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Anti-Ganglioside Q1b (GQ1b) Antibody Syndrome: A Case Series

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Abstract: Four patients were included in this case series. All tested positive for Anti-GQ1b antibody except one. All had external ophthalmoplegia, with associated clinical features. Case 1 presented with limb weakness, associated with external ophthalmoplegia, ataxia and areflexia, therefore diagnosed as a Guillain-Barre Syndrome (GBS) variant. Case 2 was diagnosed with Miller-Fischer Syndrome (MFS), due to external ophthalmoplegia, ataxia and areflexia. Case 3 was diagnosed with acute ophthalmoparesis and presented only with external ophthalmoplegia with negative Anti GQ1b-antibody. Case 4 was diagnosed with Bickerstaff's Brainstem Encephalitis (BBE), presenting with external ophthalmoplegia, ataxia, hoarseness of voice and pyramidal signs. Case 1 and Case 4 were treated with intravenous immunoglobulin (IVIg) due to the severity of the disease, while Case 2 and Case 3 had spontaneous recovery. Those treated with IVIg resolved between 5 to 6 weeks, compared to those that recovered spontaneously within 2 to 5 months.

Keywords: Anti-GQ1b antibody syndrome, Miller-Fischer Syndrome, Guillain-Barre Syndrome, Bickerstaff's Brainstem Encephalitis, external ophthalmoplegia

INTRODUCTION

Gangliosides are glycosphingolipids linked to a sialic acid. To date, over 100 gangliosides have been identified based on variations in the sialic acid structure [1]. Gangliosides are found in the plasma membrane, and particularly abundant in the nervous system. They are anchored in the lipid bilayer by their ceramide tail, and their sialylated oligosaccharide core is exposed extracellularly [2]. This glycocalyx network determines the properties and functions of cells, and is readily accessible to antibody binding [3].

Multiple studies on chronic neuropathies have led to the discovery of various gangliosides and other glycolipids that are responsible for neuropathy-associated autoantibodies [4]. Anti- GQ1b antibody is closely associated with external ophthalmoplegia [5] and strongly stains the paranodal regions of the extramedullary portions involving the human oculomotor (III), trochlear (IV), and abducens (VI) nerve; while the deep cerebellar nuclei is also weakly stained [6].

There are multiple reports of antecedent infection in patients with MFS. Among reported causes of infections includes Campylobacter jejuni, Cytomegalovirus, Epstein-Barr virus and Streptococcus pyogenes. Koga et al showed that the GQ1b epitope is also present in the lipopolysaccharide of C. Jejuni isolated from patients with MFS. Infection may trigger production of antibodies which then bind to the ocular motor nerves and deep cerebellar nuclei, causing ophthalmoplegia and cerebellar ataxia [7].

Anti-GQ1b antibody is much more useful than a cerebrospinal fluid (CSF) examination for supporting a diagnosis of MFS during the first week. In patients suspected to have MFS, once anti-GQ1b is detected in the first week of presentation, serial LP for CSF analysis may not be required [8].

The term Anti- GQ1b Antibody Syndrome now houses a spectrum of diseases that includes MFS, GBS, BBE and acute opthalmoparesis [9]. All of them are serogically supported by the presence of Anti-GQ1b IgG and share a common presenting feature – external ophthalmoplegia [10].

CASE REPORTS

Case 1

A 44-year old, Chinese gentleman with underlying GBS and Thalassemia, presented with a 4-day history of lower limb weakness and unsteady gait, progressing to upper limb weakness within 2 days. He also complained of 1-day history of drooping of eyelids and diplopia with a history of fever and cough 1-week prior to presentation.

On examination, there was diplopia in all gazes, with restriction of extraocular movements in all directions. Powers of both upper and lower limbs were 3/5, and reflexes were reduced. His gait was broad-based and unsteady. He refused lumbar puncture. MRI Brain/ Orbit done were normal. Anti-GQ1b IgG taken was positive. Patient was given IVIg for 5 days. Diplopia resolved upon completion of 5 days of IVIG and within 5 weeks, all his symptoms resolved.

Case 2

A 34-year old, Malay gentleman with no known medical illness, presented with a 5-day history of diplopia upon waking up, associated with headache. He also complained of numbness of both hands for 2 days. He had a history of fever, cough and coryza 2 weeks prior, and was treated with Ampicillin/ Sulbactam 375mg BD for 2 days.

On examination, there was diplopia in all gazes with bilateral ptosis and complete ophthalmoplegia. His upper and lower limbs had no weakness, but had areflexia and ataxic gait. Lumbar puncture was done and results were normal. MRI Brain/ Orbit were normal. Anti-GQ1b IgG was positive. Upon follow-up, all his symptoms resolved within 5 months.

Case 3

An 11-year old, Malay girl, with underlying bronchial asthma and eczema, presented with a 2-week history of diplopia, which was gradually improving. She also had a history of upper respiratory tract infection (URTI) 4 days prior to onset of diplopia.

On examination, there was diplopia in all gazes, with restriction of extraocular movements in all directions. All other examinations were normal. CT and MRI Brain scans were normal. However, Anti-GQ1b IgG was negative. Upon follow-up, all her symptoms resolved in 2 months.

Case 4

A 9-year old healthy Malay boy presented with a 1-week history of fever, coryza, productive cough and reduced appetite followed by vomiting. Three days later, he developed diplopia, drooping of both eyelids, and also hoarseness of voice.

He had proximal weakness of upper and lower limbs of 3/5 and reflexes were brisk. He had ataxic gait and down going plantar reflexes. CT and MRI brain were normal. Anti-GQ1b IgG was positive. He was started on IV Immunoglobulin 2gm/kg over 5 days. Upon follow-up, all his symptoms resolved within 6 weeks (Fig-1).

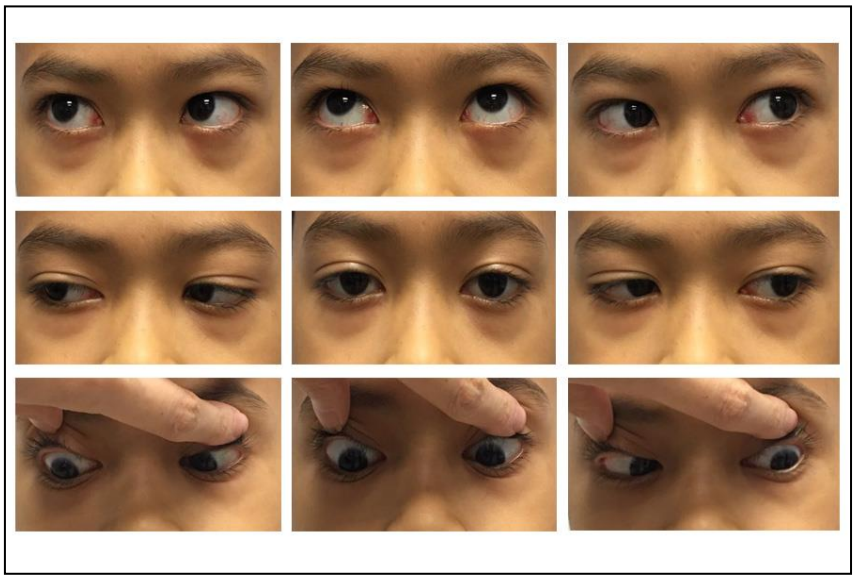

Fig-1: The patient above (Case 4) completed a 5-day course of IVIg. The photo above shows the improvement of extraocular movements at 1 month follow up.

Table−1: Summary of cases

	Case 1	Case 2	Case 3	Case 4
Age	44	34	11	09
External ophthalmoplegia	Yes	Yes	Yes	Yes
Limb weakness	Yes (Lower limb weakness progressing to upper limb weakness)	No	No	Yes (Upper and lower limb weakness)
Ataxia	Yes	Yes	No	Yes
Reflex	Hyporeflexia	Areflexia	Normal	Brisk; plantar reflex down going (Pyramidal signs)
Preceding symptoms	Fever URTI Symptoms	Fever URTI Symptoms	Fever URTI Symptoms	Fever URTI Symptoms Vomiting, drooping of eyelids and hoarseness of voice
Anti-GQ1b antibody	Positive	Positive	Negative	Positive
IV Ig	Given	-	-	Given
Time to resolution	5 weeks	5 months	3 months	6 weeks
Diagnosis	GBS variant	Miller-Fischer Syndrome (MFS)	Acute Ophthalmo-paresis	Bikerstaff's brainstem Encephalitis (BBE)

DISCUSSION

MFS is characterized by external ophthalmoplegia, ataxia and hyporeflexia/ areflexia [11] and when associated with limb strength of 3/5 or less, then it is a GBS variant. BBE is characterized by external ophthalmoplegia, ataxia and either consciousness disturbance or pyramidal signs. Acute ophthalmoparesis is diagnosed when there is only external opthalmoplegia, with absence of all other signs [12].

In the 4 cases reported above, the ages range from 9 to 44 years. All presented with an antecedent illness of fever, URTI and external ophthalmoplegia.

All had positive anti-GQ1b IgG except for Case 3 who presented at week 3 of illness, and was in recovery phase. Nishimoto et al reported that antibody titres peak at the time of onset of clinical presentation, then decay rapidly during clinical recovery [8]. Case 3 fully recovered within 2 months. Case 1 and Case 4 were given IVIg as inpatient, as their presenting symptoms were severe.

Current treatment options are immunotherapies like IVIg or plasmapharesis. Even though Anti-GQ1b Syndrome typically has a self-limiting course, IVIg and plasmapharesis act against the autoantibodies and their subsequent inflammatory response [13]. This suggests a possible efficacy in immunotherapies, in which it encourages a more rapid resolution of symptoms [14]. This is apparent where Case 1 and Case 4, despite presenting with more severe features, obtained complete resolution of symptoms within 5 and 6 weeks respectively; whereas Case 2 and Case 3 only obtained complete resolution of symptoms within 5 and 2 months respectively. However, no randomized controlled trial of immunotherapies on MFS or related disorders has been undertaken to evaluate the efficacy of immunotherapies [15].

CONCLUSION

It is important to delineate the different clinical features of the Anti GQ1b antibody variants to ensure proper diagnosis and management. The lack of evidence in the usage of immunotherapies for the treatment of Anti- GQ1b Antibody Syndrome opens a window of opportunity for a more extensive research in this area of Neuro-Ophthalmology.

Disclosure

The authors report no conflict of interest in this work.

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