



## 심한 두통을 동반한 항GQ1b 항체 증후군

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### Anti-GQ1b Antibody Syndrome Presenting with Severe Headache

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Anti-GQ1b antibody syndrome, including Miller Fisher syndrome, Guillain-Barré syndrome with ophthalmoplegia, Bickerstaff's brainstem encephalitis, and acute ophthalmoplegia without ataxia, has overlapped clinical symptoms and mostly associated with anti-GQ1b immunoglobulin (Ig) G antibody. We report two cases of anti-GQ1b antibody syndrome mainly presenting with a severe headache. The 60-year-old man was admitted for severe headache and gait disturbance. Neurological examination revealed limb and truncal ataxia, areflexia, nystagmus, and ophthalmoplegia. Serum IgG anti-GQ1b antibody was positive. He recovered after intravenous (IV) immunoglobulin and steroid. The 23-year-old man suffered from severe headache (visual analogue scale=10) within the periorbital area. Ophthalmoplegia with gaze-evoked nystagmus were revealed. Serum IgG anti-GQ1b and anti-GT1a antibodies were positive. Headache was improved by IV immunoglobulin and steroid. The pathophysiology of headache in anti-GQ1b antibody syndrome is largely unknown. The affected nerve or structures in the brainstem including the trigeminovascular system may induce intractable severe headache.

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## INTRODUCTION

Immunoglobulin (Ig) G anti-GQ1b antibody has been found in Guillain-Barré syndrome (GBS) with ophthalmoplegia, Miller Fisher syndrome (MFS), Bickerstaff brainstem encephalitis (BBE), and acute ophthalmoplegia without ataxia [1]. These diseases have overlapped clinical symptoms, so they were recently classified as 'anti-GQ1b antibody syndrome' [1]. This

syndrome represents the variable neurological spectrum including the triad features of MFS, which are ophthalmoplegia, ataxia, and areflexia, as well as motor and sensory symptoms, consciousness disturbance, facial and bulbar palsy by their subtypes [2]. However, pain or headache associated with this syndrome is very rare. Herein, we report that two patients with severe headache confirmed with anti-GQ1b antibody syndrome.

## CASE REPORT

### 1. Case 1

The 60-year-old man on regular hypertensive medication was admitted with progressive limb ataxia, binocular diplopia, and headache for 3 days. He complained of severe headache located around both periorbital and frontal area and exacerbated by routine physical activities and Valsalva maneuver. He denied previous headache. He could not move on, sit up, and even open his eyes because of severe pain (visual analogue scale [VAS] score, 10). The acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) were not effective. Initial neurological examination revealed limb and truncal ataxia, areflexia. He could not gait without assistant. Visual acuity was normal without any optic disc swelling. Although there was not spontaneous nystagmus with or without fixation, horizontal and vertical gaze-evoked nystagmus was shown with bilateral abduction palsy and adductive saccadic slowing. Cerebrospinal fluid study showed mild lymphocytosis ( $7/\mu\text{L}$ ) and elevated protein (78.4 mg/dL), and the opening pressure was 15 cmH<sub>2</sub>O. Brain and orbital magnetic resonance imaging (MRI) were normal. Since there was no evidence of other infection causes, intravenous (IV) IgG (400 mg/kg/day) and dexamethasone were prescribed. After 2 days, severe headache and gaze-evoked nystagmus were subsided. He was discharged with only mild limb ataxia on the 10th hospital day. IgM and IgG anti-ganglioside antibody test using enzyme-linked immunosorbent assay (ELISA) with acute stage serum against each single ganglioside GM1, GM2, GD1a, GD1b, GD3, GT1a, GT1b, and GQ1b as described elsewhere showed positive (1+) to IgG anti-GQ1b antibody (semi-quantitative titer using subtracted optical density [OD] decided as follows; OD 0.1–0.29 as 1+, OD 0.3–0.49 as 2+, OD 0.5–0.99 as 3+, and OD more than 1.0 as 4+) [3]. After 2 months, the antibody was converted into negative, and he got well without any neurologic problem.

### 2. Case 2

The previous healthy 23-year-old man admitted binocular horizontal diplopia for 2 days. He did not have any headache

history including migraine. In initial neurological examination, abduction limitation in both eyes was shown without other neurologic deficits. There were no abnormalities in serum laboratory studies, brain and orbital MRI. CSF analysis was also normal with 9 cmH<sub>2</sub>O of the opening pressure. On the first day of hospitalization, he complained of vertigo and severe headache, which was located on the periorbital area and aggravated by routine physical activities and Valsalva maneuver. The headache was continuous during the whole day and not improved by acetaminophen or NSAIDs. He could not move his eyes, walk, or eat because of severe pain (VAS score, 10). Fundus examination and light reflex were normal, but horizontal and vertical gaze-evoked-nystagmus was newly revealed. Smooth pursuit and saccades were normal. IV IgG and steroid (prednisolone 1 g/day) were started. One day after these medications, severe headache was improved. On the 7th day of hospitalization, he was discharged with only mild gaze-evoked nystagmus. ELISA with acute stage serum before treatment revealed positive IgG anti-GQ1b and anti-GT1a antibodies (each 1+) [3]. After 2 months, he recovered fully without nystagmus, and follow-up serum antibodies were all negative.

## DISCUSSION

Our two patients who were confirmed as anti-GQ1b antibody syndrome by clinical manifestation and ELISA, mainly suffered from a severe headache which was not controlled by acetaminophen or NSAIDs. Severe headache or pain is a very rare complication in MFS or GBS.

In a case series of 27 patients clinically diagnosed with MFS referred to a laboratory center, six patients (22%) showed painful experience in the acute phase, and three of them had headache [4]. The locations of pain were around orbit, and its nature was diverse. Interestingly, oral NSAIDs were not effective for their headache as in our cases. In other recent study, six of the 38 patients (16%) with MFS experienced headache during the acute phase. Three of them complained of pain with over moderate (over 5 score by Wong-Baker FACES Pain Rating Scale), and NSAIDs was not effective in all patients [5].

The pathophysiology of pain or headache in anti-GQ1b antibody syndrome is largely unknown. In a previous study about

pain in GBS, clinically diverse nature of pain including radicular, painful paresthesia, muscle pain, and/or arthralgia occurs on back, extremities, neck, and/or trunk [6]. Affected nerve roots can explain the occurrence of radicular nociceptive nerve pain affecting the low back or back with radiation to extremities or trunk, and inflammatory factors via the nervi nervorum may also play a role in the pathophysiology of pain [6]. Likewise, considering the high prevalence of pain in the extremities, other neuropathic factors like small fiber neuropathy and muscle weakness may contribute to the pain in GBS [6,7].

Since anti-GQ1b antibody syndrome have common pathophysiology with GBS, which is the autoimmune response generating antibodies that cross-react with ganglioside at nerve [8] pain or headache in anti-GQ1b antibody syndrome may be originated from the affected nerve and around structures. The GQ1b is broadly expressed in some cranial nerves including the trigeminal nerve [9]. Also, the GD3 and GD1b are major gangliosides of all cranial nerves along with the ventral and dorsal roots of the spinal cord [9]. Thus, demyelination of the cervical and cranial sensory nerves by anti-ganglioside antibodies may serve to activation of the trigeminovascular pain pathway within migraine pathophysiology, causing severe headache [10].

Otherwise, the direct involvements to the central trigeminovascular system by ganglioside antibodies may contribute to severe headache. Ganglioside GQ1b may be expressed in reticular formation in the brainstem, so various neurological symptoms like impaired consciousness or hyperreflexia can arise in BBE [2]. In rats, locus coeruleus and near structures in pons have GM1, GD1a, GD1b, and GT1b with diverse distribution [11]. Because these structures are the passage of trigeminovascular system, severe headache may be associated with direct inflammation on the central structures.

중심 단어: 항GQ1b 항체 증후군, 두통, 밀러 피셔 증후군

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was

reported.

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