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MULTIFOCAL MOTOR NEUROPATHY PRESENTING AS PSEUDODYSTONIA

Case Series

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MMN presenting as pseudodystonia

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

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

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

CASE REPORTS

Clinical characteristics of presented cases are summarized in Table 1.

Case 1

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

Case 2

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

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

Case 3

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

Case 4

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

DISCUSSION

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

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

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

Other features which may support a peripheral generator and argue against dystonia include the absence of specific triggers (such as writing in the case of writer's cramp), the presence of movements at rest and lack of improvement with sensory tricks. Furthermore, in Case 2, movements occurred during sleep. This would provide an argument against dystonia, which typically disappears during sleep[3]. This feature was not reported in the other cases, but is an important aspect to elucidate in the clinical assessment as it may refine the differential diagnosis.

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

muscles and hence central modulation through peripheral feedback may play a role. Furthermore, the interdependence of finger movements is affected by biomechanical factors, such as tendinous interconnections, which may also be a contributing factor[4].

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

Abnormal movements in the form of focal dystonia have also been described following peripheral trauma and nerve injury and may be related to central modulation[6] and reorganization following interruption to afferent sensory input. “Jumpy stump” is a term that has been used to describe jerking movements of a stump developing after limb amputation. Post-traumatic tremor has also been reported with neurophysiological studies in one case supporting a peripheral generator[7].

Tremor in association with peripheral neuropathy (“neuropathic tremor”) has been associated with hereditary and immune-mediated neuropathies, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, MMN and in particular, IgM paraproteinaemic neuropathy, in which tremor occurs in up to 80% of patients[8]. The underlying pathophysiology is likely to be driven by delayed and desynchronized sensory input, with impairment of central modulation through the cerebellum and its pathways[8,9]. Furthermore, in certain subgroups of chronic inflammatory demyelinating polyneuropathy, the cerebellum may be a direct immune target contributing to tremor[10].

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

Tremor associated with inflammatory and paraproteinaemic neuropathies tends to be refractory to immunomodulatory treatment although it may fluctuate with disease activity[8]. In contrast, the focal movement disorders associated with the four cases of MMN presented in this series were exquisitely

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

CONCLUSION

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

AUTHOR ROLES

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

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

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

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

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

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N. Garg and R.N.S. Heard declare that there are no additional disclosures to report. L. Kiers holds stock ownership with CSL and serves on scientific advisory boards for Baxter Immunoglobulin, CSL Intragam 10 steering committee, National Blood Authority Immunoglobulin Advisory Committee, Australia. R. Gerraty serves on the scientific advisory Board for AstraZeneca Australia Pty Ltd; is employed by Epworth HealthCare and holds contracts with Florey Neuroscience Institute. C. Yiannikas serves on scientific advisory Boards and acts as a Consultant for Biogen, Allergan, and Ipsen.

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Figure 1. Neurophysiology

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

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

Video 1

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

Video 2

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

Table 1. Clinical Characteristics

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