Acute ophthalmoparesis in the anti-GQ1b antibody syndrome: electrophysiological evidence of neuromuscular transmission defect in the orbicularis oculi

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Objective: To prospectively study anti-GQ1b antibody positive cases of acute ophthalmoparesis (AO) clinically and electrophysiologically.

Methods: Nine consecutive cases presenting with predominantly acute ophthalmoparesis were assessed clinically and had stimulated single fibre electromyography (SFEMG) of the orbicularis oculi at presentation. All had magnetic resonance imaging brain scans and anti-GQ1b antibody titres determined.

Results: Four cases had elevated anti-GQ1b antibody titres and abnormal SFEMG studies, which improved in tandem with clinical recovery over three months. Five other anti-GQ1b antibody negative cases were diagnosed as diabetic related cranial neuropathy, idiopathic cranial neuropathy, ocular myasthenia gravis, and Tolosa-Hunt syndrome. All five cases showed complete recovery over a three month period.

Conclusions: This study demonstrated electrophysiologically the dynamic improvement of neuromuscular transmission of anti-GQ1b antibody positive cases of AO, in tandem with clinical recovery. SFEMG is of value in differentiating weakness due to neuromuscular transmission defect from neuropathy in these clinical situations.

The Miller Fisher syndrome (MFS) is an autoimmune condition characterised by ataxia, areflexia, and ophthalmoplegia. A large proportion of cases are associated with high titres of anti-GQ1b antibodies. Acute ophthalmoparesis (AO) has been considered a mild form of MFS or regional variant of the Guillain-Barré syndrome (GBS). There is increasing immunological evidence to suggest that AO, MFS, GBS, and Bickerstaff's brainstem encephalitis represent a continuous spectrum of conditions with a common pathogenesis. Anti-GQ1b antibody positive MFS have been shown to affect corticospinal tract function reversibly in a previous study. Anti-GQ1b antibodies have been shown to produce structural and functional changes at the neuromuscular junction in both ex vivo and in vitro studies. Although the neuromuscular junction is believed to be a site of action of these antibodies, this has only been deduced indirectly from electrophysiological studies. Single fibre electromyography (SFEMG) is regarded as the most sensitive method for assessing neuromuscular transmission defects. In this study, we report the use of stimulated SFEMG for serial evaluation of neuromuscular transmission in anti-GQ1b antibody positive cases of acute neuromuscular conditions. The study's aim was to determine electrophysiological evidence to substantiate a defect at the neuromuscular transmission and explain some of the motor effects of the MFS and its variants, in particular, those presenting as AO.

In this prospective study, we describe nine consecutive cases presenting with acute ophthalmoplegia over a one and a half year period, mostly in the absence of other clinical features. Serial SFEMG findings and other electrophysiological studies are discussed in relation to clinical and pathophysiological issues.

CASE REPORTS

Case one
A 49 year old man was admitted with a one day history of double vision and difficulty walking. Apart from some difficulty speaking, there was no dysphagia, vertigo, bladder, or bowel symptoms. He had hypertension, which was well controlled with atenolol, and experienced symptoms of upper respiratory tract infection 10 days prior to admission.

On examination, he was alert and rational but had minimal dysarthria which resolved in the next three days. Eye movements were markedly reduced in all directions. He was generally hyporeflexic and had bilateral upper limb dysmetria. Motor power was not reduced apart from minimal proximal lower limb weakness. Facial muscle weakness was not evident. Gait was broad based and unsteady. A magnetic resonance imaging (MRI) brain scan was unremarkable. He improved rapidly over the next two weeks and was discharged with mildly reduced eye movements and mild dysmetria.

At the next review three months later, he was neurologically well and had full external ocular movements in all directions. His tendon reflexes had recovered and there was no detectable motor weakness. He was able to tandem walk steadily.

Anti-GQ1b IgG titre was 28 080 (normal <534) on admission but this reduced to 1706 during review at two months.

Case two
A 45 year old man with no significant past medical history was admitted with diplopia of two days in duration. He denied any change in voice, swallowing difficulty, weakness, or numbness of his limbs. There was no preceding fever.

Abbreviations: AO, acute ophthalmoparesis; EUSA, enzyme linked immunosorbent assay; EMG, electromyography; GBS, Guillain-Barré syndrome; MCD, mean consecutive differences; MFS, Miller Fisher syndrome; MRI, magnetic resonance imaging; NCS, nerve conduction studies; OD, optical density; PBS, phosphate buffered saline; RNS, repetitive nerve stimulation; SFEMG, single fibre electromyography
upper respiratory symptoms, gastrointestinal symptoms, visual aura, or headache. He did not drink or smoke.

Examination revealed that he was alert and orientated. There was no nuchal rigidity, conjunctival injection, or proposis. Partial, non-fatigable ptosis in the right eye and impaired adduction, elevation, and downward eye movement were noted. There was no pupillary involvement. Examination of other cranial nerves and motor power was unremarkable. Deep tendon reflexes were normal. The physical signs were consistent with a pupil-sparing right III palsy. Further neurological examination did not reveal ataxia, sensory deficits to touch, pain, temperature, and abnormal position sense. He walked with a normal gait.

A brain MRI showed enhancement of the right oculomotor nerve in the interpeduncular cistern. The Y, VII, and VIII complexes did not enhance and no ischaemic changes were seen on T2-weighted sequences. There were no brainstem MR abnormalities. Cerebrospinal fluid examination revealed absence of cells, elevated total protein of 12 g/l, and presence of globulin. Anti-GQ1b IgG titre was significantly elevated at 1828 (normal <534).

Follow up at three months showed complete clinical recovery of the right III palsy. Again, a complete neurological examination did not reveal any deficits. The repeat anti-GQ1b antibody titre at this stage was only 17.

Case three

A 61 year old man complained of double vision for a week. He had a history of diabetes mellitus diagnosed six months ago and was on oral medication. There was no history of dysarthria, sensory symptoms, or motor weakness.

Clinical examination was unremarkable apart from reduced extraocular movements in all directions bilaterally. No ptosis, facial asymmetry, or weakness was obvious. The deep tendon reflexes were preserved. No clinical ataxia was elicited.

An MRI brain scan was unremarkable apart from incidental ischaemic changes in the left basal ganglia. Cerebrospinal fluid examination showed absent cells, elevated total protein of 0.5 g/l, and presence of globulin. Acetylcholine receptor antibody titre was 0.12 nmol/l (normal <0.25). Anti-GQ1b IgG titre was markedly elevated at 35 (normal <534). Glycated haemoglobin concentration (HbA1c) was 6.9% (normal <6.4%). He was followed up and had complete recovery of eye movements at three months.

Case four

A 54 year old man had an upper respiratory tract infection, followed two weeks later by rapid onset of unsteady gait, diplopia, and giddiness. Clinical examination showed bilateral reduced eye movements in all directions, progressing onto near total ophthalmoplegia. Although there was no motor power weakness, mild and lower limb ataxia was present. There was no dysarthria, dysphagia, or hearing loss. Reflexes were preserved universally.

An MRI scan was unremarkable. Venereal Disease Research Laboratory (VDRL), thyroid function, and blood counts were normal. Cerebrospinal fluid examination did not show cells or raised proteins. Anti-GQ1b IgG titre was markedly elevated at 30144 (normal <534). Upon follow up, his symptoms improved over two weeks and he had recovered his eye movements completely by six weeks.

Cases five to nine are summarised in detail in table 1.

Case five had elevated HbA1c at 11.4% (normal <6.4%). Case eight had elevated acetylcholine receptor antibody levels of 35 nmol/l (normal <0.25). None of these cases showed any features of bulbar palsy, motor weakness, hyporeflexia, or ataxia.
METHODS

Stimulated SFEMG was performed on the orbicularis oculi muscle of the affected eye at initial presentation (within one week of admission) and follow up at three months for anti-GQ1b antibody positive cases. A Dantec 9013K0872 needle (Dantec, Skovlunde, Denmark) 40 mm in length and 0.45 mm in diameter was inserted at the edge of the muscle for single fibre recordings. Axonal stimulation was achieved with a Teca disposable monopolar needle (Teca, Old Woking, Surrey, UK) placed 2.5 cm away from the recording needle and a silver chloride disc as an anode at the malar prominence to produce visible twitches. Stimulation was achieved with square pulses of 0.04 ms duration at 10 Hz and intensity ranging from 8 mA to 15 mA. Amplifier settings were fixed at 500 to 10 kHz. All studies were performed with a Dantec Keypoint Machine.

Stimulated single fibre responses were selected based on short rise times (<300 ms) and clear separation. For each study, individual mean consecutive differences (MCD) of 20 single fibre responses with clear separation and short rise times (<300 ms) were selected for mean jitter calculation, as indicated with dots above jitter values. Sweep speeds and vertical gain are as shown in the tracings.

Figure 1  Stimulated single fibre electromyography recordings of cases one to four on admission (left panel) and during follow up (right panel). Superimposed tracings are shown. In the left panel, significant jitter is evident in single fibre responses in comparison with the right panel. Only single fibre responses with clear separation and short rise times (<300 ms) were selected for mean jitter calculation, as indicated with dots above jitter values. Sweep speeds and vertical gain are as shown in the tracings.
Acute ophthalmoplegia in the anti-GQ1b antibody syndrome

All nine cases presented with rapid onset of acute ophthalmoplegia, mainly with absence of other clinical features. Complete recovery was seen over a three month period and no recurrence was documented.

Cases one to four had significantly elevated anti-GQ1b antibody titres at initial presentation. Initial SFEMG studies showed abnormal mean jitters, which improved markedly over the three month period, in tandem with clinical recovery. Neuroimaging was unremarkable apart from case two. The levels of anti-GQ1b antibody appeared to have some correlation with the degree of ocular involvement. Case two, with a modest elevation of anti-GQ1b antibody titre, only showed signs of unilateral III palsy, in contrast to cases one, three, and four, which had reduced external ocular movements in all directions. Case one largely fulfilled criteria for MFS, considered a major subset of the ‘anti-GQ1b syndrome’ spectrum.

In AO, both unilateral and bilateral ocular palsy has been observed.11 12 The III, IV, and VI cranial nerves have been shown to possess significantly higher percentages of GQ1b than other cranial nerves and this lends support to the role of anti-GQ1b in the pathogenesis of ophthalmoplegia.13 In case two, the enhancement of the right III nerve, as with previous reports of IV,14 V,15 and VI,16 is likely to have a similar immunological pathogenesis.

Case five was clinically diagnosed as having diabetic related III palsy. Case six had an idiopathic partial III palsy with normal SFEMG and anti-GQ1b antibody titres. Case seven was diagnosed and managed as ocular myasthenia gravis with marked clinical improvement, as was case eight. Case nine was managed as a Tolosa-Hunt syndrome variant, supported by MRI findings.17–19 Cases five to nine serve as incidental negative controls for cases one to four both clinically and electrophysiologically. They illustrate the high sensitivity of SFEMG for neuromuscular transmission defects but lack of specificity as seen in cases seven and eight. However, SFEMG abnormalities appear to mirror anti-GQ1b antibody titres, as with case six. Despite the possibility of cranial neuropathy in cases five and nine, normal SFEMG results support its specificity for diagnosing neuromuscular junction abnormalities rather than abnormalities attributed to demyelinating or axonal neuropathy.

The orbicularis oculi was selected for SFEMG study for reasons of ease of stimulation, availability of normal values, and proximity to extraocular muscles. The latter reasoning is based on RNS studies in myasthenia gravis, another condition with impaired neuromuscular transmission, where a proximal muscle close to the area of maximal weakness is more likely to show electrophysiological abnormalities.20 21 The normal facial nerve conduction and lack of active denervation changes in the orbicularis oculi muscles do not favour the presence of significant VII neuropathy in all cases.

In this paper, cases one to four illustrate dynamic improvement in mean jitter in tandem with clinical recovery. The evidence for neuromuscular transmission impairment in MFS is well documented in vitro. Anti-GQ1b antibody related effects on the synaptic region,22 with complement mediation23 and structural injury at the nerve terminal,24 are recent findings. Although rapid reversibility of presynaptic blocking actions of these antibodies have been demonstrated,25 the exact electrophysiological abnormalities remains uncertain, and mild transient blocking action of antibodies to the presynaptic or postsynaptic regions cannot be completely excluded. Most recently, it has also been shown that in the absence of complement, monoclonal antibody to anti-GQ1b IgM depressed evoked quantal release of acetylcholine dose-dependently at the presynaptic region in mice hemidiaphragm.26

**RESULTS**

Case one had an initial mean jitter of 45.2 μs and a jitter of 22.6 μs at three months (fig 1). NCS was unremarkable apart from absent “H” responses. Case two had an initial mean jitter of 68.5 μs and a repeat jitter value of 21.5 μs. NCS was unremarkable apart from absent “H” responses. Case three had an initial mean jitter of 39.7 μs and a repeat jitter value of 21.6 μs at three months. Again, NCS was unremarkable. Case four’s initial SFEMG study showed a mean jitter of 34.5 μs and a repeat jitter value of 18.4 μs three months later. NCS showed absent “H” responses only.

Cases five to nine had mean jitters of 17.7, 22.9, 84.3, 57.1, and 22.6 μs, respectively. Upper limit of mean jitter was 23 μs based on a control group of 20 normal subjects from our laboratory.

Additionally, none of the nine cases showed significant decremental responses on RNS or abnormal facial NCS or EMG.
The action of anti-GQ1b antibody on neuromuscular transmission in each case can be deduced from in vitro studies. Patch clamp techniques have demonstrated reversible pre- and postsynaptic neuromuscular blocking effects of circulating IgG antibodies in MFS sera. More specifically, both failure of acetylcholine release and massive quantal acetylcholine release causing a “depolarising block” effect has been demonstrated. As all these processes have been shown to be reversible, they likely contributed to reversible neuromuscular transmission failure detected with the sensitive technique of SFEMG in our study.

It was argued that despite in vitro documentation of neuromuscular blockade in MFS, neurophysiological evidence to substantiate this, unlike in myasthenia gravis, is lacking. This is the first paper demonstrating with SFEMG the dynamic improvement of neuromuscular transmission in anti-GQ1b antibody positive cases of AO in tandem with clinical recovery. It also highlights the value of SFEMG in differentiating weakness due to neuromuscular transmission defect as opposed to neuropaathy in certain clinical situations. Future studies correlating clinical features, SFEMG findings and serial antiangioglycide antibody titre levels would certainly be of interest.

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