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Clinical Study

Ophthalmoplegic Guillain-Barré syndrome: An independent entity or a transitional spectrum?

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ABSTRACT

Ophthalmoplegia can occur in both Miller Fisher syndrome (MFS) and Guillain-Barré syndrome (GBS) with typical limb involvement. However, ophthalmoplegic GBS (OGBS) has been poorly defined. We aimed to characterize OGBS and clarify the pathophysiological implications across the overall GBS spectrum. Twenty GBS and seven MFS patients from three university based teaching hospitals in Korea were enrolled and analyzed. Six GBS patients who were classified as OGBS commonly also had facial diplegia (50%) and bulbar palsy (50%), while only a small portion of non-ophthalmoplegic GBS (NOGBS) patients had facial diplegia (21%). None of the patients had bulbar palsy in the NOGBS or MFS groups. The most frequent anti-ganglioside antibody in OGBS was the IgG anti-GT1a antibody (50%). The IgG anti-GM1 antibody was found mainly in NOGBS (57%) with high concordance with the pure motor type classification on electrophysiology. IgG anti-GQ1b antibody was positive uniquely in MFS (100%), although some patients were also positive for anti-GT1a antibody (71%). OGBS had distinct clinical features, including bulbar palsy, as well as ophthalmoplegia and limb weakness for both GBS and MFS. Relevant immunological factors were anti-GT1a antibody. Whether OGBS is an independent entity or a transitional spectrum remains to be established and further study will be needed.

1. Introduction

Ophthalmoplegia, such as oculomotor nerve palsy, can be caused by various conditions, including trauma, tumor, diabetes, aneurysm, surgery, stroke, or infection [1]. In clinical practice, differential diagnosis of ophthalmoplegia is an important and sometimes a challenging problem. Among various etiologies, ophthalmoplegia is one of the main clinical manifestations of Miller Fisher syndrome (MFS), with ataxia or areflexia as additional signs [2]. Interestingly, occasional patients with Guillain-Barré syndrome (GBS) can also manifest with various patterns of ophthalmoplegia in addition to the prominent limb motor weakness [1,3]. It is inferred that ophthalmoplegia in GBS is caused by a similar pathological mechanism as for the peripheral nerve involvement in the extremities [4].

Recent immunological developments have identified various pathogenic antibodies for axonal GBS and MFS [5–7]. These anti-ganglioside antibodies are associated with a specific clinical syndrome, due to the prominent topographical distribution of each ganglioside in human nerves. As such, this clinico-immunological association has extended our understanding of axonal GBS pathophysiology. Several variants of GBS have recently been categorized, mainly by the presence of certain anti-ganglioside antibodies [8,9].

This paradigm is pathophysiologically and clinically useful. However, some GBS patients have serological positivity for more than one anti-ganglioside antibody. In addition, they can manifest atypical clinical features (such as focal cranial nerve palsies), as a transitional symptom overlapping or evolving into typical GBS [10]. In this context, evaluation of clinical features and anti-ganglioside serology in ophthalmoplegic GBS (OGBS) can elucidate

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both the pathogenic antibody and overall pathophysiology of this atypical syndrome. Therefore, in an effort to elucidate the clinical and immunological profiles of OGBS, we analyzed and compared clinical and serological data between OGBS, typical GBS without ophthalmoplegia, and MFS.

2. Methods

2.1. Subjects

The clinical, laboratory, and electrophysiological data of patients diagnosed with GBS or MFS were collected from three university-affiliated tertiary hospitals in Busan, Korea. The data and sera of the patients used in this study were collected during the period from 2005 to 2006. All participants gave written informed consent for their participation in the study. All procedures were in accordance with the Declaration of Helsinki and study protocols were approved by the Dong-A University Hospital Institutional Review Board. Records of the patients were anonymized and de-identified prior to the analysis.

2.2. Enrollment criteria and study design

Patients who fulfilled the diagnostic criteria of GBS or MFS were enrolled. The diagnostic criteria for MFS are presence of the classic triad (ophthalmoplegia, ataxia, and areflexia within 1–2 weeks from the onset of initial symptoms), and for GBS as described by Asbury and Cornblath [11]. Then, the patients were divided into three groups according to the type and presence of ophthalmoplegia (OGBS; non-ophthalmoplegic GBS [NOGBS]; and MFS). Patient clinical and laboratory findings, including demographics, neurological findings during the acute stage, cerebrospinal fluid (CSF) examination, anti-ganglioside antibody profiles, and electrophysiological findings were compared between groups. Patients with atypical subtypes such as pharyngeal-cervical-brachial variant form or Bickerstaff brainstem encephalitis were excluded.

2.3. Anti-ganglioside antibody study

Serum samples were obtained from patients during the acute stage within 2 weeks of symptom onset. An enzyme-linked immunosorbent assay (ELISA) was used for detection of the various types of anti-ganglioside antibodies, including IgG and IgM antibodies against the gangliosides GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, and GQ1b, as described previously [9]. The presence and types of anti-ganglioside antibodies were analyzed by research physicians who were blinded to the presenting neurological manifestations.

2.4. Electrophysiological classifications

Conventional nerve conduction studies (NCS) were performed within 2 weeks of symptom onset by experienced technicians. NCS parameters including terminal latency, conduction velocity, and compound motor and sensory nerve action potentials from median, ulnar, peroneal, posterior tibial, and sural nerves were measured. For late response tests, minimal latencies of F-wave response were measured in each motor nerve and H-reflex was obtained from the soleus muscle by submaximal stimulation of the posterior tibial nerve at the popliteal fossa [12]. The results of the NCS were classified according to four groups based on the criteria described by others [13,14]. They include the classical sensorimotor demyelinating type (AIDP), acute motor conduction block neuropathy (AMCBN) or acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and unclassified (UC).

2.5. Statistical analysis

SAS v9.3 (SAS Institute, Cary, NC, USA) was used for statistical analysis. Baseline categorical variables were compared between groups using Fisher's exact test. The CSF protein was compared between groups using Wilcoxon Rank Sum test since the data was obtained from a small number of participants. All results with to p values <0.05 were considered statistically significant.

3. Results

3.1. Patients

Twenty-seven patients who fulfilled the diagnostic criteria of GBS or MFS were included in this study. There were 20 patients with GBS and seven patients with MFS. Among patients with GBS, six patients had OGBS, while the remaining 14 did not. Clinical characteristics, neurological findings, CSF findings, results of anti-ganglioside antibodies and electrophysiological classifications of patients were analyzed and compared between groups (OGBS vs NOGBS, OGBS vs MFS and NOGBS vs MFS). We found that OGBS had intermediate features between MFS and NOGBS.

3.2. Demographics and clinical information

Table 1 shows comparisons between the three groups in terms of basic demographics and clinical information. The age and sex distributions did not differ significantly between groups. The most common antecedent infection was an upper respiratory tract infection in all three groups, with no significant difference in the types of preceding infection.

Regarding the initial manifestation, diplopia was the most frequently reported complaint in MFS and in the OGBS group, and limb weakness was prevalent in the OGBS and NOGBS groups. There was no difference in gait disturbance for any reason (ataxia or limb motor weakness) and limb paresthesia between the three groups.

Among neurological manifestations during the disease course, bulbar palsy was prominent only in the OGBS group with high statistical significance (3/6, 50%). Facial palsy was frequently found in the OGBS group (3/6, 50%) compared with other groups, although it was also seen at a lower proportion in NOGBS (3/16, 21%). All cases of facial palsy were bilateral. Objective limb sensory change could not differentiate the three groups.

3.3. Anti-ganglioside antibody study

All three groups had a combination of various types of anti-ganglioside antibodies. When we consider the cut off value of corrected optical density as 0.1 in the ELISA, the positivity of the various antibodies is summarized in Table 2. None of the patients was positive for IgM type anti-ganglioside antibody. IgG type anti-GM1, anti-GD1b, anti-GT1a, and anti-GQ1b antibodies were positive in eight, seven, nine, and eight patients, respectively, including patients who were positive for more than two types of antibodies. IgG anti-GM1 antibody was found mainly in the NOGBS group (8/14, 57%) and in only one patient in the OGBS group (1/6, 17%). IgG anti-GD1b antibody was found only in anti-GM1 positive NOGBS. Although IgG anti-GT1a antibody was frequently found in MFS (5/7, 71%) and the OGBS (3/6, 50%) groups, anti-GQ1b antibody was found mainly in MFS (7/7, 100%) compared with OGBS (1/6, 17%) or NOGBS (0/14, 0%) (Fig. 1).