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Patterns of sensory nerve conduction abnormalities in Fisher syndrome: More predominant involvement of group Ia afferents than skin afferents

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HIGHLIGHTS

- This study elucidated electrophysiologic features of sensory nerve involvement in 47 patients with Fisher syndrome (FS).
- Major abnormalities included absent/reduced soleus H-reflexes with rarely reduced sensory nerve potentials, suggesting more predominant involvement of group Ia afferents than cutaneous afferents.
- Ataxia and areflexia in FS are presumably caused by immune attack by anti-GQ1b antibodies to group Ia neurons in the dorsal root ganglia in FS.

ABSTRACT

Objective: To elucidate the features of sensory nerve involvement in Fisher syndrome (FS), this study extensively investigated sensory electrophysiology.
Methods: In 47 consecutive FS patients, results of sensory nerve conduction studies in the median, ulnar and sural nerves, soleus H-reflexes, and median or tibial somatosensory-evoked potentials (SEP) were reviewed. Because of the large effects of age on amplitude of sensory nerve action potentials (SNAP), we strictly defined reduction of SNAP amplitudes by using a nomogram which age and amplitude obtained from 87normal subjects.
Results: In routine nerve conduction studies, SNAP amplitude was reduced only in 32% of the patients, and conduction velocity was decreased in 2%. In contrast, soleus H-reflexes were frequently absent or reduced (67%). SEPs were abnormal only in 17%.
Conclusions: In FS, absent soleus H-reflexes are the most frequent electrophysiologic abnormalities, whereas SNAPs amplitudes are rarely affected. The pattern is characterized by predominant involvement of group Ia afferents with relatively preserved cutaneous afferents without evidence suggestive of demyelination.
Significance: The major targets of immune attack by anti-GQ1b antibodies in FS appear to be group Ia neurons in the dorsal root ganglia, and this is presumably responsible for ataxia and areflexia in FS.

1. Introduction

Fisher syndrome (FS) is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia (Fisher, 1956). The disorder is considered a variant of Guillain–Barré syndrome (GBS), although the lesion site is still a matter of controversy (Ogawara et al., 2002; Mori and Kuwabara, 2011; Shahrizaila and Yuki, 2012). In the original paper, Miller Fisher himself postulated the presence of unusual peripheral lesions, indicating that "a unique, widespread and selective attack on the sensory neurons underlying postural adjustments must have occurred," and that "one would have to postulate a very selective involvement of special sensory neurons subserving the stretch reflex" (Fisher, 1956).

Then, electrophysiologic studies in FS have shown that peripheral sensory nerve lesions; amplitudes of sensory nerve action potential (SNAPs) decreased in some, not all, patients (Durand et al., 2001; Fross and Daube, 1987; Jamal and Ballantyne, 1988; Sauron et al., 1984). However, the extent of decreases in SNAP amplitudes were mild-to-moderate, and unlikely to be responsible for prominent ataxia in FS. Furthermore, because of the rarity of the disorder, the number of examined patients was limited in these reports; up to 10 patients. More recently, H-reflex studies showed the absent responses with frequently normal SNAP amplitudes,

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suggesting selective involvement of group Ia afferents (Dachy et al., 2010; Kuwabara et al., 1999a,b), but again, the number of examine patients was small (3–10 patients) and therefore the data did not provide conclusive results.

One of the major problems in sensory nerve conduction studies is that because of the large effects of aging on SNAP amplitudes, it is difficult to define abnormally reduced amplitudes. Many previous studies have demonstrated influence of age on nerve conduction parameters, particularly SNAP amplitudes (Fujimaki et al., 2009; Trojaborg et al., 1992; Salerno et al., 1998; Tong et al., 2004). To overcome this problem, the use of nomogram of age and SNAP amplitudes is recommended (Fujimaki et al., 2009).

Serum anti-GQ1b IgG antibody levels are frequently elevated in patients with FS, and this antibody probably plays an important role in the pathophysiology of this disorder (Chiba et al., 1992; Ito et al., 2008). Histochemical studies have shown that large neurons of the dorsal root ganglia, possibly group Ia neurons, were immunostained with anti-GQ1b monoclonal antibody. Anti-GQ1b IgG antibody may thus be associated with ataxia in FS (Kusunoki et al., 1999). Based on the accumulated data, we hypothesize that in FS, group Ia neurons are primarily involved, and validated our electrophysiologic data of sufficient number of FS patients.

2. Methods

2.1. Subjects

This study included 47 consecutive patients with FS (28 men and 19 women), seen at a single University Hospital in Japan between 1990 and 2011. All patients had the triad of ophthalmoplegia, ataxia and areflexia in 1–2 weeks, or the two symptoms of the triad with positive anti-GQ1b antibodies. All patients had acute ophthalmoplegia, ataxia and areflexia or the two symptoms with positive anti-GQ1b antibodies. Patients complicated by Guillain–Barré syndrome ($n = 3$) or Bickerstaff encephalitis ($n = 3$) were excluded. Diabetic patients ($n = 3$) were also excluded. After excluding these patients, 47 were studied. Their age ranged from 10 to 78 years (median, 43 years), and subjects were screened for other disorders affecting the peripheral nerves. Serum anti-GQ1b IgG antibodies were measured with ELISA as described elsewhere (Ito et al., 2008), and positive in 82% of the 45 FS patients. The data of 26 patients were briefly described in our previous study (Ito et al., 2008), and we recruited additional 21 patients.

A total of 87 healthy volunteers (33 men and 54 women) served as normal controls for nerve conduction studies. Their age ranged from 16 to 80 years (median, 48 years; SD, 18 years), and the data were published elsewhere (Fujimaki et al., 2009). Control data for H-reflex studies were obtained from 15 normal volunteers aged 21–52 years (mean 39 years) as described elsewhere (Kuwabara et al., 1999b). The median age and distribution were not significantly different in FS patients and normal controls. The study protocol was approved by the Ethics Committee of the Chiba University School of Medicine.

2.2. Sensory nerve conduction studies, H-reflex studies, and SEPs

We collected results of nerve conduction studies, soleus H-reflex studies, and somatosensory-evoked potentials. Electrophysiologic evaluation was performed 3–10 days after onset (median 6 days). Antidromic sensory nerve conduction studies were performed in the median, ulnar and sural nerves. Median and ulnar SNAPs were respectively recorded with surface electrodes placed on the second and fifth digit after stimulation at the site 3 cm proximal to the wrist crease. Sural nerve potentials were recorded from the lateral malleoulus with surface electrodes; the site of stimulation was 14 cm proximal to the recording electrode. Skin temperature of both arm and leg were monitored and was maintained above 32 °C using a heater if necessary.

The H-reflex in the right soleus muscle was recorded after submaximal stimulation of the tibial nerve at the knee. Stimulus duration was 1.0 ms and rate was 0.5 Hz. The patient lay in the prone position with the ankle joint maintained at approximately 120°. The ratio of the peak to peak maximum H-reflex to the maximum compound muscle action potential (H/M ratio) was measured. We have defined "absent" H-reflex as "completely no response", and "reduced" H-reflex as "H/M ratio <3%". In normal controls, the mean H/M ratio was 19% (range, 6–28%). The cut-off value of 3% was determined as 50% of the minimal value of normal controls.

SEPs were recorded after median nerve stimulation at the wrist or tibial nerve stimulation at the ankle, according to standard procedures (Nuwer et al., 1994). For median SEPs, recordings were made from Erb's point, over the fifth and second cervical spinous processes, and from 2 cm posterior to the C3 or C4 position of the 10–20 international system of scalp electrode placement. The reference electrode was placed at the left ear lobe. For tibial SEPs, lumbar N20 and cortical P37 were recorded.

Body sway was measured as displacement of the centre of foot pressure detected on a rigid platform mounted on strain gauges using posturography (G5500, Anima Corp., Tokyo, Japan), as described elsewhere (Kuwabara et al., 1999a,b). The total length (mm) traveled in 30 s was calculated from the centre of foot pressure as subjects stood on the platform. Peak frequency of body sway was calculated by Fourier analysis with a computer program (Gravi Analyzer, Anima Corp.).

2.3. Statistical analysis

All statistical tests were two-sided, and a P-value of less than 0.05 was considered to indicate statistical significance. Student t test or Mann–Whitney test was used to compare median values of electrophysiologic parameters in patients and normal controls. The frequency of abnormal response was compared with chi-square test. All statistical analyses were performed with the use

Table 1
Clinical and antibody profiles of 47 Fisher syndrome patients.

	Abnormality n (%)
Anticedent infection	
Upper respiratory infectious symptom	36 (80%)
Diarrhea	2 (4%)
Initial symptoms	
Diplopia	39 (83%)
Gait disturbance	10 (21%)
Neurological sign during illness	
Cranial nerve palsy	
Facial	9 (19%)
Oropharyngeal	7 (15%)
Sensory disturbance	
Paresthesia	14 (30%)
Pin-prick sensation	9 (19%)
Vibratory sensation	11 (23%)
Tendon reflex*	
Decreased or absent	43 (92%)
Anti-gangliosides antibodies	
IgG antibody to**	
GQ1b ($n = 45$)	37 (82%)
GT1a ($n = 30$)	20 (67%)
GD1b ($n = 45$)	2 (4%)
GM1b ($n = 30$)	1 (3%)

* Decreased or absent reflex in more than two tendon, defined as "decreased or absent".
** Antibody positive (titer >1:500) are defined as abnormal.