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Serial nerve conduction studies provide insight into the pathophysiology of Guillain–Barré and Fisher syndromes

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ABSTRACT

The electrodiagnosis of Guillain–Barré syndrome (GBS) can be broadly divided into acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). Fisher syndrome (FS) is a variant of GBS, although the underlying neuropathy of FS has yet to be established. Serial nerve conduction studies (NCS) can provide further insight into the likely pathophysiology by further subtyping of GBS and FS. We present a patient with an initial diagnosis of AIDP in whom repeated NCS revealed the AMAN variant. This led us to investigate serial NCS in five patients with GBS, FS and FS/GBS overlap presenting over a period of a year. Three patients with AIDP showed a gradual increase in distal motor latencies during the acute phase of illness. NCS of two patients with FS and FS/GBS overlap showed no demyelinating features suggesting underlying axonal neuropathy in this group of patients. The importance of serial NCS in establishing the underlying pattern of neuropathy in GBS and FS is further emphasized in this study. Larger studies incorporating serial NCS are required to confirm the observations seen in our case series especially when pathological studies are often not justified in this group of patients.

1. Introduction

Guillain–Barré syndrome (GBS) can be broadly divided into two subtypes, acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) [1]. Fisher syndrome (FS) is widely accepted as a variant of GBS presenting with its own set of unique clinical features of ataxia and ophthalmoplegia. In recent years, our understanding of AMAN has improved in leaps and bounds with the identification of the serological markers (IgG antibodies against GM1, GM1b, GD1a or GalNAc–GD1a) and proof of molecular mimicry with *Campylobacter jejuni* in some cases of AMAN [2]. There continues to be some debate as to whether FS is a demyelinating or axonal disease [3,4]. FS is strongly associated with IgG anti-GQ1b antibodies, and *C. jejuni* isolates from FS patients carry GQ1b epitope [5]. The ganglioside-like lipo-oligosaccharide (LOS) in *C. jejuni* strains are synthesized by *Campylobacter* sialyltransferase (Cst-II) encoded by *cst-II*. The genetic polymorphism of *cst-II* influences the ganglioside-like LOS that is expressed which in turn produces either AMAN or FS in susceptible patients suggesting that the pathophysiology of FS is not demyelinating, but axonal.

The clinical features and electrodiagnosis of AMAN have seen a lot of change in recent years with reports of reversible conduction block [6,7]. Reports of patients with FS overlapped by GBS (FS/GBS overlap) have also facilitated in the better understanding of FS [8,9]. It is increasingly recognized that serial nerve conduction studies (NCS) have played an important role in our improved understanding of GBS. In this article, we describe a case that was initially diagnosed as AIDP in whom repeated NCS revealed acute motor conduction block neuropathy (AMCBN). This prompted us to look at serial NCS of a further five patients who presented within a period of a year with GBS, FS or FS/GBS overlap.

2. Materials and methods

2.1. Patients

Eight patients with GBS (n=4), FS (n=2) or FS/GBS overlap (n=2) presented to University Malaya Medical Centre between April 2010 and February 2011. The diagnosis of GBS was made based on a history of progressive weakness within a period of four weeks affecting more than one limb associated with hyporeflexia or areflexia [10]. FS

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was diagnosed based on the clinical presentation of ophthalmoplegia, ataxia and hyporeflexia/areflexia without limb weakness [11]; whereas, FS/GBS overlap was diagnosed when there was associated significant limb weakness [8]. Six of the eight patients consented to having serial NCS performed on them. The study was approved by the hospital Medical Ethics Research Committee.

2.2. Nerve conduction studies

NCS were performed using the Medelec™ Synergy EMG machine. At least two limbs were assessed; four motor nerves and three sensory nerves as well as F wave latencies. Nerve stimulation and recorded compound motor action potentials (CMAPs) were as follows: median nerve was stimulated at the wrist and elbow, recording over abductor pollicis brevis muscle; ulnar nerve was stimulated at the wrist, below elbow and above elbow, recording over abductor digiti minimi muscle; tibial nerve was stimulated at the ankle and popliteal fossa, recording over the abductor hallucis muscle [12]. Sensory studies of the median and ulnar nerves were performed by using the orthodromic method of stimulating the index finger and little finger respectively and the sensory nerve action potentials (SNAPs) recorded over the wrist crease. The radial and sural nerves however, were recorded using the antidromic method. The radial nerve was stimulated at the forearm and recorded over the anatomical snuffbox whereas sural nerve was stimulated at the calf and recorded below the lateral malleolus. Reference values were derived from NCS performed on normal patients at our laboratory. The electrodiagnosis of AIDP or AMAN was made based on the electrodiagnostic criteria set by Ho et al. [13].

2.3. Enzyme-linked immunosorbent assay

Sera samples were obtained at acute progressive phase of the illness, and measured for IgG and IgM antibodies to GM1, GM1b, GD1a, GalNAc–GD1a, GD1b, GT1a and GQ1b, as described elsewhere [14]. In brief, serum samples diluted to 1:500 were placed in separate microtiter plate wells. The mean value for triplicate reference wells without antigen was subtracted from the mean value for triplicate wells of each sample, and the optical density assessed. An optical density of more than 0.5 was judged to be positive. Using the strict cut-off value, sera from patients with acute transverse myelitis ($n=9$), acute disseminated encephalomyelitis ($n=46$) and multiple sclerosis ($n=44$) were negative for those anti-ganglioside antibodies.

3. Results

3.1. Clinical features

Of the six patients, four fulfilled the clinical criteria for GBS, one for FS and one for FS overlapped by GBS (FS/GBS overlap). We describe two interesting cases; one of GBS and one of FS/GBS.

3.1.1. Patient 4

A 25-year-old Malaysian Indian male presented with a 2-day history of progressive bilateral upper and lower limb weakness. A week before his presentation, he described having a sore throat. He denied any sensory symptoms. He was admitted on Day 3 of his illness when he was unable to mobilize independently. His upper limb power was MRC grade 4 for shoulder abduction and MRC grade 2 in the first dorsal interossei and abductor pollicis brevis. In the lower limbs, power was MRC grade 3 for hip flexion, 3 for knee flexion and 2 for ankle dorsiflexion bilaterally. His tendon reflexes were depressed. His sensory examination was normal. CSF analysis on the day of admission showed albumino-cytological dissociation with protein of 1.15 g/L (normal, less than 0.45 g/L) and no leucocytes. He was treated with intravenous immunoglobulin. On Day 7, he was able to walk independently although some of his muscles were still weak. The MRC grades of his limb muscles were as follows bilaterally: shoulder abduction 5, abductor pollicis brevis 3, first dorsal interossei 3, hip flexion 4+, knee flexion 4 and dorsiflexion 3. On further review of his muscle power on Day 20, these were all normal apart from a slight weakness of his left abductor pollicis brevis and first dorsal interossei to 4.

3.1.2. Patient 6

A 61-year-old Malay female presented with a week's history of numbness in her hands and feet, unsteadiness and visual blurring. She described a history of a dry cough occurring a week before the onset of her neurological symptoms. She denied having any diarrheoa. On Day 3, her neurological symptoms had progressed and she was no longer able to mobilize and was confined to her bed. On Day 7, she was alert. There was complete ophthalmoplegia and her pupils were dilated at 5 mm and unreactive to light. Facial muscle power was intact. Her upper limb power was reduced to MRC grade 4 in shoulder abduction and 3 in abductor pollicis brevis and first dorsal interossei. In the lower limbs, her hip flexion was reduced to 4 and the rest of her muscle power was intact. Her tendon reflexes were absent throughout and plantar responses were flexor bilaterally. There was also reduced pinprick up to the elbows in the upper limbs and midthighs in the lower limbs. Proprioception was intact in the lower limbs but reduced in the upper limbs up till the wrists. She was markedly ataxic with evidence of truncal ataxia (she could not sit unsupported) as well as upper and lower limb ataxia. CSF analysis on the day of admission showed a raised protein of 0.78 g/L with no leucocytes. She was treated with immunoglobulin. By Day 17, she was able to sit unsupported and her muscle power had recovered to MRC grade 5 apart from the right APB which was grade 4. There was also now vertical and horizontal eye movement although lateral abduction was still weak. Her pupils were also responding to light.

3.2. Nerve conduction studies

NCS were performed in all six patients, and the results are shown in Table 1. Three of the four GBS patients (Patients 1, 2 and 3) fulfilled the electrophysiological criteria for AIDP. Their subsequent NCS showed prolongation of distal motor latencies (DMLs) within the first 21 days of their illness.

In Patient 4, the first NCS done on Day 5 fulfilled the criteria of AIDP based on the presence of demyelinating features of prolonged DMLs in two or more nerves. There was also evidence of conduction block in both the median and ulnar nerves. Sensory studies were within normal limits. A repeat NCS done on Day 20 showed complete recovery of the DMLs to within normal limits and also recovery of the conduction block in some nerves. The F waves also reappeared although delayed in some nerves. By Day 55, the NCS was back to within normal limits. The representative waveforms are shown in Fig. 1A.

Patient 5 had FS and the first study performed on Day 3 of her illness showed abnormal SNAPs with reduced amplitudes but these recovered to within normal limits at the second NCS on Day 128. Patient 6 had FS/GBS overlap and her initial NCS showed no demyelinating features but the motor CMAPs were reduced in amplitude with preserved conduction velocities along with absent SNAPs. A second NCS a week later showed improvement in the CMAP amplitudes although the SNAPs remained absent. On Day 31, the sensory potentials reappeared in some nerves and the motor CMAPs were within normal limits. The SNAPs were present in all nerves at Day 90. The representative waveforms are shown in Fig. 1B.

3.3. Anti-ganglioside antibodies

Sera from five patients (Patients 1, 2, 3, 4 and 6) were available for anti-ganglioside testing. Patient 4 had IgG antibodies against GM1, GD1a, GalNAc–GD1a and GD1b in serum obtained on Day 5. Each