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MULTIFOCAL MOTOR NEUROPATHY PRESENTING AS PSEUDODYSTONIA

Case Series

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14 **Running Title**

15 MMN presenting as pseudodystonia

16

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18 Multifocal motor neuropathy, cramping, dystonia, peripheral nerve hyperexcitability,
19 conduction block

20

21

22

23 **ABSTRACT**

24 Multifocal motor neuropathy is an immune-mediated neuropathy. The clinical presentation is
25 typically dominated by wasting and weakness. We describe four cases presenting with prominent
26 cramping resembling a primary movement disorder. All cases had features of focal motor conduction
27 block on neurophysiological studies. The involuntary movements resolved in all four patients
28 following treatment with intravenous immunoglobulin. The cases presented highlight an unusual
29 presentation of multifocal motor neuropathy and emphasise that peripheral nerve pathology can
30 present with movement disorders mimicking central nervous system disease. Furthermore, the
31 movement disorder appears to be particularly sensitive to standard therapy.

32

33 **INTRODUCTION**

34 Multifocal motor neuropathy (MMN) is a rare immune-mediated neuropathy, typically presenting
35 with asymmetrical, and slowly progressive, distal upper limb wasting and weakness without sensory

1 abnormalities¹. A definitive diagnosis requires demonstration of focal motor conduction block on
2 neurophysiological studies with normal sensory nerve conduction across the lesion². The disorder is
3 associated with GM1 antibodies in approximately 50% of cases but the pathogenic role of such
4 antibodies along with the mechanism of conduction block remains unclear¹. Cramp, fasciculation and
5 hypertrophy are well-recognized clinical features but prominent spasm and twitching mimicking a
6 primary movement disorder has not been described. We present four cases of MMN presenting with
7 unusual focal movements, which we describe as pseudodystonia. In addition, we discuss the spectrum
8 of involuntary movements that may be associated with peripheral nerve pathology along with possible
9 mechanisms.

11 CASE REPORTS

13 Clinical characteristics of presented cases are summarized in Table 1.

15 Case 1

16 A 26-year-old female presented with a 3-month history of involuntary movement of the right hand
17 with recurrent flexor spasm of the wrist and fingers with intermittent jerking movements (Video 1).
18 The movements occurred both at rest and with action. There was possible weakness of thumb
19 abduction, but assessment of strength was limited due to continuous movements of the hand. There
20 were no sensory abnormalities. Neurophysiological studies revealed focal motor conduction block in
21 the forearm segment of the right median nerve (Figure 1A). Sensory and other motor studies were
22 normal. Needle electromyography demonstrated fasciculations and non-rhythmic grouped discharges
23 of normal motor units in abductor pollicis brevis (APB) and flexor pollicis longus (FPL). Anti-
24 ganglioside antibodies were negative. A diagnosis of possible MMN was made and she received
25 treatment with intravenous immunoglobulin (IVIg). Involuntary movements and neurophysiological
26 abnormalities resolved completely within three months of treatment (Video 1 and Figure 1B).

28 Case 2

29 A 35-year-old female presented with a 12-month history of weakness of the right hand associated with
30 painful cramping, twitching and spasm (Video 2), which would often wake her from sleep. The
31 cramping preceded the weakness by several years. In addition, there was weakness of right ankle
32 dorsiflexion and right toe extension. The sensory examination was normal. Neurophysiological
33 studies revealed proximal conduction block involving the median nerves bilaterally and the right ulnar
34 nerve (Figure 1E). The lower limb compound muscle action potential amplitudes were preserved
35 suggesting conduction block proximal to the fibular head on the basis of neurogenic recruitment and
36 motor cortex stimulation studies. Sensory studies including somatosensory evoked responses were
37 normal. Needle electromyography showed fasciculation, myokymic discharges as well as cramp

1 discharges in APB, FPL and ulnar finger flexors. Serum was positive for anti-GM1 antibody. IVIg
2 was commenced with partial improvement in muscle power and resolution of involuntary movements,
3 although the patient experiences mild muscle twitching in the week before her next IVIg dose is due.

5 Case 3

6 A 51-year-old female presented with a 2-year history of cramps in the right hand, particularly
7 affecting the thumb and index finger, which would often curl down. In addition, there was occasional
8 cramping of the left hand. Clinical examination revealed weakness of APB, FPL, abductor digiti
9 minimi (ADM) and first dorsal interossei (FDI) bilaterally with no sensory abnormalities.
10 Neurophysiology revealed focal motor conduction block in the forearm segment of the median nerves
11 bilaterally (Figure 1C and 1D) and borderline conduction block of the right ulnar nerve above the
12 elbow. Sensory studies including somatosensory evoked responses were normal. Needle
13 electromyography demonstrated neurogenic recruitment with fasciculations and high-frequency
14 discharges in APB and FDI without evidence of active denervation. Anti-ganglioside antibodies were
15 negative at the time of diagnosis, but a repeat sample three years later was positive for anti-GM1 IgM
16 antibodies. Cramping and weakness improved after commencement of IVIg, but recurred when IVIg
17 dosing frequency was increased from four- to five-weekly.

19 Case 4

20 A 59-year-old male presented with a 6-month history of dystonic posturing of the left hand with ulnar
21 deviation of digits III-V and the wrist. On examination, there was moderate weakness of left FDI and
22 ADM. The sensory examination was normal. Nerve conduction studies demonstrated reduced
23 persistence of left median F-wave responses and absent left ulnar F-wave responses with normal
24 compound muscle action potential amplitudes and sensory studies. Needle electromyography revealed
25 fasciculation potentials in APB and ADM and markedly reduced recruitment in ulnar-innervated
26 muscles as well as a mild reduction in recruitment in APB. In the context of normal compound muscle
27 action potential amplitudes and significant weakness of FDI and ADM, the findings were in keeping
28 with proximal conduction block. Serum was positive for anti-GM1 IgM antibodies. Pseudodystonia
29 and muscle power improved following treatment with IVIg.

31 **DISCUSSION**

32 While movement disorders are primarily classified as disorders of the central nervous system, the four
33 cases described highlight that peripheral nerve pathology may also be associated with prominent
34 involuntary movements which may dominate the clinical presentation and be difficult to differentiate
35 from central disease processes. Involuntary movements can be seen in a variety of peripheral
36 disorders including immune-mediated neuropathies, peripheral nerve hyperexcitability syndromes,
37 following peripheral trauma and post-irradiation plexopathy.

1
2 Although the precise mechanisms for abnormal movements in peripheral nerve disease remain
3 elusive, they are likely to be multifactorial and to vary between different disease processes. Such
4 movements may result from activation of peripheral nerve fibers causing spontaneous impulse
5 generation due to motor fiber hyperexcitability which may manifest as cramping, focal spasms, or
6 twitching with semirhythmical movements. Furthermore, loss of or disruption to afferent pathways
7 due to abnormal sensory input may secondarily leads to abnormal movements such as tremor and
8 pseudoathetosis.

9
10 In the cases presented, abnormal movements were unusual and striking, and may have been confused
11 with dystonia or other central disease processes, such as chorea or athetosis. The phenomenology in
12 Case 1 with the appearance of slow writhing movements, could easily have been mistaken for
13 athetosis. However, when the phenomenology is examined closely, it is apparent that there is an
14 element of sustained posturing in all cases, which is not consistent with chorea or athetosis.
15 Furthermore, in all cases, components of the movements are segmental and in the distribution of one
16 or more peripheral nerves with demonstrable motor conduction block on neurophysiological studies,
17 although they progress in Cases 1 and 2 into widespread muscle involvement and fist formation. For
18 example, Video 1 (00:45 – 01:15) demonstrates initial movements involving FPL, APB, and flexor
19 digitorum profundus (II) prior to flexion of digits III-V followed by fist closure and wrist flexion. This
20 phenomenology suggests initial median, followed by ulnar and subsequent widespread muscle
21 involvement. Although ulnar nerve conduction studies were normal, there may have been proximal
22 pathology involving the ulnar nerve not demonstrable on standard nerve conduction studies.

23
24 Other features which may support a peripheral generator and argue against dystonia include the
25 absence of specific triggers (such as writing in the case of writer's cramp), the presence of movements
26 at rest and lack of improvement with sensory tricks. Furthermore, in Case 2, movements occurred
27 during sleep. This would provide an argument against dystonia, which typically disappears during
28 sleep³. This feature was not reported in the other cases, but is an important aspect to elucidate in the
29 clinical assessment as it may refine the differential diagnosis.

30
31 The presence of electrophysiological manifestations of peripheral nerve hyperexcitability (such as
32 fasciculations, myokymia, continuous motor unit activity and cramp potentials) and evidence of
33 conduction block in all cases along with the presence of segmental movements on examination
34 supports a peripheral process underlying the primary aetiology. However, both videos demonstrate
35 prominent cramping with synchronized movements of fist closure and wrist flexion. The mechanism
36 of sustained contraction and synchronized activation of multiple muscles is uncertain. Evidence
37 suggests that there is substantial shared central input to the motoneuron pools innervating the finger

1 muscles and hence central modulation through peripheral feedback may play a role. Furthermore, the
2 interdependence of finger movements is affected by biomechanical factors, such as tendinous
3 interconnections, which may also be a contributing factor⁴.

4
5 Although it is accepted that involuntary movements may occur in MMN, why the peripheral nerve
6 becomes hyperexcitable is unclear and the precise source of ectopic activity remains undefined. The
7 most plausible hypothesis stems from results of nerve excitability studies which suggest
8 hyperpolarisation in the nerve just distal to the site of conduction block. It has been proposed that
9 depolarisation at the lesion site leads to sodium influx into the distal axon resulting in overactivity of
10 the Na⁺/K⁺ pump with juxtaposed lengths of depolarised and hyperpolarised axonal membrane
11 leading to ectopic discharges⁵.

12
13 Abnormal movements in the form of focal dystonia have also been described following peripheral
14 trauma and nerve injury and may be related to central modulation⁶ and reorganization following
15 interruption to afferent sensory input. “Jumpy stump” is a term that has been used to describe jerking
16 movements of a stump developing after limb amputation. Post-traumatic tremor has also been
17 reported with neurophysiological studies in one case supporting a peripheral generator⁷.

18
19 Tremor in association with peripheral neuropathy (“neuropathic tremor”) has been associated with
20 hereditary and immune-mediated neuropathies, including Guillain-Barré syndrome, chronic
21 inflammatory demyelinating polyneuropathy, MMN and in particular, IgM paraproteinaemic
22 neuropathy, in which tremor occurs in up to 80% of patients⁸. The underlying pathophysiology is
23 likely to be driven by delayed and desynchronized sensory input, with impairment of central
24 modulation through the cerebellum and its pathways^{8,9}. Furthermore, in certain subgroups of chronic
25 inflammatory demyelinating polyneuropathy, the cerebellum may be a direct immune target
26 contributing to tremor¹⁰.

27
28 Pseudoathetosis may be seen in peripheral neuropathies and ganglionopathies, as well as posterior
29 column pathology. In contrast to tremor which is likely to result from slowed sensory conduction with
30 desynchronisation, pseudoathetosis represents a more severe form of sensory dysfunction with
31 deafferentation and loss of sensory input due to neuronal loss or conduction block and results from
32 failure to maintain sustained motor output and muscle contraction.

33
34 Tremor associated with inflammatory and paraproteinaemic neuropathies tends to be refractory to
35 immunomodulatory treatment although it may fluctuate with disease activity⁸. In contrast, the focal
36 movement disorders associated with the four cases of MMN presented in this series were exquisitely

1 sensitive to IVIg therapy supporting a rapidly reversible functional mechanism such as antibody-
2 mediated ion channel blockade.

4 **CONCLUSION**

5 Although movement disorders are usually of central origin, peripheral nerve disorders should be
6 included in the differential diagnosis. Assessment for MMN should be considered, particularly when
7 movements are focal, segmented and in the distribution of one or more peripheral nerves. Our
8 experience suggests that pseudodystonia associated with MMN is highly responsive to IVIg therapy.

35 **AUTHOR ROLES**

1 **Dr N. Garg:** Contributed to the design and conceptualization of the manuscript, analysis
2 and interpretation of data, and writing of the first draft and revising the manuscript.

3
4 **Professor R. Heard:** Contributed to the analysis and interpretation of data and review
5 and critique of the manuscript.

6
7 **Associate Professor L. Kiers:** Contributed to the analysis and interpretation of data
8 and review and critique of the manuscript.

9
10 **Professor R. Gerraty:** Contributed to the analysis and interpretation of data and review
11 and critique of the manuscript.

12
13 **Professor C. Yiannikas:** Contributed to the design and conceptualization of the
14 manuscript, analysis and interpretation of data, and writing of the first draft and review
15 and critique of the manuscript.

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20
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22 No specific funding was received for this work. The authors declare that there are no conflicts
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26 N. Garg and R.N.S. Heard declare that there are no additional disclosures to report. L. Kiers
27 holds stock ownership with CSL and serves on scientific advisory boards for Baxter
28 Immunoglobulin, CSL Intragam 10 steering committee, National Blood Authority
29 Immunoglobulin Advisory Committee, Australia. R. Gerraty serves on the scientific advisory
30 Board for AstraZeneca Australia Pty Ltd; is employed by Epworth HealthCare and holds
31 contracts with Florey Neuroscience Institute. C. Yiannikas serves on scientific advisory
32 Boards and acts as a Consultant for Biogen, Allergan, and Ipsen.

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 4 associate with disabling tremor and poor response to IVIg. *Neurology* 2014; 82(10): 879-886.

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7 **Figure 1. Neurophysiology**

8 **Figure legend:** Nerve conduction studies. Case 1: focal motor conduction block in the
 9 forearm segment of the median nerve (A) with resolution following treatment with
 10 intravenous immunoglobulin (B). Case 3: bilateral conduction block in the forearm segment
 11 of the median nerves (C and D). Case 2: proximal conduction block between Erb's point and
 12 the axilla (E).

13 *W: wrist; E: elbow; A: axilla; EP: Erb's point; IVIg: intravenous immunoglobulin; APB: abductor*
 14 *pollicis brevis; a = amplitude; A = negative peak area; d = negative peak duration*

15
16 **Video 1**

17 **Video legend:** Case 1: Flexor movements start in the thumb and finger in a median nerve
 18 distribution and then progressively involve all the fingers and wrist in a cramping fashion with
 19 later ulnar nerve involvement. In the second part of the video, involuntary movements have
 20 dramatically resolved following intravenous immunoglobulin therapy.

21
22 **Video 2**

23 **Video legend:** Case 2: Video demonstrating semi-rhythmic twitching of digits with
 24 abduction and flexion movements. This is followed by flexor spasm of the wrist and fingers of
 25 the hand. The patient tries to extend the fingers to reduce the amount of pain she is
 26 experiencing.

27
28 **Table 1. Clinical Characteristics**

29 *RUL: right upper limb; LUL: left upper limb; RLL: right lower limb; IVIg: intravenous*
 30 *immunoglobulin*