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Case Report

Anti-GQ1b ganglioside positive Miller Fisher syndrome – evidence of paranodal pathology on nerve biopsy

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Abstract.
Background: Miller Fisher syndrome is a regional variant of Guillain-Barre syndrome with a characteristic clinical triad of ophthalmoplegia, areflexia and ataxia and occasionally distal limb sensory loss. 90% of patients have associated antibodies to the GQ1b ganglioside. The pathophysiology of antibody-mediated peripheral nerve impairment remains uncertain. This report includes the first description of a peripheral sensory nerve biopsy in Miller Fisher syndrome.
Results: A single case report is described of a 46 year old woman who presented with 2 weeks of distal glove and stocking sensory loss to both deep and superficial sensory modalities, areflexia and weight loss. This was followed by rapid onset of ataxia, ophthalmoplegia, and bulbar impairment. Peripheral neurophysiology showed reduced sensory nerve amplitudes with preserved conduction velocities in keeping with an axonal pattern of impairment. Clinical concerns of a systemic inflammatory disorder led to a diagnostic peripheral nerve biopsy from the sensory branch of the radial nerve. However she subsequently made a complete recovery over 5 weeks. Combinatorial glycoarrays confirmed restricted serum binding for GQ1b in acute serum which later resolved in a convalescent sample. The nerve biopsy showed lengthening of nodes of Ranvier, myelin splitting and macrophage internodal axonal invasion without any features of demyelination.
Conclusions: The pathological features were strikingly similar to those found in acute motor axonal neuropathy and indicate the region of the node of Ranvier to be a primary focus of GQ1b induced damage in Miller Fisher syndrome, at least in this particular overlap syndrome with prominent sensory nerve involvement.

Keywords: Nerve biopsy, Miller Fisher syndrome, GQ1b ganglioside, node of Ranvier, pathophysiology

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ABBREVIATIONS

AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor-sensory axonal neuropathy
ASAN	Acute sensory ataxic neuropathy
GBS	Guillain-Barré syndrome
MFS	Miller Fisher syndrome
MRI	Magnetic resonance imaging
CT	Computed tomography
PET-CT	Positron emission tomography - computed tomography
SAP	Sensory nerve amplitude

A 46 year old Caucasian female sales assistant was admitted to our unit on the 7th March 2011 with a two week history of symmetric numbness and paraesthesiae initially of both hands, then her legs, and four days of rapidly progressive unsteadiness, diplopia, dysarthria and dysphagia. Her sensory symptoms were preceded by flu-like symptoms with lethargy and fever one week earlier. She gave a history of unexplained weight loss of several months duration. She had stopped smoking 3 months earlier but otherwise past medical and family history were unremarkable.

On examination she was alert and orientated. She had an ataxic gait, without Rombergism. Pupils were equal and reactive to light but not to accommodation. She had a lid retraction without ptosis and a complex ophthalmoplegia comprising restricted upgaze, normal downgaze, and markedly restricted horizontal gaze bilaterally. Nasal speech was noted with reduced elevation of the soft palate and nasal regurgitation. There was no facial weakness and tone and power of all four limbs were normal. She had an intention tremor with dysmetria in both upper limbs. She was areflexic throughout with flexor plantar responses. Sensation to pinprick was reduced to above the wrists and knees bilaterally. Vibration sense was absent below the hips but proprioception was intact. There was no evidence of autonomic instability. General physical examination, apart from being underweight with a body mass index of 16, was unremarkable.

Her complete blood cell count, vitamin B12, erythrocyte sedimentation rate, renal, liver and thyroid function were all normal. Anti-nuclear antibody, acetylcholine receptor antibody, voltage-gated calcium channel antibody and borreliosis serology were negative. Anti-GQ1b antibodies in serum collected on admission were positive on enzyme-linked immunosorbent assay (ELISA) at 1/1200 (normal range <1/500) conducted according to standard protocols [1]. Combinatorial glycoarrays allow detection of anti-glycolipid complex antibodies (conducted as previously described [2]) and these glycolipid immunoblots for the serum collected on admission and for a convalescent sample taken 5 months later are shown in Fig. 1. They demonstrate strong reactivity exclusively for GQ1b in the acute serum which is absent in the convalescent serum.

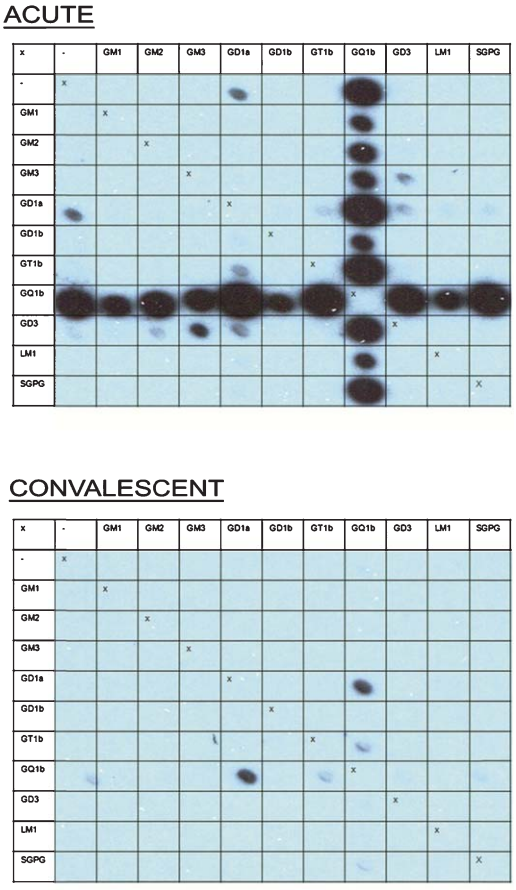

Fig. 1. Combinatorial glycoarray demonstrating restricted anti-GQ1b IgG reactivity of patient. Combinatorial glycoarrays are designed to identity antibody reactivity to single glycolipids (duplicated in top row and left-hand row) and 1:1 glycolipid complexes (remainder of grid). A line of symmetry runs top left to bottom right, representing analysis in duplicate. In the acute phase serum, strong reactivity to GQ1b is seen that is not substantially enhanced or inhibited when in complex with other glycolipids. In the convalescent serum, anti-GQ1b antibody activity is no longer detectable, except for a low antibody signal for the complex of GQ1b with GD1a.

Lumbar puncture on the day of admission showed normal cerebrospinal fluid constituents including cell count and protein. Peripheral neurophysiology on the 8th March showed normal motor nerve conduction studies but reduced amplitudes in sensory nerve conduction studies with preserved conduction velocities

Table 1
Serial sensory nerve conduction studies

Nerve tested	Latency (msec)		Amplitude (μV)		Conduction velocity (m/sec)	
	First study	Second study	First study	Second study	First study	Second study
Radial digit I L	2.1 (<3.3)	**NR**	**2.9** (>4)	**NR**	**49** (>50)	**NR**
Radial trunk L	2.2 (<2.7)	1.8	**22** (>28)	11	52 (>50)	51
Median digit III L	**3.3** (<3.0)	**NR**	2.4	**NR**	**41**	**NR**
Median PW L	**1.7** (<1.2)	1.5	15 (NA)	10	**44** (>50)	53
Sural R	2.7 (<3.2)	**NR**	5.5 (>5)	**NR**	**44** (>52)	**NR**

NA, not applicable due to wide variation in population; NR, no response; PW, palm to wrist; R, right side; L, left side. First study performed 2 weeks after onset of symptoms, second study 3 weeks after onset of symptoms. In parentheses, cut-off value of normal range used in our laboratory (derived from published values of mean ± 2SD, adjusted for age). Abnormal results highlighted in bold.

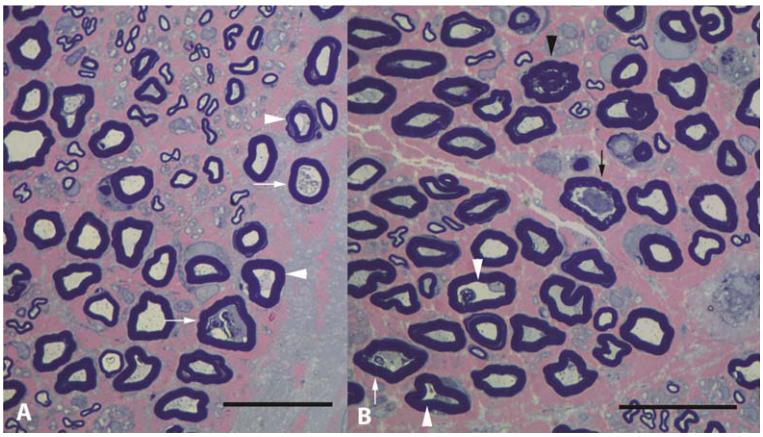

Fig. 2. Acute axonal degeneration of myelinated fibres. Transverse sections show axons that are either filled with amorphous material (white arrows in A and B) or are shrunken in size and/or surrounded by clear spaces/oedema (white chevrons in A and B). Some axons are replaced by macrophages (black arrow in B). Myelin ovoids containing myelin debris have formed following axon loss (black chevron in B). Focal loss of small myelinated axons is noticeable in B compared to A. Semi-thin plastic section, thionine and basic fuchsin stain, bar = 27μm.

(or mild reduction in conduction velocity commensurate with the loss of amplitude) in keeping with a sensory nerve-restricted axonopathy rather than a demyelinating process (Table 1). One week later, there was further deterioration in sensory nerve action potentials (SAPs) with loss of more distal nerve responses (such as median digital response), whereas more proximal sensory studies such as the median palm to wrist were still present, although with reduced amplitudes, in keeping with distal conduction block. MRI of the brain and cervical spine were unremarkable.

A diagnostic biopsy of the right superficial sensory branch of the radial nerve was performed on the 21st of March 2011. There was a variable loss of large myelinated fibres of mild extent in the majority of nerve fascicles and of moderate degree in a few fascicles with sparing of small myelinated fibres other than for rare areas of focal loss. Higher magnification revealed that scattered large myelinated fibres showed acute stages of axonal degeneration whilst myelin sheaths remained relatively intact with no signs of acute segmental demyelination or onion bulbs (Figs. 2 and 3). Both transverse and longitudinal sections revealed several large myelinated fibres with lengthening of nodes of Ranvier and myelin splitting at paranodes and at Schmidt-Lanterman incisures through internodes and macrophage invasion of the axonal space.

Five days after admission, her ophthalmoplegia and ataxia continued to worsen and she was treated with intravenous methylprednisolone 1gm for three days, starting on the 12th March. Over the next two weeks her condition initially stabilised and then rapidly improved such that her dysarthria and dysphagia had resolved and she had diplopia only at extremes of gaze, with minimal reduction of abduction bilaterally. Sensory abnormalities had partially improved at this time with complete recovery over the following 3 weeks.

DISCUSSION

Miller Fisher syndrome (MFS) is a regional variant of Guillain-Barré syndrome (GBS). Antibodies

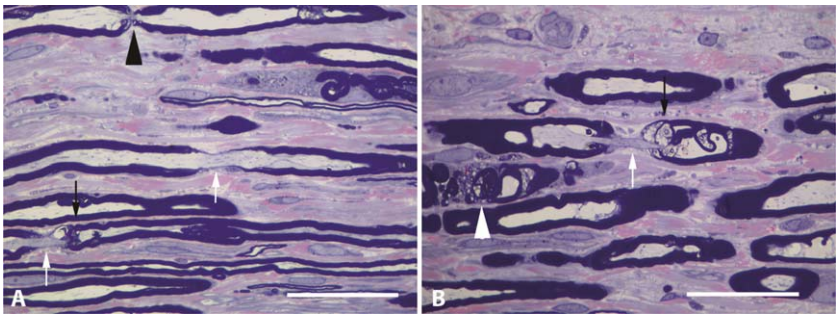

Fig. 3. Disruption of nodes of Ranvier and paranodal region. Longitudinal sections of large myelinated fibres exhibiting lengthening of nodes of Ranvier (*white arrows in A and B; normal - black arrowhead in A*) and myelin splitting at paranodes (*black arrows in A and B*). Compare with normal width of nodes of Ranvier (*black arrowhead in A*). Remnants of a degenerating myelinated fibre with myelin debris lying in ovoids (*white arrowhead in B*). There is no evidence of segmental demyelination. Semi-thin plastic section, thionine and basic fuchsin stain, bar = 37 μm.

to the GQ1b ganglioside are present in over 90% of patients [3]. It has a characteristic clinical triad of acute ophthalmoplegia, areflexia and ataxia with variable additional features including sensory loss, facial weakness and bulbar palsy [4]. Patients typically present acutely with a mean interval to nadir from onset of 4 days [5]. In a recent series of 466 Japanese patients, distal paraesthesiae were reported frequently but uncommonly as a presenting complaint (14%) and with superficial sensory loss (spinothalamic modalities) on examination in only half of these [5]. In our patient an acute sensory axonal neuropathy developed 2 weeks prior to the ophthalmoplegia, ataxia and bulbar impairment. In conjunction with a history of weight loss this atypical presentation raised concerns of an underlying systemic inflammatory disorder and so to diagnostic nerve biopsy. It was only with the subsequent rapid and complete recovery and the elevated anti-GQ1b antibody titre that the diagnosis of a sensory neuropathy as part of an extended MFS syndrome was established.

Sub-types of GBS are classified on the basis of the anatomical site of the predominant pathological mechanism leading to peripheral nerve impairment [4]. In MFS the core clinical features result from disturbance of function to the oculomotor cranial nerves causing ophthalmoplegia and with ataxia and areflexia secondary to impairment of dorsal root ganglia and / or muscle spindles. None of these structures is readily accessible to either neurophysiological interrogation or pathological study of biopsy material to clarify the site of the anti-GQ1b antibody mediated nerve damage. Motor neurophysiological studies are normal or near-normal in most patients in keeping with the lack of substantial limb weakness. In a minority of cases where there is significant superficial sensory impairment, neurophysiological studies reveal reduced sensory nerve amplitudes without demyelinating features. The typical rapid clinical recovery suggests that the sensory nerve impairment results from non-demyelinating, reversible conduction failure rather than axonal damage [6].

Reversible conduction failure was first recognised in patients with acute motor axonal neuropathy (AMAN) associated with antibodies to GM1 antibodies. It results from interruption of the action potential propagation at the nodes of Ranvier [7]. Immune-mediated damage causes structural and functional disruption of ion channels and terminal myelin detachment at the paranode. A similar mechanism has been invoked for a restricted sensory ataxic variant with axonal neurophysiological abnormalities (ASAN) and accompanying antibodies to gangliosides including GQ1b and GD1b [8]. An alternative terminology suggested for these axonal GBS variants associated with conduction block is of a "nodo-paranodopathy" [9].

The histological features observed in the sensory nerve of our patient closely mimic those described in AMAN where macrophage entry occurs via the nodes of Ranvier and Schmidt-Lanterman incisures, invading between the axon and the Schwann cell axolemma and producing lengthening of the nodes and myelin splitting which causes conduction failure. A paranodal distribution of GQ1b epitope has not been studied in human sensory nerves but is found in the extramedullary portion of oculomotor nerves [10]. *In vitro* GQ1b-specific antibodies also bind both at the nerve terminals contacting intrafusal fibres in muscle spindles [11] and in the human dorsal root ganglion [12] suggesting that sensory nerve impairment in Miller Fisher syndrome results from damage at multiple sites.

Our case is the first description of a peripheral nerve biopsy in MFS as the clinical phenotype is

often characteristic and the course usually self-limiting and benign. Two previous post mortem reports on patients considered to have MFS demonstrated patchy but extensive segmental demyelination of peripheral nerves but the poor clinical outcome in both these cases would be highly unusual for MFS and anti-GQ1b antibodies were not measured [13, 14].

In conclusion, our patient demonstrates that a similar pathophysiological process occurs in the peripheral sensory nerves in GQ1b-restricted MFS as has been reported in axonal GBS variants. This would support the classification of MFS either as a regional variant of AMSAN or alternatively as a member of the "nodo-paranodopathies".

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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