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Does delayed facial involvement implicate a pattern of "descending reversible paralysis" in Fisher syndrome?

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ABSTRACT

Objective: Delayed facial palsy (DFP) has often been described during the recovery stage of Fisher syndrome (FS), but the implications of DFP in FS pathophysiology have not been reported previously. The aim of this study was to identify the incidence and clinical course of DFP in FS, and to determine its clinical/pathophysiological implications in FS.
Methods: About 71 FS patients were enrolled from seven university-based hospitals in Korea. DFP was defined with respect to new development of unilateral or bilateral facial palsies with delayed onset after either the nadir or improvement of initial neurological signs of FS.
Results: Eleven of the 71 patients (16%) satisfied the definition of DFP. No other cranial palsies developed as a delayed pattern. With the exception of two patients with bulbar involvement, DFP developed after a latent period of upper-cranial neuropathies. Comparison of FS patients without and with DFP revealed no significant clinical, serological, or electrophysiological differences. All except one patient with DFP exhibited a good outcome within 1 month of follow-up.
Conclusion: DFP was identified as a common and specific phenomenon in FS. Nearly all cases of DFP were developed in a descending manner and were associated with a good outcome, while other cranial neuropathies developed or followed as a sequential pattern. These findings suggest the involvement of so-called "descending reversible paralysis" in the pathophysiology of FS.

1. Introduction

While the central role of the anti-GQ1b immunoglobulin (IgG) antibody is well established in Fisher syndrome (FS), [1] the specific immunological cascade of this antibody is yet to be determined. Furthermore, the initial target region of the anti-GQ1b antibody across the neural axis—proximal (neuron) vs distal (axon)—remains a matter of debate. Although objective measurement of cranial nerve function has considerable limitations, some clues can be obtained from nerve conduction studies (NCSs) of the limbs [2–4].

It has been established that the anti-GQ1b antibody has a greater affinity for Ia afferent fibers than for skin afferents in human sensory nerves [2]. The occurrence of reversible conduction failure (RCF) in nodo-paranodopathy is a concept that has recently been proposed to explain the rapid recovery of acute motor axonal neuropathy [5,6]. Some authors have demonstrated the RCF pattern in sensory NCS, and have suggested that the targets of the anti-GQ1b antibody are the nodes of axons or distal nerve terminals [4]. However, somewhat heterogeneous results have been reported using serial sensory NCSs [6]. It therefore appears that in addition to RCF, there exists a persistent and mixed pattern of conduction failure [3].

While delayed facial palsy (DFP) has often been described in association with FS, even during the improving stage, its clinical/pathophysiological implications in FS have not been reported

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previously. This phenomenon cannot be fully explained by the concept of RCF, because RCF represents a clinical and electrophysiological pattern with an abrupt onset and rapid recovery of neural dysfunction.

The aims of the present study were to establish the incidence and the clinical characteristics of DFP in FS in order to identify any sequential patterns of cranial nerve involvement in FS, and to determine its pathophysiological implications in FS.

2. Methods

2.1. Subjects

The clinical, laboratory, and electrophysiological data of patients who were diagnosed with FS were collected from seven university-affiliated tertiary hospitals in Korea. Staff at each hospital reviewed the data of the most recent years (i.e., minimum = 1 year, maximum = 7 years). All participants gave written informed consent before study inclusion. All procedures were in accordance with the Declaration of Helsinki and approved by the Hallym University Kangdong Sacred Heart Hospital Institutional Review Board (IRB NO. 14-1-21). Records of patient were anonymized and de-identified prior to analysis.

2.2. Enrollment criteria

The following criteria were used to diagnose FS: (1) presence of the classic triad of FS (ophthalmoplegia, ataxia, and areflexia 1–2 weeks from the onset of initial symptoms), or (2) presence of two of the triad symptoms and positivity for anti-GQ1b antibodies. Patients also exhibiting Guillain–Barré syndrome (GBS) or Bickerstaff brainstem encephalitis (BBE) were excluded, as were those with FS superimposed with cranial neuropathies of other etiologies.

DFP was defined by an abrupt and delayed onset of facial palsies after the nadir (or even after the beginning of improvement) of the other initially developed FS symptoms such as cranial neuropathies and ataxia.

2.3. Electrophysiological study

Conventional nerve conduction study (NCS) were administered by an experienced technician using the standard method with supra-maximal stimulation and surface recording. NCS parameters, including terminal latency, conduction velocity, and compound muscle and sensory nerve action potentials in median, ulnar, peroneal, tibial, and sural nerves were measured. As late response tests, minimal latencies of F-wave response were measured in each motor nerves and H-reflex was obtained from soleus muscle after stimulation of the tibial nerve at the popliteal fossa. Facial NCS was performed by using Oh's method [7] and blink reflex test was obtained by stimulation of the supraorbital nerves, the method described by Kimura [8]. All of the electrophysiological tests were performed within 1 week of symptom onset. Interpretation for abnormal results was determined by the reference values in respective hospitals.

2.4. Antiganglioside antibody study

Serum samples were obtained from the patients during the acute stage, within 2 weeks of symptom onset. The samples of 27 patients were analyzed for the presence of IgG antibodies against GQ1b, GM1, and GD1b using the enzyme-linked immunosorbent assay (ELISA) at commercial specialty laboratories (Green Cross Reference Laboratory, Seoul, Korea). The samples of the remainder of the patients were subjected to ELISA at the neuroimmunology laboratory at Dong-A University (JKK) to detect various types of antiganglioside antibodies, including IgG and immunoglobulin M (IgM) antibodies against the gangliosides GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, and GQ1b, as described previously [9,10].

2.5. Statistical analysis

Differences in proportions between groups were tested using the chi-square test or Fisher's exact test, and differences in medians or means were tested using the independent t test or Mann–Whitney U test. The cutoff for statistical significance was set at $P < 0.05$, and all statistical analyses were conducted using SPSS (v18.0 for Windows, SPSS, Chicago, IL, USA).

3. Results

3.1. Patient enrollment

Initially, the data of 79 patients who were diagnosed with FS by a neurologist were collected from the involved hospitals. Of these, eight patients were excluded from the analysis due to incomplete clinical data regarding the progression of their disease course ($n = 4$), prominent motor weakness of limbs (possibility of GBS-FS overlap syndrome; $n = 2$), presumptive diagnosis of BBE ($n = 1$), and possible superimposition of multiple cranial neuropathies of other etiologies ($n = 1$). Therefore, the data of 71 FS patients who satisfied with the criteria of FS were ultimately analyzed in this study

3.2. Dichotomization of groups according to delayed facial palsies

Amongst the 71 included FS patients, 26 (37%) developed facial palsy during either the initial or advanced stages of FS. Of these, 11 patients (16%) satisfied the criteria for DFP during the disease course: 5–21 days after initial symptom onset (mean ± SD: 11.9 ± 4.2 days). Four patients presented with unilateral facial palsy, while the others presented with bilateral facial palsies. None of the patients with FS developed only facial palsy before the development of ophthalmoplegia, ataxia, or any neurological features of FS. One patient initially presented with facial diplegia; however, in this patient the symptom was accompanied by external ophthalmoplegia and ataxia at the first manifestation of FS. The enrolled patients were dichotomized into two groups according to the development of DFP: FS with DFP (FS-DFP+) and FS without DFP (FS-DFP−). Clinical, immunological, and electrophysiological findings were compared between these two groups.

3.3. Basic demographics and clinical information

Table 1 compares basic demographics and clinical information between two groups. The age and sex distributions did not differ significantly between the FS-DFP+ and FS-DFP− groups. The most common antecedent infection was upper respiratory tract infection in both groups. Regarding the initial manifestation, diplopia was the most frequently reported complaint in both groups. Although either the time taken to reach the clinical nadir or the delay before the first unequivocal improvement appeared to be slightly longer in FS-DFP+ compared with FS-DFP−, the difference was not statistically significant. Comparison of the profiles of neurological manifestation (including cranial nerve function) during the entire course of the disease revealed no significant difference between groups, with the exception of facial nerve involvement, which was more prevalent among FS-DFP+ than FS-DFP+ ($P < 0.01$).

The three-dimensional graphical representation of the development of cranial nerve involvement over the disease course shown in Fig. 1 for individual cases provides some information regarding the pattern of clinical evolution of FS. First of all, facial nerve involvement developed only after the development of upper-cranial-nerve