Yet another atypical presentation of anti-GQ1b antibody syndrome

Raed Alroughani,^{1,2} Anil Thussu,^{1,2}
Raouf T. Guindi³

¹Division of Neurology, Department of Medicine, Amiri Hospital, Sharq;

²Neurology Clinic, Dasman Diabetes Institute, Dasman; ³Department of Medicine, Al-Seef Hospital, Salmiya, Kuwait

Abstract

Variants of Guillain-Barre syndrome such as Bickerstaff encephalitis and Miller-Fisher syndrome have been reported. We report a 15-year-old boy who presented, after a prodromal illness, with 3-day progressive limb weakness, diplopia, and acute urinary retention. Clinically, he had horizontal gaze-evoked and upbeat nystagmus, bilateral extensor plantars in addition to quadriplegia and areflexia. Magnetic resonance imaging of the brain and spine was unremarkable and cerebral spinal fluid analysis showed lymphocytic pleocytosis. Nerve conduction study revealed symmetrical axonal neuropathy. Anti-GQ1b antibody was positive. A combination of IV methylprednisone followed by IVIg was instituted which led to remarkable clinical recovery. This case underpins the importance of recognizing atypical presentations of acute autonomic dysfunction and central nervous system features such as nystagmus, which may be associated with anti-GQ1b antibody syndrome. Features mimicking myelitis and brainstem encephalitis may pose diagnostic and therapeutic dilemma among the treating physicians.

Introduction

Guillain-Barre syndrome (GBS) is one of the acute flaccid paralysis syndromes. Different subtypes producing the clinical picture of GBS have been described including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), acute sensory neuropathy, acute pandysautonomia and the Fisher syndrome.^{1,2}

Presentations with central features such as depressed level of consciousness, and hyperreflexia were reported in Bickerstaff Brainstem Encephalitis (BBE). In Bickerstaff's

original papers, he noted extensor plantars with areflexia.³ Ophthalmoplegia and ataxia were common among patients diagnosed with Bickerstaff encephalitis and Fisher Syndrome (FS). It was always thought that both BBE and FS were distinct disorders from GBS, but considered as a spectrum disorder with an autoimmune mechanism targeting primarily the central nervous system. The discovery of anti-GQ1b antibody was a turning point in explaining the fact that certain patients share similar clinical features suggestive of GBS, BBE or FS.⁴ The GQ1b antigen is highly expressed in the paranodes and the neuromuscular junctions of the oculomotor, trochlear and abducens nerves, muscle spindles in the limbs, and probably reticular formation in the brainstem.^{5,6} The neurological effects of anti-GQ1b antibodies are induced by complement-mediated destruction of both perisynaptic Schwann cells (by inhibiting Ca²⁺ influx) and axonal terminals resulting in neuromuscular junction blockade and ultimately muscle weakness.^{7,8} Herein, we report a case of atypical anti-GQ1b syndrome in a patient presented with both central and peripheral nervous system involvements.

Case Report

A fifteen years-old right-handed boy presented to the emergency department with progressive weakness of upper and lower extremities for 3 days. He described a prodromal illness including diarrhea and fever preceding the development of weakness. He was unable to walk and was having difficulty elevating his arms above the shoulder. Although he did not describe any bulbar symptoms, he was complaining of significant binocular diplopia. In addition, he described abdominal pain associated with urinary retention, and a Foley's catheter was inserted draining over 500 mL of urine. There was no associated history of headache, fever, recent immunization or travel, or any changes in level of consciousness. On initial exam, he was hemodynamically stable with temperature 36.7°C and O₂ saturation of 98% on room air. Mental status exam was normal. Cranial nerve examination revealed normal pupillary reaction, upward and gaze-evoked horizontal nystagmus. There was no gaze paresis or facial weakness. Neck flexor weakness was evident. Motor exam assessment according to Medical Research Council (MRC) scale revealed flaccid tone with significant symmetrical proximal more than distal weakness as follows: deltoid 3/5, biceps 2/5, triceps 3/5, wrist and finger extensors 3/5, wrist and fingers flexors 2/5, hip flexors 1/5, knee flexors 2/5, knee extensors 3/5, dorsiflexors 4/5, plantarflexors 4/5. Deep tendon reflexes

Correspondence: Raed Alroughani, Division of Neurology, Department of Medicine, Amiri Hospital, Arabian gulf Street, Sharq 13041, Kuwait.

Tel.: +965.2245.0005/4444 - Fax: +965.2246.8971
E-mail: alroughani@gmail.com

Key words: Neurology; medicine; Guillain-Barre syndrome.

Acknowledgments: the authors acknowledged the patient and family for their acceptance in reporting this case to enhance our understanding in the diagnosis and management of atypical neurological cases.

Contributions: RA, AT, RG were involved in the care of the reported case in terms of diagnosis and management; RA drafted the manuscript; AT and RG provided critical discussion and comments.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 19 December 2014.

Revision received: 18 May 2015.

Accepted for publication: 15 June 2015.

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Neurology International 2015; 7:5770
doi:10.4081/ni.2015.5770

were reduced (1+) in triceps and biceps and absent in brachioradialis, knees, and ankles. His plantars were extensors bilaterally. There was no sensory level or any objective sensory loss. Cerebellar and gait exam were deferred due to his significant weakness.

His basic laboratory investigation including hematological, liver and renal function tests were within normal limits. Erythrocyte sedimentation rate was elevated at 32. Magnetic resonance imaging (MRI) of brain/spine with Gadolinium was unremarkable. Cerebral spinal fluid (CSF) examination revealed 20 white cells (100% lymphocytic) while protein and glucose were within normal limits. The gram-stain was unremarkable.

Given that he had a prodromal illness along with the presentation of symmetrical proximal more than distal weakness with areflexia, GBS was suspected. However, given the presence of brainstem features (nystagmus), pyramidal signs (extensor plantars) along with acute urinary retention, other diagnoses such as Bickerstaff encephalitis and Acute Disseminated Encephalomyelitis (ADEM)-like syndrome were considered despite the preser-

vation of consciousness and normal MRI.

He received IV methyl prednisolone 1g once daily for 4 days. Forced vital capacity was 2.2 L on second day of admission and remained between 2.0-2.6 L in the first week. An improvement in the power of upper limbs and neck flexor weakness were evident on day 3 (deltoid 4/5, biceps 3/5, triceps 4/5, wrist and finger extensors 4/5, wrist and finger flexors 3/5). His lower limb power was essentially the same apart from improvement of knee extensors 4+/5, knee flexors 3/5. He continued to have the indwelling urinary catheter. Nerve conduction study was performed on day 4 of admission, and revealed normal sensory nerve action potentials (SNAPs) but absent compound muscle action potentials (CPAMs) in the lower limbs and reduced CMAPs in the upper extremities without conduction block. On day 4, he developed bilateral lateral abduction paresis and mild facial weakness indicative of the involvement of both CN VI and VII. He remained hemodynamically stable with FVC remaining above 2L. The decision was made to start IV Immunoglobulin 2 g/kg course over 3 days given his clinical progression. He continued to have supportive measures by means of physical therapy, DVT prophylaxis along with urological follow-up in order to train his bladder muscles. Anti-GQ1b antibody returned positive while CSF and stool cultures were negative. A follow-up MRI brain and spine, which was performed on day 10, was unremarkable. On day 14, he started to regain the function of upper extremities and was able to lift his arms above his shoulders with good support of neck muscles. On day 30, the power of hip flexors was 3/5 and he was able to stand with 2-person assist. On day 42, he started to walk unassisted but needed support in rising from a chair. On day 50, the urinary catheter was removed after bladder training and he was able to urinate without any difficulty. On day 62, his neurological examination revealed mild limitation of both lateral recti with no evidence of nystagmus. Facial and neck muscles were normal. In terms of power testing, his MRC grade for muscles were as follows: deltoid 4+, biceps 5, triceps 5, intrinsic hand muscles 4+, hip flexor 4-, knee flexors 4+, knee extensor 4+, dorsiflexors 5, planterflexors 5. He remained areflexic. Sensory exam was unremarkable while cerebellar exam revealed mild dysmetria in the upper extremities. His gait was ataxic. He was referred to an outpatient rehabilitation center. At one-year follow-up, his neurological examination was unremarkable apart from areflexia and mild ataxic gait.

Discussion

Our case illustrated atypical presentations

and findings, which pointed toward a central involvement since gaze-evoked horizontal nystagmus is usually localized to the cerebellum while upbeat nystagmus is commonly associated with lesions in the rostral pons. In addition, the presence of extensor plantars was indicative of corticospinal tract involvement, which in association with acute urinary retention, was pointing towards spinal cord localization. On the other hand, certain clues in the examination (distribution of weakness being proximal more than distal, neck flexor weakness and areflexia) were indicative of polyradiculitis, raising the suspicion of a GBS-variant. Although few cases were reported in the literature with central features in GBS patients, it was proposed that corticospinal tract might be functionally involved in patients with anti-ganglioside antibody associated syndromes.^{9,10} Kariyama *et al.* described a patient who had asymmetrical weakness, which was confused for a stroke initially but later was diagnosed with GBS. The central weakness was confirmed by mean of abnormal central motor conduction time (CMCT) on a motor evoked potential study.¹¹

The autonomic dysfunction manifested by the acute urinary retention in our patient added to the dilemma of the co-existence of both upper and lower motor signs. In GBS, bladder or bowel disturbance at presentation had been reported especially in children due to dysautonomia.^{12,13} Watson *et al.* studied 26 children with GBS, of whom 7 had bladder or bowel disturbance at presentation. One patient presented with, and three subsequently developed urinary retention necessitating catheterization for a median of 7.5 days. Urinary retention was associated with MRC 2/5 weakness in all four limbs.¹⁴ Dysautonomia is usually associated with AIDP and it is rare in other types such as AMAN,^{1,2} and the nerve conduction study in our patient revealed features supportive of the latter. On the other hand, it is not unusual to have urinary retention with areflexia in a spinal shock stage resulting from an acute myelitis. In our case, the persistent urinary retention makes it different from GBS where urinary retention is a transient occurrence.

The presence of anti-GQ1b antibody in our patient reflects a unique clinical spectrum, which represents an existing continuum between several conditions (Fisher, Bickerstaff and Guillain-Barre syndromes) presenting with variable central and peripheral nervous system involvements. Fisher syndrome presents when the binding of anti-GQ1b antibodies to GQ1b antigens expressed on the relevant cranial nerves and muscle spindles whereas Bickerstaff brainstem encephalitis is induced when the anti-GQ1b antibodies enter the brainstem and bind to GQ1b antigens.¹⁵ A

more inclusive nomenclature such as *anti-GQ1b antibody syndrome* could be used to include the common serological profile when referring to the clinical syndromes described by both Bickerstaff and Fisher.¹⁶ However, nystagmus (observed in our patient) was never reported in the literature to be associated with anti-GB1b antibody syndrome despite the occasional presence of ophthalmoplegia and other brainstem features

Odaka *et al.* evaluated 194 anti-GQ1b seropositive patients, among whom 110 had FS, 31 had an overlap of FS with GBS, 12 had BBE, and 11 had an overlap of BBE with GBS.¹⁶ In another study of 62 patients with BBE, the authors described positive anti-GQ1b antibody in 66% of patients and approximately 60% of the overall cohort associated flaccid symmetrical tetraparesis.¹⁷ Further supportive evidence of the clinical spectrum of overlap syndromes came from autopsy reports.^{18,19} Maier *et al.* studied 13 autopsy cases of GBS patients and they revealed evidence of pathological mononuclear cell infiltrates composed of macrophages and T-lymphocytes within the spinal cord in 8 out of 13 cases, within the medulla oblongata in 8 out of 12 cases, within the pons in 5 out of nine cases, and in one out of four midbrains. The authors did not find any evidence of primary demyelination in the CNS but rather axonal with secondary myelin impairment, microglial activation and inflammatory infiltration.¹⁸

Given the challenging diagnostic nature of our case, and the predominant central features, we elected to treat the patient with a combination of IV Methylprednisone (IVMP) and IV Immunoglobulin (IVIg). The rationale was based on the faster effect of IVMP in view of myelitis-like picture, which tends to respond to high dose parental steroids. On the hand, given that the pathogenesis of anti-GQ1b antibody syndrome is similar to GBS, IVIg was subsequently added as it has been shown to be efficacious in improving outcomes in GBS.^{20,21} Although there have been reports of clinical improvement with steroid administration, its role in the anti-GQ1b antibody syndrome is less clear.²²

Conclusions

The presence of nystagmus along with other central features may pose diagnostic dilemma in patients suspected to have GBS variants. Our case highlights the importance of broad-based approach in dealing with atypical presentations involving both peripheral and central nervous system where the clinical spectrum of anti-GQ1b syndrome might be considered.

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