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Mixed IgG and IgM anti-GM1 ganglioside antibody positive multifocal motor neuropathy with severe secondary axonal loss in a Filipino female

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Abstract

Approximately 40% of patients with multifocal motor neuropathy had anti-GM1 IgM antibodies, while only 1 out of 88 patients had anti-GM1 IgG antibodies. Unlike its predominantly demyelinating IgM counterpart, the anti-GM1 IgG antibody is often seen in the axonal variant of Guillain Barre syndrome. As it affects axons, it is also associated with worse prognosis. We report here a 58-year-old woman who was admitted for 3 months history of progressive asymmetric weakness, initially involving the right-hand extensors, eventually affecting the contralateral side and the lower extremities. The electrodiagnostic examination revealed multifocal pure motor demyelinating neuropathy with severe axonal loss. On nerve ultrasound, the axons were small in non-compressive areas. The extremely elevated anti-GM1 IgM titer (1:51,200, nv<1:800) was consistent with the diagnosis of MMN. Her anti-GM1 IgG antibodies (1: 12,800, nv<1:800) was also elevated. In conclusion, the presence of concomitant anti-GM IgG and anti-GM1 IgM may lead to an MMN with more severe axonal loss.

Keywords: Multifocal motor neuropathy, MMN, anti-GM1 IgG, anti-GM1 IgM, ganglioside

INTRODUCTION

Multifocal motor neuropathy (MMN) is a rare, chronic, progressive, asymmetric, purely motor demyelinating neuropathy, which primarily affects the distal extensors of the upper extremities.[1,2] Approximately 40% of patients had anti-GM1 IgM antibodies, while only 1 out of 88 patients in the MMN cohort had anti-GM1 IgG antibodies.[3] Unlike its predominantly demyelinating IgM counterpart, the anti-GM1 IgG antibody is often seen in the axonal variant of Guillain Barre syndrome (GBS). As the latter affects axons, it is also associated with worse prognosis.[4,5]

Here we present a case of MMN with severe secondary axonal loss which we hypothesized to be secondary to the concomitant presence of anti-GM1 IgG antibody.

CASE REPORT

A 58-years old right-handed, woman, was admitted for progressive hand weakness. Her symptoms started 3 months prior to admission when she noted worsening right hand extensor weakness, initially involving the little finger, then the thumb, until all digits were involved. In the interim, she developed weakness in both feet causing ambulation difficulties. One month prior to admission, left hand and right-hand finger flexors were also involved, leading to difficulty in gripping objects, fine motor tasks such as buttoning shirt, turning keys and writing. Progression of the above symptoms led to her admission. She had no neck pain, bulbar symptoms, bowel and bladder changes, or any sensory complaints. Aside from hypertension and controlled diabetes, she has no other known co-morbidities. Her daily medications include amlodipine, metformin and vitamin B complex.

Her vital signs and systemic physical examination were unremarkable. Her cranial nerves and neck extensor and flexor strength were normal. There were no atrophy and fasciculations in the tongue. She had marked atrophy of the muscles of the hands, forearm and feet. The muscle power of her elbow flexors was right (R) 4, left (L) 4+, extensors and pronators (R3 L4); wrist flexors and extensors (R3 L3+); and

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finger flexors at metacarpal phalangeal, proximal interphalangeal, distal interphalangeal joints and thumb (R3 L3+) have mild to moderately severe weakness. Her thumb extensors, adductors, abductors; little finger abductor, adductor; finger extensors at metacarpal phalangeal, proximal interphalangeal and distal interphalangeal joints were profoundly affected (R1 L2). Aside from mild to moderate weakness in the bilateral hip flexors (R4 L4), ankle dorsiflexors (R4 L4) and big toe extensors (R4 L4); the rest of the lower extremity muscle group strengths were normal (R5 L5). She had MRC grade of 44/60. She had reduced reflexes in all extremities and flexor toe response on plantar reflex. The sensory tests for pain and temperature, vibration sense and proprioception were normal. Spurling's test was negative.

Aside from slightly elevated HBA1c (6.7%), the rest of her basic laboratories, including complete blood count, ESR, CRP, Chest Xray, sodium, potassium, creatinine, AST, ALT were unremarkable. Electrodiagnostic examination of the 4 extremities showed severely reduced compound muscle action potential (CMAP) amplitudes in the median, ulnar, radial, peroneal and tibial nerves of both sides, with prolonged distal motor latencies and slowed conduction velocities (Table 1). Meanwhile, the sensory potentials of the median, ulnar, superficial radial and sural nerves were all normal on both sides (Table 2). Nerve cross sectional area (CSA) for median, ulnar and radial nerves were markedly decreased on nerve ultrasound (Figure 1). She was initially started on prednisone 20mg per day and

Table 1: Motor nerve conduction studies of the 4 extremities

	Nerves	Distal Latency (ms)	Amplitude (mV)	Conduction Velocity (m/s)	F-Wave Latency (ms)
Median Nerve	Right				
	Wrist	6.5	1.91	38.7	Not done
	Elbow	11.4	1.58		
	Left				
	Wrist	8.2	2.09	40.9	Not done
	Elbow	12.6	1.97		
Ulnar Nerve	Right				
	Wrist	7.2	0.74	35.0	Not done
	Below Elbow	12.9	0.77	37.5	
	Above Elbow	15.3	0.74		
	Left				
	Wrist	4.5	2.58	44.6	Not done
	Below Elbow	9.2	1.78	38.4	
	Above Elbow	11.8	1.42		
Radial Nerve	Right				
	Forearm	7.0	0.44	35.2	
	Lateral arm	12.1	0.37		
	Left				
	Forearm	4.1	0.43	58.6	
	Lateral arm	7.0	0.49		
Peroneal Nerve	Right				
	Ankle	5.7	0.42	42.8	Not done
	Below Knee	13.4	0.24	42.8	
	Above Knee	15.5	0.26		
	Left				
	Ankle	6.2	0.66	37.6	Not done
	Below Knee	14.7	0.54	64.7	
	Above Knee	16.4	0.46		
Tibial Nerve	Right				
	Ankle	5.4	0.81	33.3	Not done
	Popliteal Fossa	15.6	0.30		
	Left				
	Ankle	5.3	1.07	32.1	Not done
	Popliteal Fossa	16.2	0.74		

was referred for physical therapy, however, the symptoms continued to progress. On further work up she was found to have an extremely elevated anti-GM1 IgM titer (1:51,200, nv<1:800) which was consistent with the diagnosis of MMN. Her anti-GM1 IgG antibody titer (1: 12,800, nv<1:800) were likewise elevated. She was subsequently admitted and started on intravenous immunoglobulin 2g/kg infused over 2 days with noted slight improvement of motor symptoms 4 weeks after discharge. Specifically, the grip (now 4/5), hand and finger extensors (now 3/5) and the proximal lower extremities weakness (now 4+/4+) improved.

DISCUSSION

Based on the European Federation of Neurological Sciences (EFNS), a case of definite MMN should present with at least a month duration of asymmetric, progressive or stepwise weakness, primarily of the upper extremities with no clinical and objective sensory abnormalities in combination with definite conduction block in the NCS.[1] In addition, upper motor neuron signs, marked bulbar involvement and diffuse symmetrical weakness during initial weeks should be absent.[2] Conduction blocks are often associated with this condition. In most cases however, these are not sensitive and specific clinical markers of the disease as detection is barred by its proximal or extremely distant location; non-examination of the less affected extremity; and severe axonal loss, as in our patient.[6] Conduction blocks may also be found in other demyelinating condition such as GBS, and typical and atypical variants of chronic inflammatory demyelinating polyneuropathy (CIDP). Our patient did not satisfy the electrophysiologic criteria for conduction block. Nevertheless, she satisfied the EFNS clinical criteria for MMN.

Motor neuron disease, specifically progressive muscular atrophy (PMA) may present similarly with MMN with no conduction block. In fact, the sizes of the nerves in our case were too small for MMN and that it may be more compatible with the atrophic nerves in PMA.[7] Nevertheless, the signs and symptoms of most PMA described in the literature as well as in the cases we saw were slowly progressive (takes years).[1] In addition, asymmetric decrease in conduction velocity (in the demyelinating range based on our NCS-EMG local value), not typical for MND was observed. An EMG in some select muscles (tibialis anterior and first dorsal interosseous) was done, no fasciculations were found, only chronic denervation changes, which can be seen in both MND and MMN with severe axonal loss. The absence of fasciculations was further confirmed by the more sensitive ultrasound.[7] A lumbar tap was planned however, the patient did not consent, hence an anti-GM1 antibody was ordered to increase the diagnostic probability of MMN. Although some case reports of MND having positive anti-ganglioside antibodies were reported in the literature, these antibodies were found to be more specific to MMN than MND.[2] Lastly, the slight improvement after IVIG was characteristic of MMN. The peculiarity of this case lies on the ultrasound finding of severely atrophic motor nerves which we hypothesize to be secondary to the concomitant presence of anti- GM1 IgG and IgM antibodies.

Gangliosides like GM1 are glycosphingolipids with sialic acid moieties, which are often found in the axolemma and myelin sheath, responsible for ion channel clustering and maintenance of tight junction in the nodes and paranodes, respectively.[8] These are often attacked by anti-GM1 IgM

Table 2: Sensory nerve conduction studies of the 4 extremities

Nerves		Onset Latency (ms)	Amplitude (uV)	Conduction Velocity (m/s)
Median Nerve	Right	2.9	49.8	41.9
	Left	2.6	71.3	53.8
Ulnar Nerve	Right	2.2	69.4	45.4
	Left	2.1	85.9	56.0
Radial Nerve	Right	2.0	58.0	60.0
	Left	2.2	44.4	59.0
Sural Nerve	Right	2.6	8.6	50.0
	Left	2.3	9.7	52.1

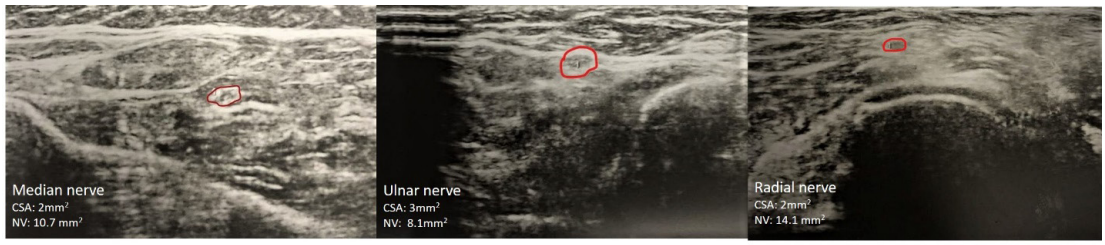

Figure 1: Ultrasound of median nerve at the forearm, ulnar nerve at the wrist and radial nerve at the elbow. The cross-sectional area of each nerve was indicated in the left lower corner, along with the upper limit of normal for comparison.

antibody through direct or indirect action via activation of the classical complement pathway, leading to destruction of Na channels in the nodes, dispersion of the current in the paranodes, and eventual calcium-induced Wallerian-like degeneration.[6] The same patho-mechanisms are found in acute motor axonal neuropathy (AMAN) variant of GBS, although in the latter, axons are primarily damaged instead of the myelin sheath, and IgG is the predominant immunoglobulin.[9]

Based on the nerve structure affected, anti-GM1 IgG portends poorer prognosis.[4,10] Although anti-GM1 IgG and IgM affect the same ganglioside, the former readily crosses the blood nerve barrier (BNB) and affects the segment between the roots and distal segments. (11) Our patient had marked reduction in CMAP amplitudes on top of demyelinating features of prolonged distal latencies and slowed conduction velocities in nerve conduction study, which is reflective of a possible severe secondary axonal loss in almost all nerves tested. We believe that the extremely high titers of anti-GM1 IgM and IgG contributed to this loss. Sixty seven percent of MMN patients show nerve enlargement in ultrasound, usually attributed to demyelination-remyelination. Our case showing a decreased nerve size on ultrasound further supports the hypothesis of a chronic axonal loss, which is present similarly in conditions showing such pathologies as motor neuron diseases (Figure 1).[2]

Recently, a move to lump AMAN, CIDP and MMN together in a new class of peripheral nerve disorder termed nodo-paranodopathy was proposed.[6] The proposed pathology for the latter is the presence of anti-ganglioside antibodies against NF-186 and GM1 in the nodes; contactin 1, CASPR1 and NF 155 in the paranodes; and CASPR2 in the juxtaparanode.[6,8,12] Aside from asymmetry and chronicity of symptoms, AMAN and MMNCB affect GM1 albeit with different immunoglobulin classes, all respond to IVIG. These conditions were also found to harbor similar mechanisms in inducing conduction block, hinting that they may be a spectrum rather than two distinct disorders.

In conclusion, the presence of concomitant anti-GM IgG and anti-GM1 IgM may lead to an MMNCB with more severe axonal loss.

DISCLOSURE

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Conflict of interest: None

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