Transcranial magnetic stimulation studies in the Miller Fisher syndrome: evidence of corticospinal tract abnormality

Y L Lo, P Ratnagopal

Abstract

Objectives—To evaluate serial central motor conduction time in the Miller Fisher syndrome.

Method—Three patients with classic Miller Fisher syndrome were evaluated clinically. They had serial central motor conduction times measured with transcranial magnetic stimulation and nerve conduction studies. Motor evoked potentials were recorded from the first dorsal interossei and abductor hallucis muscles.

Results—All three patients showed reduction in central motor conduction times in tandem with gradual clinical improvement at each review.

Conclusions—There is electrophysiological evidence of a central reversible corticospinal tract conduction abnormality in the Miller Fisher syndrome.

Keywords: Miller Fisher syndrome; central motor conduction time; corticospinal tract abnormality

The Miller Fisher syndrome, clinically defined by the triad of ataxia, areflexia, and ophthalmoplegia, is an uncommon form of acquired inflammatory demyelinating polyneuropathy. An immunological process is likely to be involved in its pathogenesis akin to the more common forms of axonal or demyelinating Guillain-Barré syndrome, but its exact site of involvement remains poorly defined in terms of clinical, radiological, or neurophysiological evidence. In particular, there is minimal evidence to suggest upper motor corticobulbar or corticospinal tract involvement. The disease is thought to be primarily demyelinating in nature, with rapid onset and often spontaneous complete resolution of signs and symptoms. In view of this, its rarity and relatively short disease process, clinical and pathological information are primarily lacking.

Transcranial magnetic stimulation (TMS) is a well established method for studying the functional integrity of the corticospinal system electrophysiologically. For the first time we have utilised TMS, a rapid, reproducible, and safe technique, in a serial study of three consecutive patients presenting with classic Miller Fisher syndrome. Central motor conduction times were studied over a 3 to 6 month period with the aim of demonstrating dynamic corticospinal tract dysfunction in correlation with the resolution of clinical features. The findings are discussed in relation to existing evidence on the pathogenesis of the disease.

Case histories

PATIENT 1

A 39 year old women had no relevant medical history. She developed giddiness, diplopia, and limb numbness of acute onset, worsening over 3 days. A history of upper respiratory infection 1 week before admission was elicited. Physical examination on admission disclosed diminished eye movements in all directions, mild bilateral ptosis, areflexia, upper limb incoordination, and reduced limb sensation to touch and pain. No detectable motor weakness was present. Brain MRI and CSF examination were unremarkable. An antiGQ1b assay was positive. The patient's eye movements progressed to near complete ophthalmoparesis over 2 days. Transcranial magnetic stimulation studies were performed on admission. She was discharged 1 week after admission with minimal improvement of eye movements. She continued to improve when reviewed fortnightly. At 1.5 months after admission, she recovered to having near complete eye movements and a repeat TMS study was done. At 7.5 months after admission, there was complete recovery of eye movements and ataxia but reflexes remained slightly diminished. A repeat TMS study was performed then.

PATIENT 2

A 55 year old women had no relevant medical history. She experienced double vision on waking as the only presenting complaint. Examination on admission disclosed abduction failure in the left eye with an otherwise unremarkable examination. On the second day of admission, abduction failure in the right eye and generalised hyporeflexia was elicited. This progressed to areflexia and total ophthalmoplegia by the 5th day of admission. In addition, there was mild upper limb incoordination and bilateral ptosis despite preserved motor power. Brain MRI was unremarkable. Examination of CSF was normal. She was tested positive for antiGQ1b antibody. Transcranial magnetic stimulation was performed on the 8th day of admission.

On review 3 weeks later, there was evidence of improved eye movements in all directions and normal coordination despite areflexia. The second outpatient review showed complete resolution of eye movements, ataxia, and a definite return of some tendon reflexes. A repeat TMS study was performed then. A third review, with a TMS study, was performed 6 months after admission. There was complete recovery of eye movements, ataxia, and normalisation of reflexes.

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PATIENT 3
A 70 year old man with no relevant medical history presented with a 4 day history of unsteady gait preceded by an upper respiratory infection 1 week earlier. Examination showed reduced eye movements in all directions, limb incoordination, and generalised areflexia in the absence of detectable motor weakness. Brain MRI and CSF examination were unremarkable. He was tested positive for antiGQ1b antibody. Transcranial magnetic stimulation was performed on the 6th day of admission. On review 1 month later, clinical examination showed mildly improved eye movements and coordination despite generalised areflexia. A repeat TMS study was done. A second out patient review 8 weeks later showed near normalisation of eye movements, coordination, and return of tendon reflexes. A repeat TMS study was performed on this review date.

Methods
PATIENTS
All patients gave informed consent before TMS was performed. History of seizures, heart disease, and intracranial operations were excluded. Magnetic stimulation was performed with a Dantec Mag 2 Stimulator (Dantec Co, Denmark) with a Dantec S100 circular 10 cm diameter coil generating up to 1.9 Tesla in output. Motor evoked potential (MEP) recordings were made with adhesive surface electrodes in the first dorsal interosseous and abductor hallucis muscles. The coil was positioned over the vertex to obtain consistent MEPs of maximum amplitude with the relevant muscle in slight contraction. Patients had multiple cortical stimulations, sometimes up to 20 for each muscle, to obtain distinctly recordable MEPs of consistent morphology. The average latency of the shortest of three most consistent responses was accepted. The minimum latency of 20 F responses was obtained; CMCT was calculated with the formula: MEP latency–(F latency+M latency–1)/2 in ms.

Nerve conduction studies of the median, ulnar, sural, tibial, and peroneal nerves with relevant late responses were performed. Additional tests including evoked response studies were performed if clinically indicated.

CONTROLS
We performed CMCT measurements on 15 healthy volunteers with informed consent using the above technique. The ages ranged from 20 to 70 and included six men and nine women.

Results
NEUROPHYSIOLOGICAL STUDIES
Nerve conduction studies in patient 1 showed a mild sensory demyelinating polyneuropathy of the lower limbs and absent H reflexes. Auditory, median, and tibial somatosensory evoked responses were within normal limits. Nerve conduction studies in patient 2 were unremarkable. In patient 3, nerve conduction studies showed diminished lower limb sensory velocities, prolonged late responses, and absent H reflexes.

CENTRAL MOTOR CONDUCTION TIME
Patient 1 had severe prolongation of CMCTs to the upper limbs on presentation despite preservation of CMCTs to the lower limbs. The upper limb CMCTs showed marked reductions in the next two studies. Patient 2, similarly had prolonged CMCTs to the upper limbs in the initial study, although to a lesser extent. These two patients also showed a reducing trend towards the normal range by the second study. Again, CMCTs to the lower limbs were not prolonged and were relatively unchanged in subsequent studies. In patient 3, CMCTs to the lower limbs were mildly prolonged in the initial study but showed gradual reductions in subsequent studies. Although upper limb CMCTs were not initially prolonged, there was evidence of gradual reduction in the later studies.

Mean (SD) for upper and lower limb CMCTs in control subjects were 5.85 (1.028) and 12.262 (1.875) ms respectively. The upper limit of normal at 2SDs were 7.745 and 16.011 ms.

The results are summarised in figures 1 and 2 for upper and lower limbs respectively; M and F wave latencies are summarised in table 1.

Figure 1 Dynamic CMCT changes in upper limb recordings. Dynamic CMCT reduction over time is evident in patients 1 and 2. The dashed horizontal line represents the upper limit of CMCT at 2 SDs from controls. Continuous lines link left upper limb CMCTs. Dotted lines link right upper limb CMCTs.
Discussion
The evidence for a CNS lesion in the Miller Fisher syndrome from clinical, immunological, and pathological aspects are few by contrast with the Guillain-Barré syndrome. Although a brain stem lesion has been suggested, direct pathological evidence of demyelination in the CNS is lacking. Serum antibody binding to human and mouse cerebellum has been implicated as a cause for ataxia, but current immunological evidence has mainly shown binding to cranial nerves involved in eye movements. Magnetic resonance imaging studies have shown enhancement in the lumbosacral root, cauda equina, facial nerve, and trigeminal nerves. Isolated cases of medullary, midbrain, and pontine abnormalities have also been reported, but the nature of these lesions remains obscure.

Neurophysiological variables have not been used extensively in patients with this condition. Separate studies gave conflicting results on brain stem auditory evoked potentials, whereas blink reflex studies have not been useful for electrophysiological localisation. Peripheral nerve conduction studies in general do not differ significantly from those in patients with Guillain-Barré syndrome.

Central motor conduction time is an established variable in assessing the speed of corticospinal tract conduction from the motor cortex to the spinal motor neurones. It is used in the diagnosis and follow up of central demyelinating disorders, most notably multiple sclerosis. Although it can be suggested that prolonged MEP latencies are the result of abnormal F wave latencies, our study showed that they are relatively stable and not significantly prolonged (fig 3), with the exception of patient 3 in the later studies (table 1). Also, the mathematical method of CMCT calculation has taken into account prolonged F and M latencies.

Our findings of dynamic reduction of CMCTs in tandem with clinical improvement support the hypothesis of a transient neuronal insult. The lesion or lesions in question are also likely to be central and variable in localisation, as evidenced by separate involvement of upper and lower limb central connections in different patients. This finding is also in keeping with radiological reports of MRI abnormalities in varied locations in separate patients with this disease. AntiGQ1b positivity in all three patients lends supportive evidence for a diffuse immunological disease process. It is possible that the ongoing immunological attack is patchy, multifocal, or variable in location.

Although isolated studies have reported MRI abnormalities, this has been the exception rather than the rule, as seen in this study. The relevance of the absence of radiologically detectable lesions in the presence of electrophysiological abnormalities is uncertain, but could imply the presence of a transient non-structural immunological attack causing blockage of impulse transmission with no permanent axonal damage. All three patients hence showed complete recovery on follow up. The concept of reversible conduction disturbances has been studied for peripheral nerves in the Guillain-Barré syndrome, in terms of

Table 1 Summary table of M wave latency, F wave latency, and CMCT of all patients in each follow up study. All values are in ms. The first column shows right sided values of each measurement.

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td></td>
<td>M Wave</td>
<td>F Wave</td>
<td>CMCT</td>
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<tr>
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<td>3.4</td>
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<td>3.5</td>
<td>31.4</td>
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<tr>
<td>Lower limb:</td>
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<td></td>
<td></td>
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<tr>
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<td>7.8</td>
<td>6.0</td>
<td>49.9</td>
</tr>
<tr>
<td>Patient 2</td>
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<td>5.9</td>
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</table>
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antibody facilitated immune attack\(^1\) and serial electrophysiological studies.\(^{25-27}\) A recent study suggested antiGQ1b-mediated blockage of acetylcholine release from motor nerve terminals in a patient with Miller Fisher syndrome.\(^{28}\)

It is hypothesised that similar mechanisms could be responsible for the electrophysiological findings in the central corticospinal pathways in our cases.

Although all three patients had electrophysiological evidence of corticospinal tract conduction abnormalities, none had demonstrable upper motor neuron-type deficits clinically. It is argued that central motor conduction time prolongation probably represents desynchronisation of descending volleys during transcranial magnetic stimulation caused by a transient immunologically mediated “functional demyelinating process”, which is not sufficiently translated into obvious clinical weakness or upper motor release signs.

In conclusion, we have provided supportive evidence of central, transient, and reversible corticospinal tract dysfunction in the Miller Fisher syndrome. The tendency to clinical recovery, absence of radiological abnormalities, and rapid reduction of central motor conduction times favour a non-axonal disease process.


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Lewy described chronic cell atrophy and glial overgrowth in the putamen and globus pallidus, with reduction of fibres in the ansa lenticularis. These lesions are the lesions of senility. Later, in 1923, he observed that most of the pathological changes were characteristic of a senile fibroblastic process, and the great cellular loss in the pallidum, the dorsal nucleus of the substantia nigra, with the lenticular nucleus of the corpus striatum, but less often in the substantia nigra. He found in these changes showing that they occur in neurons carrying neuromelanin pigment: the locus coeruleus, autonomic ganglia, amygdala, and hypothalamus. They can be seen throughout the cortex in smaller numbers.

A cautious observer, Lewy wrote: “They (intracellular inclusions) are simply findings which I up till now have found in all cases of paralysis agitans that I have examined, but which were absent in the other (control) cases.”

Lewy noted that the atrophic brain has many neuromelanin bodies. Now it is known they are the result of breakdown of intracellular catecholamines, including dopamine, but whether it protects the cell or is itself toxic when it accumulates is uncertain. It is of interest that neuromelanin is preserved in albinos. Lewy bodies are circular cosinophilic structures with a dense core protein complex surrounded by a peripheral halo located within the cytoplasm of neurons. The ultrastructural appearance is like a sunflower with a dense central core of circular shaped structures and a rim of radiating filaments (7 to 20 nm in diameter), the largest filaments at the periphery, which corresponds to the halo. Their size and number vary. Lewy bodies result from neuronal degeneration, with accumulated altered cytoskeletal elements that stain with antibotulinum and antibodies to neurofilaments.