups in upper extremities was 5/5. Both triceps tendon reflexes were present, whereas others were absent. In the lower limbs, muscle strength was normal, except for a weakness of right foot dorsiflexion causing a slight stepping gait. Patellar and Achilles tendon reflexes were absent.

A titer of anti-GM1 antibodies was markedly elevated (anti-GM1 IgM 114 and abnormal threshold >30; June 2018).

A follow-up evaluation took place 1 month following a first intravenous immunoglobulin (IV Ig) treatment given in August 2018. The patient reported a partial resolution of tremor and the improvement of muscle force. A test of grip strength confirmed the improvement to 31.5 (+1.5) kg on the right and 26 (+8) kg on the left. The reappearance of feeble right biceps and left Achilles reflexes was observed.

Between May and September 2018, in addition to standard nerve conduction studies, two evaluations used the "quadriceps combined technique" (QCT; see Methods).

2.2. Patient 2

This patient (woman, right handed, and height 165 cm) was 42 years old in 1995, when she was diagnosed with MMN following 2 years of weakness and cramps affecting the muscles of her left hand. An examination disclosed an unnoticed weakness of her right foot dorsiflexion. Tendon reflexes were present from both triceps brachii and weak from both lower limbs adductors; all others were absent. Sensory examination was normal.

A titer of anti-GM1 antibodies was elevated at 78 (abnormal threshold >20; May 1995).

After good response to IV Ig, her condition remained stable.

In 2008, an acute painful right shoulder with sensory motor complaints concerning the lower trunk of the brachial plexus was attributed to Parsonage-Turner syndrome with spontaneous recovery and no response to IV Ig.

In 2017, the patient had increased weakness in her right hand and anterior forearm. Some atrophy was observed in both thenar and interossei muscles. In the lower limbs, muscle bulk and strength remained normal, except for a minor atrophy of the anterior compartment of the right leg with the foot dorsiflexion being 4/5. A test of grip strength, following 1 month after the IV Ig course (May), showed improvement to 25 (+13) kg on the left and 10 (+8) kg on the right. After two IV Ig courses with favorable, but short-lasting responses, the treatments were continued subcutaneously.

In 2019, the weakness relapsed in both hands, mainly the right. The patient's grip strength was 19 kg on the left and 0 kg on the right (June). Areflexia was observed in all four extremities. Sensory examination remained normal.

In addition to 13 electrophysiological investigations between 1995 and 2019, a single QCT evaluation was performed in September 2019.

2.3. Methods

The electroneuromyographic studies were conducted using a Viking apparatus (Nicolet, Madison, Wisconsin, USA). Motor and antidromic sensory conduction studies were performed using standard procedures. Bandpass filters were set to 2–10 kHz. For proximal stimuli of the upper limb, monopolar stimuli used a small hand-held surface cathode probe (diameter 0.8 cm) and a large remote anode plate electrode (30 cm^2) taped over the internal region of the suprascapular fossa (Roth and Magistris, 1987). The amplitude, area, and duration of maximal M-waves were that of the negative peak, whereas the amplitude of antidromic sensory nerve action potentials was measured peak to peak and duration was measured to the end of the repolarization phase. The evaluation of CB on motor nerves was defined according to the criteria of Olney et al. (2003), which led to the determination of "definite CB" and "probable CB."

The lower limbs clinical areflexia was studied using the QCT, with search for H-reflex to quadriceps and soleus muscles. The QCT, used routinely in our laboratory since 2005, combines a femoral nerve conduction study, motor-evoked potentials (MEPs), and patellar T (tendon) responses, with recordings from quadriceps muscles (vastus medialis). For technical details and reference values, see Ališauskienė et al. (2007) and Truffert et al. (2007). The size of MEP and that of the M-wave were used to calculate the *MEP/M amplitude ratio* in percent; it was compared to the mean of the values measured in 100 normal subjects (Truffert et al., 2007). The same was done for the T-response using the *T/M amplitude ratio* in percent.

3. Results

3.1. Patient 1

The electrophysiological evaluations performed in May and July 2018 are detailed in the Supplementary Tables S1 and S2. In brief, they showed focal partial probable CB of the left radial and median nerves between the axilla and Erb's point; focal temporal dispersion precluding the description of CB of the left median nerve in forearm segment and right ulnar nerve between the axilla and Erb's point. Amplitudes of M-waves of ulnar nerves (more on left), of left radial and right peroneal nerves were decreased. In some regions, unusually strong stimuli were required where the nerve was considered "hypoexcitable". F-waves showed diminished persistence, prolonged latency, and chronodispersion for both ulnar and for the left median nerves. Sensory nerve conductions were normal, without change from those recorded in 2006.

Two QCT evaluations were performed in July and September 2018, 1 month before and after a first course of IV Ig. The results of QCT recordings are detailed in Table 1 and Fig. 1. In brief, M-waves and MEPs to the quadriceps were of normal amplitudes and latencies were slightly prolonged in the examination performed on July 11, 2018 (before IV Ig treatment). The MEP/M amplitude ratio was high; in contrast, only very small T-responses could be identified on both sides with prolonged latencies, more on the right. The H-reflex was absent from both quadriceps and soleus muscles.

The results of needle EMG are provided in Supplementary Table S2.

Table 1
Electrophysiological parameters. Recording using the quadriceps combined technique (QCT) is from the quadriceps muscle (vastus medialis). Abnormal values are printed in bold. Patient 1 was evaluated before and after a first course of IV Ig. Patient 2 was evaluated once.

	Patient 1				Patient 2		Normal values
	1st evaluation 11.07.2018		2nd evaluation 11.09.2018		Single evaluation 02.09.2019		
	R	L	R	L	R	L	
M latency (ms)	**5.7**	**5.7**	5.2	5.4	4.8	4.7	≤5.6
M amplitude (mV)	12.3	14.0	13.1	13.3	8.3	11.8	≥8.5 men ≥6.5 women
T latency (ms)	**45.6**	**28.8**	**39.1**	**26.7**	**NR**	**NR**	≤25.0
T amplitude (mV)	**≈0.05**	**≈0.10**	**≈0.10**	**≈0.05**	**NR**	**NR**	–
T/M amplitude ratio (%)	**≈0.40**	**≈0.70**	**≈0.70**	**≈0.40**	**NA**	**NA**	≥8.5
MEP latency (ms)	23.6	22.6	**24.2**	23.0	21.2	21.4	≤23.7
MEP amplitude (mV)	13.1	14.3	12.7	14.5	10.5	14.1	–
MEP/M amplitude ratio (%)	107	102	97	109	128	120	≥30.0

Abbreviations: M, motor response; T, patellar tendon response; MEP, motor evoked potential; ≈, almost equal to; NR, no response; NA, not available.

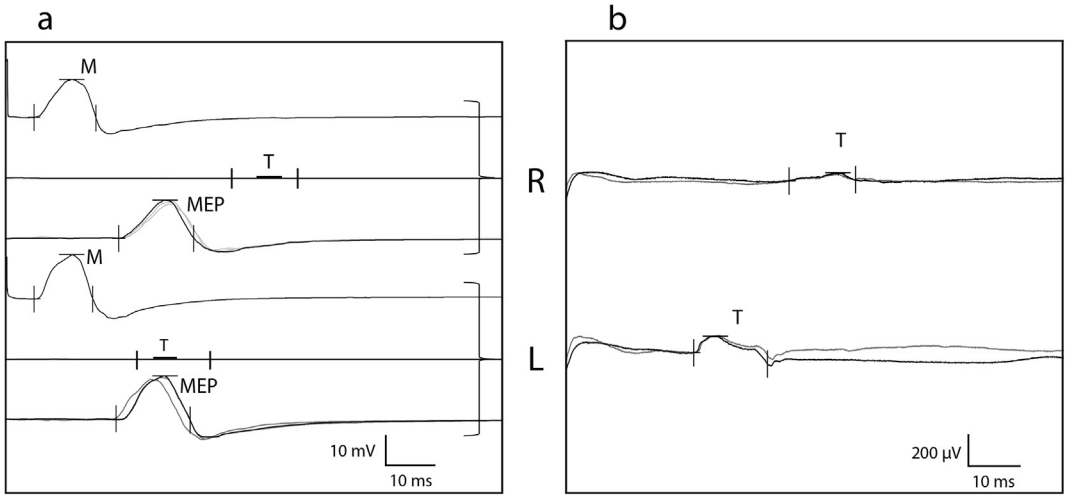

Fig. 1. Quadriceps combined technique (QCT) parameters (1st evaluation – 11.07.18) showing normal M-waves and MEPs, asymmetrically prolonged T latencies, and very low T amplitudes bilaterally. M-waves are those during voluntary activity (to compare with MEP performed during voluntary activity required to obtain a maximal response). Superimposed MEPs show normal variability of the response. Abbreviations: R, right; L, left; M, motor response; T, patellar tendon response; and MEP, motor evoked potentials.

A control of nerve conductions after the IV Ig treatment showed the following: persistence of the temporal dispersion of the left median nerve in the forearm but increased amplitude and area ratios of the M-wave evoked at the elbow compared with the test performed before treatment (Supplementary Table S1). Similarly, a marked increase of the M-wave size of the right ulnar nerve to stimulation performed at Erb's point demonstrated that a CB existed previously on these nerves. In the lower limbs, nerve conduction parameters showed a slight shift of patellar T latencies toward normal values, although responses remained very small (Table 1).

3.2. Patient 2

The electrophysiological evaluations in 1995, showed definite and probable partial CB of the left ulnar and median nerves in the forearm and focal temporal dispersion of the left ulnar nerve in the forearm and between Erb's point and axilla. F-waves were rare. Sensory conduction studies were normal in the four limbs. Definite CB decreased by 50% after the IV Ig treatment.

In 2008, electrophysiological testing showed a prolonged distal latency and focal temporal dispersion within the forearm of the right median nerve. A decreased amplitude of M-wave of the right ulnar nerve and a focal probable CB between Erb's point and axilla were found. Amplitude of the right ulnar nerve sensory response on the fifth finger (17 µV) was lower than previously observed (51 µV). Needle EMG showed fibrillations and positive sharp waves in the right first dorsal interosseous.

In 2017, a focal partial CB of the right median nerve (to flexors of the forearm) on segment axilla-elbow and an important loss of M-wave amplitude was observed on the hand.

In 2019, on upper limbs, M-waves of markedly reduced amplitudes precluded the determination of CBs. Sensory nerve conduction studies remained unchanged. Reduced M-wave amplitudes were found on both fibular nerves (tibialis anterior muscles, predominantly on the right) as well as on the right tibial nerve (plantar muscles). Sensory nerve conduction studies disclosed low amplitude responses of the suralis and superficial peroneal nerves on both sides.

The results of the QCT investigation are detailed in Table 1. In brief, the M-waves and MEPs to the quadriceps muscles were of

normal size and latencies, with a high value of MEP/M amplitude ratio. There were no recordable T- and H-responses from both quadriceps and soleus muscles.

4. Discussion

We report two patients displaying the primary features of MMN, a patchy involvement of several peripheral nerves causing weakness without sensory loss. In both patients, weakness predominated in the upper limbs and evolved over more than a decade. Motor nerve conduction studies were abnormal, whereas sensory studies were normal. The presence of high titers of anti-GM1 antibodies and favorable clinical response to IV Ig treatment with an increase of muscle strength and partial alleviation of CB supported the diagnosis.

In these patients, we were puzzled by the contrast between absent patellar and Achilles tendon reflexes and normal strength of quadriceps and calf muscles. Normal M-wave amplitudes and high MEP/M amplitude ratios to the quadriceps confirmed the functional integrity of the motor pathways. Recordings of T-responses from the quadriceps that were markedly decreased in size (patient 1), or even absent (patient 2), quantified the phenomenon. Altogether, these findings were demonstrative of a dysfunction of the sensory aspect of the tendon reflex, namely of an impairment affecting Ia afferents of muscle spindles. In both patients, H-responses were absent from the quadriceps and soleus muscles, ruling out a role of the muscle spindles or of their gamma motor innervation (muscles spindles being bypassed by direct nerve stimulation performed upstream of the muscles).

Such findings are similarly observed in Miller Fisher syndrome (Fisher, 1956) in which areflexia is explained by the involvement of Ia afferents (Sekiguchi et al., 2013). In this disorder, acutely absent tendon reflexes and H-responses occur in the absence of weakness and often in the absence of conspicuous abnormal cutaneous sensations. In Miller Fisher syndrome, the dysfunction of afferents has been attributed to either a group of Ia neurons of the dorsal root ganglia or to Ia axons (Umapathi et al., 2014; Kuwabara et al., 2014). In our patients with MMN, the asymmetric conduction slowing and the reduction of the prolonged T latencies that followed the course of IV Ig (patient 1, Table 1) suggest that the dysfunction concerned the axons rather than neurons of the dorsal root ganglia. In MMN, the loss of deep tendon reflexes may usually be attributed to the motor deficit, and although the disorder may occasionally be accompanied or complicated by minor abnormal sensory findings, a marked compromise of the afferent aspect comes as a surprise and may have gone under-recognized by clinicians. It is the absent tendon jerks and T-responses in otherwise unaffected lower limbs that attracted our attention and eventually led to this first description of Ia afferent involvement in MMN.

The actual time of onset of this dysfunction in our patients is imprecise. The electrophysiological demonstration was performed late following the initial symptoms of MMN (i.e., after 13 years in patient 1 and 26 years in patient 2). However, for patient 2, the suggestive clinical discordant finding of absent tendon reflexes with otherwise normal strength and cutaneous sensation existed from the first evaluation, 2 years after first symptoms of MMN.

In some patients with MMN, sensory signs and symptoms develop during the course of the disorder (Delmont et al., 2009; Lievens et al., 2009; Mezaki et al., 1999; Parry, 1999). This was not conspicuous for our patient 1, who had no obvious sensory deficit and normal sensory nerve studies throughout, whereas patient 2 developed some sensory axonal loss in the lower limbs. The dysfunction of Ia afferents, almost total for patient 1 and total for patient 2, as per the magnitude of loss of their T- and H-responses, seems too severe to represent a mere component of a more diffuse subclinical sensory deficit.

5. Conclusion

Impaired conduction of Ia sensory axons subserving the tendon reflex afferent pathways was observed in two patients with MMN. These patients were particularly suitable for this observation, because they lost their tendon reflexes and concomitant neurophysiological responses from muscles of the lower limbs, where a motor dysfunction could not be held responsible for this loss. Further clinical and neurophysiological studies correlating reflex responses with motor findings, particularly combining recordings of MEPs, T-responses, and H-responses should enable to further assess the frequency and relevance of this phenomenon in MMN.

Declaration of interests

Eglė Sukockienė has received a travel grant from Takeda-Shire-Baxalta Company. Michel R. Magistris received honoraria for lectures from Takeda-Shire-Baxalta Company. Other authors Ruxandra Iancu Ferfoglia, Agustina M. Lascano, and André Truffert report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cnp.2020.07.002.

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