

Original Research

Anti-GQ1b Antibody Syndrome with Visual Impairment: A Retrospective Case Series

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Abstract

Background: Anti-GQ1b antibody syndrome referred to a clinical spectrum characterized by acute onset of ataxia, ophthalmoplegia and areflexia, while visual deterioration was rarely reported in terms of ocular disorders. This study aimed to describe the clinical characteristics of anti-GQ1b antibody syndrome with visual impairment. **Methods:** The database at the First Affiliated Hospital of Sun Yat-sen University was searched from 2014 to 2020. Patients with anti-GQ1b IgG were identified and divided into two groups according to the existence of optic neuropathy. Clinical and laboratory data of these subjects between the two groups were collected and analyzed. All patients were followed up by telephone to assess the outcome. **Results:** A total of 12 patients with seropositive anti-GQ1b antibody were included, 75% of which got antecedent infection. Of these cases, 3 showed visual deterioration accompanied by abnormal orbital magnetic resonance imaging or visual evoked potentials, and the other 9 didn't show any evidence of vision impairment. Patients in the optic neuropathy group presented prominent visual impairments as initial symptoms and were more likely to suffer from facial weakness. There were 4 patients in normal visual acuity group complaining of blurred vision due to intraocular muscle paralysis, which was distinguished by subsequent examination. The combination of glucocorticoids and intravenous immunoglobulin was applied to treat patients with optic neuropathy. **Conclusions:** This study provides strong evidence that anti-GQ1b antibody syndrome can exhibit visual impairment, which helps further expand the clinical spectrum of anti-GQ1b antibody syndrome. More attention should be paid to the physical and supplementary ophthalmological examination to explore the pathogenesis and treatment of anti-GQ1b antibody syndrome.

Keywords: GQ1b ganglioside; Miller Fisher syndrome; Guillain-Barré syndrome; vision disorders; optic neuritis

1. Introduction

Anti-GQ1b antibody is frequently detected in sera of patients with Miller Fisher syndrome (MFS), Bickerstaff's brainstem encephalitis (BBE), Guillain-Barré syndrome (GBS) with ophthalmoplegia, and acute ophthalmoparesis (AO) in the acute phase [1]. Since Chiba *et al.* [2] first reported the specific appearance of anti-GQ1b IgG in Miller Fisher syndrome, the significant association between anti-GQ1b IgG and illnesses with ophthalmoplegia and ataxia has been substantiated and extended in subsequent studies [3]. To gain a better understanding of the etiological relation among the various illnesses with seropositive anti-GQ1b antibody, Odaka *et al.* [4] introduced the term "Anti-GQ1b antibody syndrome", referring to a continuous autoimmune disease spectrum mainly characterized by acute onset of ataxia, ophthalmoplegia and areflexia following an antecedent infection. Surrounding this established spectrum, previous studies focused on ophthalmoplegia in terms of ocular disorders, whereas optic neuritis

was rarely reported despite high concentrations of GQ1b ganglioside found in optic nerves [5].

In this study, we summarized 12 cases of anti-GQ1b antibody syndrome, among which 3 presented with prominent visual deterioration. Furthermore, we determined the detailed clinical features of these 3 subjects with optic neuropathy, and compared them with the other 9 patients without optic neuropathy as well as other cases from literatures for further understanding of the diagnostic, therapeutic and prognostic implications of anti-GQ1b antibody syndrome.

2. Methods

2.1 Patients and Diagnostic Criteria

We searched the database at the First Affiliated Hospital of Sun Yat-sen University (Guangdong, China) between 2014 and 2020 and identified 12 patients diagnosed with anti-GQ1b antibody syndrome. This retrospective research complies with the principles of the Declaration of Helsinki and received approval from the local clinical trial commit-



tee of the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. All the patient information was de-identified so that the identity of the patients may not be ascertained in any way.

In addition to positive anti-GQ1b antibody, the diagnosis of the clinical entities within the anti-GQ1b antibody syndrome were based on the criteria established by Wakerley *et al.* [6]. The features of GBS spectrum disorders were mainly characterized by a symmetric pattern of limb and/or motor cranial-nerve weakness. Specifically, the criteria for MFS included relatively symmetric ophthalmoplegia, ataxia and areflexia/hyporeflexia in the course of diseases, as well as absence of limb weakness or hypersomnolence. The criteria for BBE included hypersomnolence, ophthalmoplegia and ataxia, with a normal limb strength. In some cases, prominent limb weakness as well as ophthalmoplegia and ataxia were considered as overlapping MFS and GBS (MFS/GBS), or overlapping BBE and GBS (BBE/GBS) when hypersomnolence were accompanied. On entry to the study, patients did not have toxic exposure, malnutrition or vitamin B deficiency, or mitochondrial diseases. Moreover, patients were classified into the optic neuropathy group if the best-corrected visual acuity (BCVA) on the Standard Logarithmic visual acuity chart was 0.6 or worse. The use of BCVA eliminated decreased vision due to refractive error [7].

2.2 Dot Immunoassay Method

The profiles of anti-ganglioside IgG and IgM autoantibodies against GM1, GM3, GD1a, GT1a and GQ1b gangliosides were tested semi-quantitatively using a commercial kit (Generic Assays, Germany). Briefly, patients' sera as well as positive and negative control sera were acquired and added to the wells with buffer solution. The samples were then incubated with autoantibodies to the gangliosides immobilized on the membrane at 4 °C for 120 minutes. Unbound serum samples were removed by several wash steps followed by an anti-human secondary antibody. The substrate 3,3',5,5'-Tetramethylbenzidine (TMB) was subsequently pipetted and incubated for 10 minutes at room temperature (18–25 °C). After drying for 30 minutes, the strips were read using a DotDiver2.0 device (Generic Assays, Germany). Positive response was considered if the coloration of the test line could be discriminated from the background [8].

2.3 Data Collection

Cases of anti-GQ1b antibody syndrome were divided into two groups according to the existence of optic neuropathy. We reviewed medical records of each patient and recorded age, gender, antecedent infections at presentation, neurological signs during the course of disease, treatment, and follow-up results. We assessed the following signs: visual impairment, internal or external ophthalmoplegia, facial weakness, bulbar palsy, limb weakness,

truncal or limb ataxia, superficial sense impairment, deep tendon reflexes (brisk, normal, decreased, or absent) and Babinski's sign. The paraclinical characteristics included cerebrospinal fluid anomalies, electrophysiological parameters, orbital magnetic resonance imaging (MRI) and visual evoked potentials (VEPs). Albumino-cytological dissociation in the cerebrospinal fluid (CSF) was defined as a normal white cell count ($<5 \times 10^6/L$) with an elevated protein level (>450 mg/L, normal values 150–450 mg/L) [9].

2.4 Statistical Analysis

Analysis was performed with SPSS statistics version 26.0 (IBM Corp., Armonk, NY, USA). As the total sample size ($n = 12$) was less than 40 and the distribution was unclear, numerical variables were analyzed using Wilcoxon rank sum test and the p values were obtained by consulting the rank sum test T-bound table (two-tailed). Differences in proportions were tested by Fisher's exact test (two-tailed). A p value < 0.05 was used for significance in all comparisons.

3. Results

3.1 Characteristics of Patients with or without Optic Neuropathy

Twelve patients (5 males and 7 females) with positive anti-GQ1b antibodies were identified. Age at onset was 12 to 63, and the median age was 45. Out of 12 patients, 3 (1 male and 2 females) presenting optic neuropathy with noticeable visual deterioration, were assigned to the ocular neuropathy (ON) group. The age at presentation ranged from 42 to 63. The normal visual acuity (NVA) group included 4 males and 5 females with the median age of 48 (ranging from 12 to 60). One patient in the ON group were diagnosed with GBS, 1 with MFS/GBS, and 1 with MFS. In the NVA group, 5 were diagnosed with MFS/GBS, 2 with GBS, 1 with BBE/GBS, and 1 with MFS. All cases had acute onset.

The clinical and paraclinical characteristics of all enrolled patients were summarized (Table 1, **Supplementary Fig. 1**). Antecedent infections occurred in 9 patients (75%), including upper respiratory tract infections and gastroenteritis. All patients in the ON group presented with visual impairments as their initial symptoms, and 4 in the NVA group also complained of blurring vision due to intraocular muscle paralysis. No signs of pain in eye movement, color desaturation or field deficits were observed in the ON group. Extraocular muscle paralysis was presented in 11 (3 in the ON group and 8 in the NVA group). A higher proportion of facial weakness was presented in the ON group than in the NVA group (100% and 22% respectively, $p = 0.045$, 2-sided). No statistical significance was found in terms of other cranial nerve impairments, including extraocular muscle paralysis (100% and 88.9%, $p > 1.000$), intraocular muscle paralysis (0 and 44.4%, $p = 0.491$) as well as bulbar palsy (66.7% for both group, $p > 1.000$). As for limb

symptoms, the differences in the ratio of ataxia, sensory and motor disturbance, and areflexia/hyporeflexia were not statistically significant between the two groups. Cerebrospinal fluid analysis showed albumin-cytological dissociation in 10 patients. Two patients in the NVA group didn't present with albumin-cytological dissociation, which may be the result that lumbar punctures were undergone too early (within one week) after onset. The main features of the nerve-conduction study (NCS) were also summarized in the table. None of the 12 patients got signs of brainstem or cerebellar abnormalities by cranial MRI or Computed tomography (CT) scanning.

On admission, 11 cases were administered with intravenous immunoglobulin at 0.4 g/kg/d for five days except for 1 in the NVA group. Ten cases except for 2 in the NVA group received glucocorticoids from 1 week to 1 month. All patients received vitamin B treatment. In the ON group, recovery occurred within a mean period of 2.3 months. In the NVA group, one diagnosed with BBE/GBS experienced altered consciousness and made a slow recovery (up to 14 months), which was considered as an outlier and was removed. Thus, the average period of recovery in the NVA group was 2.2 months. The statistical analysis showed that the recovery time of the two groups was not significantly different (**Supplementary Fig. 2**). As for prognosis, all patients were followed up from 2 months to 6 years after discharge. Eleven patients made full recoveries, and the other one in the NVA group had mild numbness and weakness in the distal limbs. It was noteworthy that the visual impairments of patients in the ON group recovered much later than other symptoms (Table 2).

3.2 Case Series of Patients with Optic Neuropathy

3.2.1 Case 1

A 42-year-old, previously healthy woman presented with visual deterioration, doubling vision, and limb numbness, and was admitted to our hospital. A month before admission, she experienced cough, expectoration, and sore throat. Four days after the resolution of her illness, she had an acute onset of progressive dizziness, blurring vision, and numbness in distal extremities. In the following 5 days, her symptoms were aggravated significantly, and developed binocular diplopia accompanied by ptosis on the right side, numbness and weakness on the right-sided face, speech difficulty, excessive coughing during drinking, limb weakness and gait disturbance. Most of the symptoms were alleviated after immunoglobulin therapy. At admission, a visual examination revealed bilateral loss of BCVA, with 0.4 for both eyes, accompanied by slightly sluggish response of papillary light reflex. She presented limitation of bilateral ocular movement in the lateral gaze, numbness on the right face and bilateral middle fingertips and toes. Tendon reflex was hyperactive. Positive Babinski sign and Oppenheim sign on the right were observed.

The patient's white blood cell (WBC) and erythro-

cyte sedimentation rate (ESR) were both slightly increased (respectively $10.14 \times 10^9/L$ and 68 mm/h). Anti-GQ1b and anti-GT1a were reported seropositive (Table 2). CSF analysis (5 weeks after onset) showed that the protein was 628.9 mg/L, and the CSF white cell count was $3 \times 10^6/L$, indicating mild albumin-cytological dissociation. Aquaporin4 (AQP4) and Oligoclonal bands of CSF were negative. The orbital MRI revealed significant enhancement of bilateral optic nerves and sheaths (Fig. 1). The VEPs test, somatosensory evoked potentials (SEPs) and electromyogram were normal (Fig. 2). The vitreous and fundi were normal bilaterally.

She was treated with intravenous methylprednisolone (320 mg/d) for 3 days, which was reduced to oral prednisolone. The patient was discharged on the 7th hospital day, when her BCVA restored to 0.6, accompanied with minor abduction difficulties of both eyes. The clinical follow-up revealed that her visual impairment lasted longer than other symptoms and took 2.5 months to a complete recovery.

3.2.2 Case 2

A 42-year-old man was admitted to our hospital for limb numbness and vision loss. Six days before admission, he had an acute onset of limb numbness and blurring vision without antecedent infection, after which his numbness worsened and he developed dysarthria, diplopia, excessive coughing during drinking and dysphagia. An optical examination revealed bilateral loss of BCVA, with 0.3 for both eyes. Neurological examination showed limitation of ocular movement in the lateral gaze of both eyes, facial weakness on the right, poor lifting of the soft palate and tongue deviation to the left. The tendon reflexes disappeared. There was no ptosis, pupil dilation, limb weakness, or pathological signs. The anti-GQ1b and anti-GT1a antibodies were reported seropositive. CSF analysis revealed albumin-cytological dissociation, with the protein of 1261.1 mg/L and the CSF white cell count of 1×10^6 cells/L. MRI showed no abnormalities in the orbits or brain. His VEPs revealed low amplitude of bilateral P100 potentials (Fig. 3). Nerve conduction study (NCS) detected sensory impairment in the right upper extremity.

The patient was treated with immunoglobulin therapy (22.5 g/d in the first 2 days and 20 g/d in the following 3 days), after which dexamethasone immune-modulating therapy (10 mg/d, once daily) was administrated for 12 days and then was switched to oral methylprednisolone (20 mg/d, once daily). He was discharged after 21 in-hospital days, when limb numbness had been improved markedly, whereas the visual acuity, diplopia, facial weakness and finger-to-nose test hadn't yet restored to normal. In the telephone follow-up, the patient's visual impairment took two months to heal while other symptoms had an earlier recovery.

Table 1. Clinical and paraclinical characteristics of 12 cases of anti-GQ1b antibody syndrome with or without visual impairment.

| | ON | NVA |
|--|----------------------|----------------------|
| Number of patients | 3 | 9 |
| Gender (male/female) | 1/2 | 4/5 |
| Median age (range) | 42 (42–63) | 48 (12–60) |
| Antecedent illness | | |
| upper respiratory infection | 2 | 6 |
| Gastrointestinal infection | 0 | 1 |
| Neurological symptoms | | |
| Visual impairment | 3 | 0 |
| Extraocular muscle paralysis | 3 | 8 |
| Diplopia | 3 | 7 |
| Ptosis | 2 | 3 |
| Intraocular muscle paralysis (Pupil dilation and photophobia) | 0 | 4 |
| Other cranial nerve impairment | 3 | 6 |
| facial weakness* | 3 | 2 |
| bulbar palsy | 2 | 6 |
| Limb weakness | 2 | 8 |
| Cerebellar ataxia | 3 | 6 |
| Sensory disturbance | 3 | 7 |
| Tendon reflex (diminution or loss) | 2 | 9 |
| Tendon reflex (active or hyperactive) | 1 | 0 |
| Babinski sign (positive) | 1 | 3 |
| CSF alterations | | |
| Albumino-cytologic dissociation | 3 | 7 ¹ |
| Mean protein level: mg/L (range) | 918.7 (628.9–1261.1) | 996.3 (180.0–1680.0) |
| NCS features | | |
| Prolonged DML | 1 | 1 |
| Reduced CV | 2 | 7 |
| Decreased amplitude | 1 | 5 |
| Abnormal F wave (decreased occurrence or prolonged mean latency) | 0 | 5 |
| Conduction blocks | 0 | 0 |
| Temporal dispersion | 0 | 0 |
| Treatment and outcome | | |
| Intravenous immunoglobulins | 3 | 8 |
| Plasma exchange | 0 | 1 |
| B vitamins | 3 | 9 |
| Steroids | 3 | 7 |
| Mean time between onset and recovery (months) | 2.3 | 2.2 ² |

ON, optic neuropathies; NVA, Normal visual acuity; DML, distal motor latency; CV, conduction velocity; CSF, cerebrospinal fluid; NCS, nerve-conduction study. *100% and 22% respectively, $p = 0.045$, 2-sided. ¹ Two patients undergoing lumbar puncture within one week of onset didn't show Albumino-cytologic dissociation; ² One patient recovered at the 14th month was removed as an outlier. The mean time was 3.5 months in the case of inclusion.

3.2.3 Case 3

A 63-year-old woman was referred to our hospital for bilateral ptosis, diplopia, vision impairment, and limb weakness. A month before the admission, the patient had coughing and expectoration. Two weeks after the resolution, she had an acute onset of bilateral ptosis, doubling and blurring of vision, as well as numbness of bilateral fingertips, numbness and weakness of lower limbs. She was

sent to a local hospital and diagnosed with cerebral infarction until the CSF examination reported the pressure of 120 mmH₂O and the protein level of 1195.2 mg/L. She was treated with intravenous methylprednisolone (1000 mg/d, once daily) followed by IVIg treatment (20 g/d, once daily) for 5 days, which didn't significantly ease her symptoms. On day 16, she was transferred to our hospital. Optical examination indicated bilateral impairment of visual acuity,

Table 2. Clinical and paraclinical characteristics of 3 cases of anti-GQ1b antibody syndrome with ON.

| Patient No. | ON1 | ON2 | ON3 |
|-----------------------------------|---|--|---|
| Age/gender | 42/F | 42/M | 63/F |
| Initial Symptom(s) | Visual impairment, Dizziness, Paresthesia in extremities | Visual impairment, Paresthesia in both hands | Visual impairment, Paresthesia in bilateral fingers, Diplopia |
| Neurological symptoms | | | |
| Visual impairment | Bilateral | Bilateral | Bilateral |
| Ocular muscle paralysis | Bilateral | Bilateral | Bilateral |
| Facial weakness | Right | Right | Right |
| Bulbar palsy | Dysphagia | Dysphagia, Nasal voice | No |
| Ataxia | Bilateral | Bilateral | Bilateral |
| Paresthesia | Both hands and feet | Both hands and feet | Both hands and feet |
| Tendon reflex | Brisk | Absent | Absent |
| Best-corrected visual acuity | | | |
| Admission | L = R = 0.4 | L = R = 0.3 | L = 0.25, R = 0.5 |
| Discharge | L = R = 0.6 | / | / |
| MRI (magnetic resonance imaging) | | | |
| orbital | Abnormal | Normal | Normal |
| cranial | Normal | Normal | Normal |
| spinal cord | Normal | / | / |
| VEP (visual evoked potential) | | | |
| Latency (ms) ¹ | L = 103 | L = 113 | L = 100.3 |
| | R = 108 | R = 113.8 | R = 103 |
| Amplitude (μ V) ² | L = 5.2 | L = 1.56 | L = 2.64 |
| | R = 3.7 | R = 2.43 | R = 1.8 |
| Anti-ganglioside IgG | anti-GQ1b IgG, anti-GT1a IgG | anti-GQ1b IgG, anti-GT1a IgG | anti-GQ1b IgG |
| AQP4 | Negative | Negative | / |
| Classification | GBS | MFS | MFS/GBS |
| Treatment | IVIg, steroids | IVIg, steroids | IVIg, steroids |
| Outcome ³ | bulbar palsy, ataxia, sensory disturbance, bulbar palsy, sensory disturbance, limb weakness, diplopia, sensory diplopia, vision (2.5 months) ⁴ | | |

ON, optic neuropathies; AQP4, Aquaporin4; F, female; M, male; L, left; R, right; GBS, Guillain-Barré syndrome; MFS, Miller Fisher syndrome. ¹ The upper limit of latency is 114 ms; ² The lower limit of amplitude is 3 μ V; ³ Recovery sequences of main symptoms; ⁴ The complete recovery time.

with 0.25 for the left eye and 0.5 for the right. Restriction of ocular movement and minor right-sided facial weakness were observed. Tendon reflex of four limbs disappeared. Prostigmine test result was negative. Anti-GQ1b antibody was seropositive. CSF protein was 866 mg/L, without WBCs. The level of complement 3 and 4 decreased (respectively 0.76 g/L and 0.12 g/L). Nerve conduction study showed mildly slow conductive velocity of the right median sensory nerve, while the F-wave latency was within the normal range. VEPs revealed low amplitudes of bilateral P100 potentials (Fig. 4).

The patient was started on intravenous methylprednisolone treatment (500 mg/d) and then changed to oral prednisolone. Her visual impairment as well as motor and sensory disturbance of extremities had improved markedly in the following two weeks.

4. Discussion

4.1 GQ1b Antibody and Optic Neuropathies

Gangliosides, a kind of structurally distinct membrane glycolipids which is abundant in the nervous system, can modulate a wide variety of neuronal functions and act as bacterial toxin receptors as well as the target for autoantibodies [10,11]. Infection with some Gram-negative bacteria such as *Campylobacter jejuni* and *Haemophilus influenzae* that bears GQ1b-like lipopolysaccharides may trigger the production of anti-GQ1b antibody due to molecular mimicry. The autoantibody can bind to the brain and nerve sections rich in GQ1b gangliosides, leading to a series of clinical manifestations [12,13]. It has been reported that GQ1b gangliosides are abundant in the optic nerve only second to cranial nerves innervating extraocular muscles [14–16]. However, the accumulation of anti-GQ1b epitope was

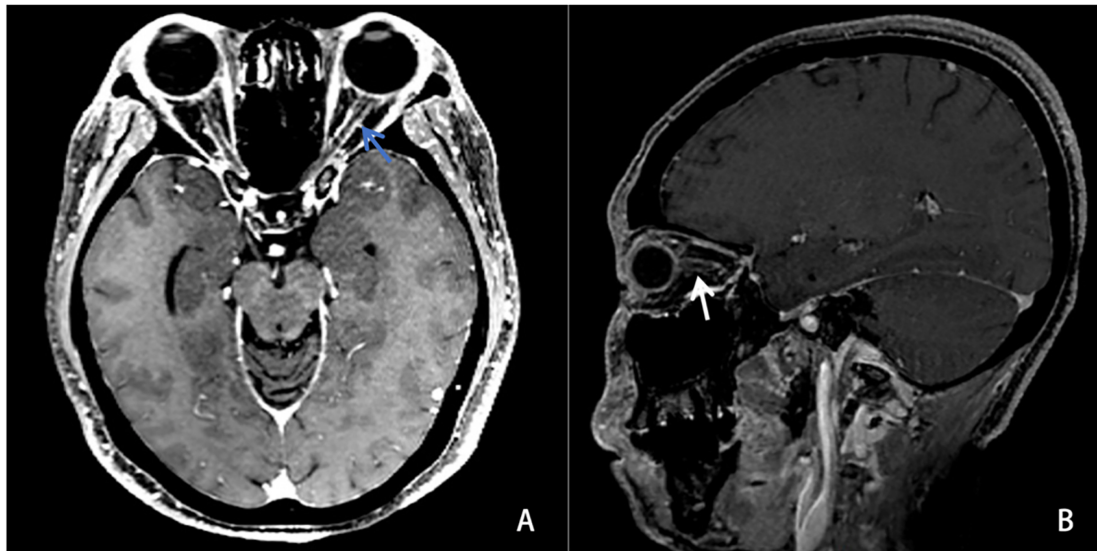


Fig. 1. Orbital MRI of Case 1 in ON group. (A) Axial T1-enhanced image. The blue arrow indicates significant enhancement of bilateral optic nerves and sheaths. (B) Sagittal T1-enhanced image of the same patient. The white arrow indicates enhancement of right optic nerves and sheaths.

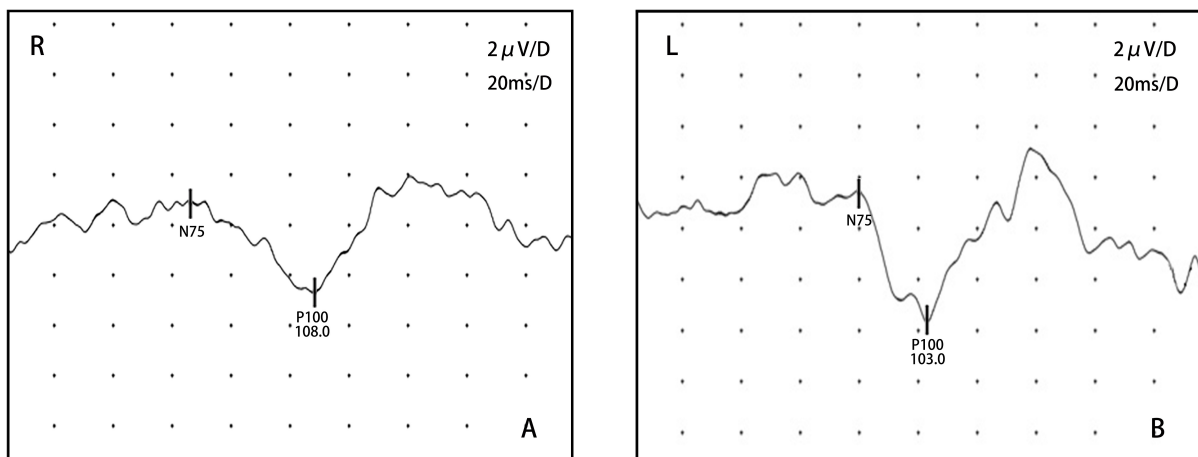


Fig. 2. Visual evoked potentials (VEPs) of Case 1 in ON group. VEPs showed normal latency and amplitudes of bilateral P100 potentials. (A) The latency of the right eye was 108.0 ms, amplitude of P100 was 3.7 μ V (The upper limit of latency is 114 ms and the lower limit of amplitude is 3 μ V). (B) The latency of the left eye was 103.0 ms, amplitude of P100 was 5.2 μ V. 2 μ V/D: Each vertical division is 2 μ V. 20 ms/D: Each horizontal division is 20 ms. μ V, microvolt; ms, millisecond; D, division.

only observed in the paranodal regions of extramedullary portion of the IIIrd, IVth, and VIth cranial nerve, which was also the main attack site of anti-GQ1b antibody [17]. The damage to the regions blocks impulse generation at the node of Ranvier. The optic nerve, whose myelin is composed of oligodendrocytes, might lack the binding site like the paranodal regions, accounting for a low incidence of optic neuropathy in anti-GQ1b antibody syndrome. Moreover, the blood-brain barrier (BBB) might prevent these autoantibodies from entering the intracranial space and binding to the

corresponding antigen. To date, the underlying mechanism in the anti-GQ1b antibody positive patients with visual impairment remains unclear. Seito *et al.* [18] showed that the sera of BBE patients with positive anti-GQ1b antibody can disrupt BBB via inducing the secretion of matrix metalloproteinase. There have also been reported abnormalities in cerebellar MRI of MFS patients [19]. Moreover, it is well-established that different subclasses of anti-GQ1b IgG and IgM may lead to various clinical spectrum [20]. Thus, we speculate that in some specific cases, disruption

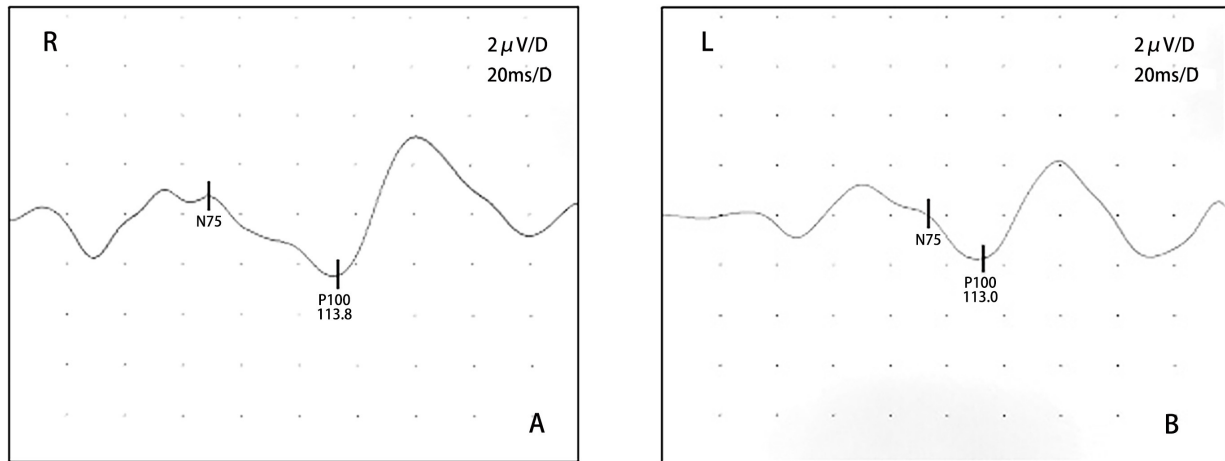


Fig. 3. Visual evoked potentials (VEPs) of Case 2 in ON group. VEPs showed lower amplitudes of bilateral P100 potentials. (A) The latency of the right eye was 113.8 ms, amplitude of P100 was 2.43 μ V. (B) The latency of the left eye was 113.0 ms, amplitude of P100 was 1.56 μ V. 2 μ V/D: Each vertical division is 2 μ V. 20 ms/D: Each horizontal division is 20 ms. μ V, microvolt; ms, millisecond; D, division.

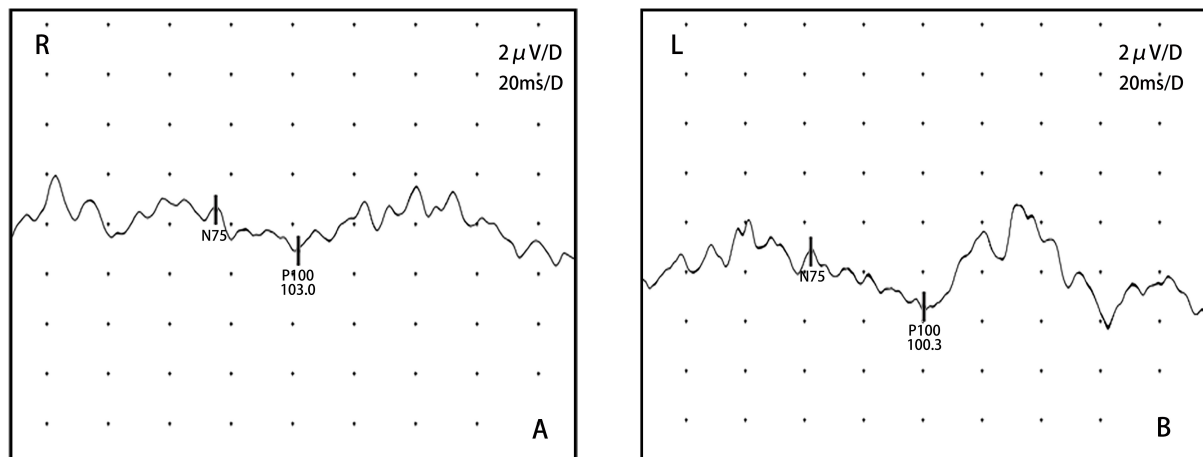


Fig. 4. Visual evoked potentials (VEPs) of Case 3 in ON group. VEPs showed low amplitudes of bilateral P100 potentials. (A) The latency of the right eye was 103 ms, amplitude of P100 was 1.8 μ V. (B) The latency of the left eye was 100.3 ms, amplitude of P100 was 2.64 μ V. 2 μ V/D: Each vertical division is 2 μ V. 20 ms/D: Each horizontal division is 20 ms. μ V, microvolt; ms, millisecond; D, division.

of the BBB barrier may occur, while the undefined subtypes of GQ1b antibodies simultaneously enter the central nerve system and attack optic nerve. A comprehensive examination of anti-GQ1b antibody in CSF and a serological test for pathogens in antecedent infections should be emphasized.

4.2 Clinical Symptoms and Examinations

Odaka *et al.* [4] reported that a high proportion of patients (94%) had a history of early infection, of which 75%

were respiratory tract infections and 9% were gastrointestinal infections. In our study, we also noted antecedent infections in 9 patients (75%), with respiratory infections in 8 cases and gastrointestinal infection in 1 case. The proportion was slightly lower than that reported in the literature. In terms of clinical manifestations of our study, once the optic nerve was involved, visual deterioration tended to present as an initial symptom and lasted longer than other clinical disorders, suggesting that the damage of GQ1b antibody

Table 3. Reported cases describing the clinical features of GQ1b antibody syndrome with visual impairment.

| case | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|--------------------|----------------------------------|---------------|--------------------------------------|--------------------------|---------------------------|--------|---------------|--------------|
| sex/age | 73/M | 72/F | 43/F | 23/F | 81/F | 33/M | 31/M | 57/F |
| antecedent illness | GI | RTI | RTI | ND | NI | PI | GI | RTI |
| diagnosis | GBS | BBE | GBS | MFS | MFS | / | MFS/GBS | MFS |
| visual impairment | bilateral | bilateral | bilateral | left | right | right | right | bilateral |
| ophthalmo-plegia | + | + | + | + | + | + | - | + |
| cerebellar ataxia | - | + | - | + | + | - | + | + |
| tendon reflex | hyporeflexia | hyperreflexia | normal | absent | normal | normal | hypoactive | hypoactive |
| bulbar palsy | - | - | + | ND | ND | - | + | + |
| facial weakness | bilateral | - | - | ND | ND | - | + | + |
| visual acuity | R = 0.6; L = 0.3 ¹ | ND | R = 20/30; L = 20/25 ² | R = 20/20; L = 20/200 | R = 20/100; L = 20/400 | ND | R = L = 20/20 | R = L = 6/24 |
| VEP | ND | abnormal | abnormal | abnormal | ND | ND | ND | ND |
| outcome | CR | CR | NCR | CR | CR | NCR | CR | CR |
| reference | [21] | [22] | [23] | [24] | [25] | [26] | [27] | [28] |

M, male; F, female; GI, gastrointestinal infection; RTI, respiratory tract infections; ND, not documented; NI, no infection; PI, pulmonary infection; R, right; L, left; CR, complete recovery; NCR, near complete recovery (extremity numbness; limb weakness; central scotoma). ¹ Measured using standard logarithmic visual acuity chart; ² Measured using the Snellen eye chart.

to optic nerve be rapid and last longer than other nerves. Moreover, the incidence of facial weakness in the ON group was higher than that in the NVA group ($p = 0.045$), suggesting a higher probability of facial nerve damage for patients with visual impairment.

To better understand the clinical characteristics of patients with visual impairment in anti-GQ1b antibody syndrome, we summarized the clinical features of 8 patients reported in literature (Table 3) [21–28]. Out of all 11 cases, 7 cases showed bilateral visual impairment, indicating that the anti-GQ1b antibody often attack bilateral optic nerves. Consistent to our study, most patients had visual impairment as initial symptoms. In addition, 2 patients presented with hyperreflexia, which may be attributed to damage to the pyramidal tract.

The results of lumbar puncture suggested that 10 patients (3 in the ON group and 7 in the NVA group) showed albumin-cytological dissociation in CSF, which followed the characteristics of CSF in GBS [4]. Moreover, Nobuhiro *et al.* [29], reported that 50–66% of GBS patients presented with an elevated protein level but normal cell count within the first week or over 75% within the third week after the symptom onset. Our data indicated that the occurrence of albumin-cytological dissociation in the anti-GQ1b antibody syndrome followed a similar time course as in GBS.

4.3 Other Disorders Related to Vision Disturbance

Lee *et al.* [30] showed that 54.5% of patients with acute ophthalmoplegia and seral anti-GQ1b antibody also presented intraocular muscle paralysis. In our study, 4 patients in the NVA group had different degrees of unilateral/bilateral pupil dilatation. Interestingly, they also complained of blurring vision as their initial symptoms, which may mislead to the diagnosis of optic neuritis. We noticed

that these patients mainly presented with deterioration of near vision accompanied by photophobia due to the dilation of pupils. Moreover, the visual acuity of the patients could be improved after correction, similar to the manifestation of ametropia. The characteristics above can serve as evidence to distinguish from optic neuropathy. It was hypothesized that anti-GQ1b antibody binding to the intraocular neuromuscular junction led to a massive release of acetylcholine, resulting in immunopathologic involvement of the ciliary ganglion and super sensitivity of the iris sphincter muscles due to denervation, which eventually caused the destruction of the motor nerve terminal structure and thus the pupil dilatation [31,32].

Besides, the manifestation of vision loss and optic neuritis in the ON group should be differentiated from neuromyelitis optica, multiple sclerosis or MOG spectrum disorders. All 3 patients presented with symmetrical glove-sock hypoesthesia or symmetrical limb weakness, without observed lesions in the spinal cord or in the brain by MR scanning. Meanwhile, neither AQP4 nor oligoclonal band was found in serum or cerebrospinal fluid. In terms of MOG spectrum disorders, the anti-MOG antibody was negatively detected in 1 patient. There was no detection for this antibody in the other 2 patients due to unavailability in the earlier years. Furthermore, none of the cases in the ON group had signs of encephalitis or CNS demyelination, either any indication of relapses in our follow-up. Therefore, the diagnosis of neuromyelitis optica, multiple sclerosis or MOG spectrum disorders was not supported in the enrolled cases.

4.4 Treatment

Given the autoimmunity of GBS, immunoglobulin therapy is considered effective. The mechanisms mainly attributed to its ability to provide specific antibodies, block

Fc receptors on macrophages, inhibit complement activities, and regulate B cell and T cell functions [33]. The published data suggested that oral and intravenous administration of glucocorticoids have no benefit, even a combination of IVIg and glucocorticoids is not more effective than IVIg alone [34,35]. Eleven cases in our study were treated with intravenous immunoglobulins except for 1 case, who was initially diagnosed with encephalitis and close to complete recovery at the time of GBS diagnosis. Significantly, visual acuity of patient 1 in the ON group had no improvement after receiving immunoglobulin. According to the Optic Neuritis Treatment Trial (ONTT) [36], high-dose corticosteroids administered intravenously was the standard therapy for optic neuritis. Therefore, methylprednisolone was given intravenously to the patients with optic neuropathy. The usage of glucocorticoids in treating GQ1b antibody syndrome with visual impairment has also been reported elsewhere, suggesting an individualized therapy should be considered for this kind of patients [21,23,26].

4.5 Limitations

There are some limitations in our study: (1) As anti-GQ1b antibody syndrome with visual impairment is extremely rare, and only a few cases have been reported by far, we have collected 3 eligible patients. The difference between the ON and NVA groups was difficult to draw a statistically significant conclusion, and the sampling error was large due to the small number of sample cases. Therefore, we summarized the clinical features of the other 8 patients reported in literature and made a discussion together with our cases to illustrate a more comprehensive clinical spectrum. (2) No examination of anti-GQ1b antibody in CSF and no serological tests for pathogens in antecedent infections was performed in our patients. Although these examinations were not taken as routine items in the past, our study suggested that they serve as significant evidence for uncovering the mechanisms of vision impairment in anti-GQ1b antibody syndrome.

5. Conclusions

In this case series, we concluded the clinical features of anti-GQ1b antibody syndrome by listing clinical manifestations and examination results of 12 patients with or without visual impairment. Visual deterioration tended to present as the initial symptoms and lasted longer than other neurological dysfunction in the clinical course. Compared with patients without visual deterioration, those with vision loss might be accompanied by facial weakness more frequently, which expects a larger sample to draw a more specific conclusion. Attention should also be paid to distinguish optic neuritis from cases complaining of blurring vision due to intraocular muscle paralysis. In addition, the treatment of glucocorticoids combined with intravenous immunoglobulin on patients with optic neuropathy was applied in our cases. Whether the treatment of such diseases

can draw on the treatment scheme of optic neuritis needs to be further investigated by more clinical practice. Generally, the specific pathogenesis of optic neuropathy in anti-GQ1b antibody syndrome remains unclear. Examination of anti-GQ1b antibody in CSF, serological tests for pathogens, the subtype of antibody and epitope of antigens in optic nerve might be helpful to reveal the mechanisms.

Author Contributions

All authors contributed to the study conception and design. JL and SXF collected the data and wrote part of the manuscript. QZ was a major contributor in writing and revising the manuscript. PYX and YFZ checked and analyzed the data. SJL commented on previous versions of the manuscript as well as supervised and mentored over the study. CZ was also a supervisor and mentor of this study. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

We have acquired ethics approval for this study from the Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University. The approval number was [2021]369. Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2103081>.

References

- [1] Susuki K, Yuki N, Hirata K. Fine specificity of anti-GQ1b IgG and clinical features. *Journal of the Neurological Sciences*. 2001; 185: 5–9.
- [2] Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. *Annals of Neurology*. 1992; 31: 677–679.
- [3] Kusunoki S, Hitoshi S, Kaida K, Arita M, Kanazawa I. Monospecific anti-GD1b IgG is required to induce rabbit ataxic neuropathy. *Annals of Neurology*. 1999; 45: 400–403.
- [4] Odaka M. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. *Journal of Neurology, Neurosurgery & Psychiatry*. 2001; 70: 50–55.
- [5] Saul RF. Neuro-ophthalmology and the anti-GQ1b antibody syndromes. *Current Neurology and Neuroscience Reports*. 2009; 9: 379–383.
- [6] Wakerley BR, Uncini A, Yuki N. Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. *Nature Reviews Neurology*. 2014; 10: 537–544.
- [7] Morrow SA, Fraser JA, Day C, Bowman D, Rosehart H, Kremenchtzky M, *et al*. Effect of Treating Acute Optic Neuritis with Bioequivalent Oral vs Intravenous Corticosteroids: A Randomized Clinical Trial. *JAMA Neurology*. 2018; 75: 690.
- [8] Conrad K, Schneider H, Ziemssen T, Talaska T, Reinhold D, Humbel R, *et al*. A new line immunoassay for the multiparametric detection of antiganglioside autoantibodies in patients with autoimmune peripheral neuropathies. *Annals of the New York Academy of Sciences*. 2007; 1109: 256–264.
- [9] de Bruyn A, Poesen K, Bossuyt X, Heremans IP, Claeys T, Depuydt CE, *et al*. Clinical spectrum of the anti-GQ1b antibody syndrome: a case series of eight patients. *Acta Neurologica Belgica*. 2019; 119: 29–36.
- [10] Willison HJ, O’Hanlon G, Paterson G, O’Leary CP, Veitch J, Wilson G, *et al*. Mechanisms of action of anti-GM1 and anti-GQ1b ganglioside antibodies in Guillain-Barré syndrome. *The Journal of Infectious Diseases*. 1997; 176: S144–S149.
- [11] Tettamanti G, Riboni L. Gangliosides and modulation of the function of neural cells. *Advances in Lipid Research*. 1993; 25: 235–267.
- [12] Houlston RS, Koga M, Li J, Jarrell HC, Richards JC, Vitiazeva V, *et al*. A Haemophilus influenzae Strain Associated with Fisher Syndrome Expresses a Novel Disialylated Ganglioside Mimic. *Biochemistry*. 2007; 46: 8164–8171.
- [13] Kimoto K, Koga M, Odaka M, Hirata K, Takahashi M, Li J, *et al*. Relationship of bacterial strains to clinical syndromes of Campylobacter-associated neuropathies. *Neurology*. 2006; 67: 1837–1843.
- [14] Yoshino H, Maeda Y, King M, Cartwright MJ, Richards DW, Ariga T, *et al*. Sulfated glucuronyl glycolipids and gangliosides in the optic nerve of humans. *Neurology*. 1993; 43: 408–411.
- [15] Paparounas K. Anti-GQ1b ganglioside antibody in peripheral nervous system disorders: pathophysiologic role and clinical relevance. *Archives of Neurology*. 2004; 61: 1013–1016.
- [16] Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Ganglioside composition of the human cranial nerves, with special reference to pathophysiology of Miller Fisher syndrome. *Brain Research*. 1997; 745: 32–36.
- [17] Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology*. 1993; 43: 1911–1917.
- [18] Saito K, Shimizu F, Koga M, Sano Y, Tasaki A, Abe M, *et al*. Blood-brain barrier destruction determines Fisher/Bickerstaff clinical phenotypes: an in vitro study. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2013; 84: 756–765.
- [19] Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2013; 84: 576–583.
- [20] Lardone RD, Irazoqui FJ, Nores GA. Neurological disorders-associated anti-glycosphingolipid IgG-antibodies display differentially restricted IgG subclass distribution. *Scientific Reports*. 2020; 10: 13074.
- [21] Zhao T, Deng Y, Ding Y, Zhang R, Zhou C, Lin W. Anti-GQ1b antibody syndrome presenting with visual deterioration as the initial symptom: A case report. *Medicine*. 2020; 99: e18805.
- [22] Kurihara M, Bannai T, Otsuka J, Kawabe Matsukawa M, Terao Y, Shimizu J, *et al*. Optic neuropathy and decorticate-like posture as presenting symptoms of Bickerstaff’s brainstem encephalitis: a case report and literature review. *Clinical Neurology and Neurosurgery*. 2018; 173: 159–162.
- [23] Wen H. Acute bilateral vision deficit as the initial symptom in Guillain-Barre syndrome: a case report. *Experimental and Therapeutic Medicine*. 2018; 16: 2712–2716.
- [24] Chan JW. Optic neuritis in anti-GQ1b positive recurrent Miller Fisher syndrome. *The British Journal of Ophthalmology*. 2003; 87: 1185–1186.
- [25] Lamotte G, Laballe R, Dupuy B. Bilateral eyelid retraction, loss of vision, ophthalmoplegia: an atypical triad in anti-GQ1b syndrome. *Revue Neurologique*. 2014; 170: 469–470.
- [26] Biotti D, Boucher S, Ong E, Tilikete C, Vighetto A. Optic neuritis as a possible phenotype of anti-GQ1b/GT1a antibody syndrome. *Journal of Neurology*. 2013; 260: 2890–2891.
- [27] Robbins MS, Roth S, Swerdlow ML, Bieri P, Herskovitz S. Optic neuritis and palatal dysarthria as presenting features of post-infectious GQ1b antibody syndrome. *Clinical Neurology and Neurosurgery*. 2009; 111: 465–466.
- [28] Colding-Jørgensen E, Vissing J. Visual impairment in anti-GQ1b positive Miller Fisher syndrome. *Acta Neurologica Scandinavica*. 2001; 103: 259–260.
- [29] Yuki N, Hartung HP. Guillain-Barré syndrome. *The New England Journal of Medicine*. 2012; 366: 2294–2304.
- [30] Lee S, Lim G, Kim JS, Oh S, Kim JK, Cha J, *et al*. Acute ophthalmoplegia (without ataxia) associated with anti-GQ1b antibody. *Neurology*. 2008; 71: 426–429.
- [31] Plomp JJ, Molenaar PC, O’Hanlon GM, Jacobs BC, Veitch J, Dahan MR, *et al*. Miller Fisher anti-GQ1b antibodies: alpha-latrotoxin-like effects on motor end plates. *Annals of Neurology*. 1999; 45: 189–199.
- [32] Boylu EE, Toğrol RE, Senol MG, Özdağ MF, Saraçoğlu M. Role of anti-GQ1b antibody in differential diagnosis of acute ophthalmoparesis. *Neuropsychiatric Disease and Treatment*. 2010; 6: 119–122.
- [33] Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *The Cochrane Database of Systematic Reviews*. 2014; 2014: CD002063.
- [34] Hughes RAC, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. *The Cochrane Database of Systematic Reviews*. 2012; 2012: CD001446.
- [35] Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet*. 2016; 388: 717–727.
- [36] Beck RW, Cleary PA, Anderson MM, Keltner JL, Shults WT, Kaufman DI, *et al*. A Randomized, Controlled Trial of Corticosteroids in the Treatment of Acute Optic Neuritis. *New England Journal of Medicine*. 1992; 326: 581–588.