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# Expanding horizons in anti-GQ1B antibody syndrome: Recognizing atypical and overlap forms

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## Abstract

Since the initial descriptions of Miller Fisher Syndrome (MFS) and Bickerstaff Brainstem Encephalitis (BBE), substantial advancements have refined our understanding of these disorders, highlighting shared features such as anti-GQ1b IgG antibodies, preceding infectious triggers, and overlapping neurophysiological findings. These commonalities support the hypothesis that MFS and BBE are not distinct entities but rather components of a unified autoimmune condition, often referred to as "Fisher-Bickerstaff syndrome."

The subsequent identification of anti-GQ1b-positive atypical variants, incomplete forms with shared serological profiles that fail to meet the full clinical criteria for MFS or BBE and overlap syndromes with features of Guillain-Barré Syndrome (GBS), has broadened this classification. This evolving understanding has led to the conceptualization of a broader entity termed "Anti-GQ1b Antibody Syndrome."

This syndrome encompasses a spectrum of disorders characterized by a consistent serological hallmark and a variable degree of involvement of the Peripheral (PNS) and Central Nervous Systems (CNS). Within this spectrum, MFS and BBE represent opposite ends, with intermediate and atypical phenotypes bridging these extremes.

This review aims to provide a comprehensive analysis of Anti-GQ1b Antibody Syndrome, emphasizing its phenotypic continuum and the atypical variants that contribute to its expanding classification. By integrating recent advances in diagnostic approaches and clinical understanding, we propose a unified framework for conceptualizing this syndrome as a dynamic spectrum of anti-ganglioside antibody-associated diseases.

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## Introduction

The article "The Spectrum of Anti-GQ1B Antibody Syndrome: Beyond Miller Fisher Syndrome and Bickerstaff Brainstem Encephalitis", authored by our group, examines the evolving understanding of Anti-GQ1b Antibody Syndrome, emphasizing the importance of identifying atypical and overlapping forms as part of an expanding spectrum. This syndrome encompasses a wide range of neurological disorders characterized by anti-GQ1b IgG antibodies targeting gangliosides expressed in the Peripheral (PNS) and Central Nervous Systems (CNS).

The classical forms of the syndrome include Miller Fisher Syndrome (MFS) and Bickerstaff Brainstem Encephalitis (BBE). MFS primarily affects the PNS and is classically defined by ophthalmoparesis, gait ataxia, and tendon areflexia, while BBE predominantly affects the CNS, presenting with brainstem dysfunction, including altered consciousness (ranging from mild drowsiness to coma), hyperreflexia, and long tract signs.

Historically, MFS was first identified by Fisher as a distinct variant of Guillain-Barré Syndrome (GBS), and BBE was originally described as a form of encephalitis affecting the brainstem, typically following infection [1,2]. The discovery of anti-GQ1b antibodies as a key target in both MFS and BBE revolutionized the understanding of these diseases, leading to the concept of a unified syndrome known as the "Fisher-Bickerstaff Syndrome" [3-5].

The subsequent identification of anti-GQ1b-positive atypical variants has broadened the concept into a continuum now recognized as Anti-GQ1b Antibody Syndrome.

## Atypical forms- formes frustes

Atypical presentations challenge the conventional diagnostic criteria for MFS and BBE. These incomplete forms share a common serological profile but do not fully meet the clinical criteria for either disorder. Atypical forms encompass a broad range of clinical presentations, including Acute Ataxic Neuropathy (AAN), acute Ophthalmoparesis (AO), Pharyngeal-Cervical-Brachial (PCB) weakness, Acute Ptosis (AP), acute mydriasis (AM), Acute Oropharyngeal Palsy (AOP), Acute Bulbar Palsy (ABP), and Acute Vestibular Syndrome (AVS) [6].

PCB weakness is characterized by areflexia and muscle weakness affecting the oropharyngeal, cervicobrachial, and proximal muscle groups. The most frequent initial symptom is arm weakness (present in 29% of cases), followed by dysphagia (17%) and diplopia (17%). Less common symptoms include blepharoptosis, facial weakness, photophobia, and dysgeusia. Hypo- or areflexia is reported in 91% of cases in the arms and 86% in the legs, often accompanied by superficial sensory loss in both the upper (59%) and lower limbs (38%). Ophthalmoparesis occurs in 55% of cases. Other features may include ataxia (43%), autonomic dysfunction (20%), and altered consciousness (5%) [7].

Initially classified as a Guillain-Barré Syndrome (GBS) variant, PCB weakness was later incorporated into the anti-GQ1b syndrome spectrum following a study of 100 "pure PCB" patients, 39 of whom were seropositive for anti-GQ1b antibodies. In certain instances, overlap with MFS (26%) and BBE (5%) was observed, alongside the subsequent development of ataxia, ophthalmoparesis, or disturbances in consciousness, reinforcing its classification within the anti-GQ1b spectrum [7,8].

Acute Vestibular Syndrome (AVS), more recently recognized as part of this spectrum, is characterized by sudden-onset dizziness or vertigo (spontaneous or positional, present in 80% of patients) [9]. Other common features include truncal ataxia (100%) or limb ataxia (86%), along with sensory disturbances (43%), and ocular motor findings such as spontaneous nystagmus (50%), gaze-evoked nystagmus (50%), positional nystagmus (30%), or head-shaking nystagmus (40%), all without ophthalmoplegia. Additional signs may include saccadic dysmetria (20%), ocular flutter or opsoclonus, downbeat nystagmus, and central positional nystagmus [10].

Acute Bulbar Palsy (ABP) is another form characterized by sudden bulbar muscle paralysis, typically presenting with cranial nerve involvement or ataxia, but without significant limb or neck weakness. Bulbar palsy commonly manifests with dysarthria (50%), diplopia (35%), and dysphagia (35%). Less frequent features include gait ataxia (14%), rhinolalia (11%), facial palsy (11%), and ptosis (3.6%). As the disease progresses, patients may develop external ophthalmoplegia (71%), hypo/areflexia (64%), facial palsy (61%), gait ataxia (50%), and sensory deficits (50%) [11].

Acute Ataxic Neuropathy (AAN), defined by severe ataxia without ophthalmoplegia, includes two conditions: ataxic GBS and Acute Sensory Ataxic Neuropathy (ASAN). Ataxic GBS, which accounts for 69% of AAN cases, is typically associated with a negative Romberg sign, hypo/areflexia, distal paresthesias, and Cerebrospinal Fluid (CSF) Albuminocytological Dissociation (ACD), classifying it as a GBS variant [12,13]. ASAN, accounting for 31% of AAN cases, more frequently presents with a positive Romberg sign, the absence of Sensory Nerve Action Potentials (SNAPs), normal CSF findings, loss of large myelinated fibers, and axonal damage [14].

Initial symptoms in both conditions may include distal dysesthesias (51% in ataxic GBS vs. 71% in ASAN) and gait disturbances (49% in ataxic GBS vs. 35% in ASAN). As the disease progresses, patients often develop more pronounced distal dysesthesias (70% in ataxic GBS vs. 88% in ASAN) and superficial sensory impairments (27% in ataxic GBS vs. 24% in ASAN). Symptom severity tends to peak around day 4 in ataxic GBS (range: 2–15 days) and day 7 in ASAN (range: 3-13 days) [15].

Acute Ophthalmoparesis (AO) is characterized by sudden, symmetrical involvement of both external and internal eye muscles, without the presence of ataxia or areflexia, and is associated with anti-GQ1b antibodies [16]. In approximately 27% of cases, unilateral eye involvement complicates diagnosis [17,18].

Overlap syndromes, in which patients exhibit features of both MFS-BBE and other related disorders like GBS, further underscore the complexity of this spectrum [6,19]. The development of more generalized GBS features, such as limb weakness with flaccid tetraparesis in the context of a form of the anti-GQ1b antibody syndrome spectrum, may represent the epiphenomenon of an overlapping condition that significantly impacts patient outcomes [20,21].

Other symptoms associated with GBS overlap include moderate to severe back pain refractory to analgesic therapy and headache [22,23]. The headache is hypothesized to result from autoantibodies (GQ1b, GT1a, GD3, GD1b) targeting cranial nerves and sensory cervical roots, potentially activating the trigeminovascular pain pathway [23-25].

The occurrence of such overlaps can influence prognosis, with approximately 25% of patients scoring 3 on the Medical Research Council (MRC) scale experiencing persistent limb

weakness [20,26,27].

These atypical presentations, viewed as intermediate forms within the spectrum, highlight the expanding clinical diversity of the syndrome and emphasize the need for heightened clinical vigilance and the consideration of anti-GQ1b antibodies in patients presenting with isolated, post-infectious acute symptoms.

## Pathogenesis

The pathogenesis of anti-GQ1b antibody syndrome is primarily driven by molecular mimicry, wherein an immune response is misdirected against host neuronal gangliosides following infection. This process most commonly occurs after exposure to Campylobacter jejuni, although other pathogens may also trigger the syndrome [20]. The immune system, in response to bacterial lipooligosaccharides that mimic the structure of human gangliosides, produces IgG autoantibodies that target gangliosides [28]. The type of antibody generated is determined by the 51st amino acid of CstII, which influences its enzymatic function. When Threonine (Thr51) is present, the enzyme produces Lipooligo Saccharides (LOS) resembling GM1 and GD1a. Conversely, when Asparagine (Asn51) is present, it results in the formation of GQ1b-like LOS [29,30].

GQ1b is highly expressed in various regions of the peripheral and central nervous systems, including the oculomotor, trochlear, and abducens nerves (cranial nerves III, IV, and VI), as well as the dorsal root ganglia and muscle spindles, especially the Ia afferent fibers responsible for proprioception. The antibodies bind to these gangliosides, disrupting normal neural function and causing clinical manifestations such as ophthalmoplegia, ataxia, and areflexia [31].

In peripheral nervous system involvement, the binding of anti-GQ1b antibodies to the paranodal regions of motor and sensory nerves impairs nerve conduction, leading to the hallmark features of Miller Fisher Syndrome (MFS), including acute ophthalmoparesis and ataxia. The absence of overt demyelination, as seen in Guillain-Barré Syndrome (GBS), suggests that the mechanism is more functional rather than structural, possibly involving disruption of ion channel function or nerve conduction rather than destruction of the myelin sheath [32,33].

When the Central Nervous System (CNS) is involved, as in Bickerstaff Brainstem Encephalitis (BBE), the breakdown of the blood-brain barrier allows these antibodies to penetrate the brainstem. Here, anti-GQ1b antibodies may attack gangliosides within the brainstem nuclei, particularly those related to motor coordination and consciousness, leading to symptoms such as drowsiness, hyperreflexia, and long tract signs, including Babinski's sign. The involvement of the reticular formation and cranial nerve nuclei explains the altered consciousness and ophthalmoplegia observed in BBE [34].

The damage is not uniform across the spectrum, as some variants, such as atypical forms like Acute Ophthalmoparesis (AO) or Acute Ataxic Neuropathy (AAN), exhibit more selective impairment of nerve function.

Other antibodies besides GQ1b, such as anti-GT1a and anti-GM1, can function as GQ1b equivalents, acting similarly to anti-GQ1b antibodies in two distinct ways. First, these antibodies cross-react with structurally related gangliosides, producing similar symptoms like ophthalmoplegia and ataxia [35,36]. Second, these antibodies target different regions of the nervous system where GT1a and GM1 gangliosides are prevalent, particularly the glossopharyngeal and vagus nerves, leading to additional symptoms like bulbar weakness, dysarthria, and dysphagia, complicating the clinical picture [37,38].

## Diagnostic approach

### Cerebrospinal fluid analysis

Diagnostic evaluation of Anti-GQ1b Antibody Syndrome primarily relies on the detection of anti-GQ1b antibodies in the serum, although Cerebrospinal Fluid (CSF) analysis, neuroimaging, and electrophysiological studies play crucial roles in confirming the diagnosis.

CSF often shows Albuminocytological Dissociation (ACD)—elevated protein levels without increased white blood cells-though its frequency and severity varies across syndrome subtypes.

Hyperproteinorrachia, a recognized hallmark of Guillain-Barré Syndrome (GBS), may be absent in the early stages of the anti-GQ1b antibody spectrum and, in certain cases, may not manifest at all. The incidence of hyperproteinorrachia in this spectrum tends to progressively increase over the first three weeks following the onset of symptoms. Its incidence typically rises within three weeks of symptom onset, from 47% in Miller Fisher Syndrome (MFS) patients during the first week to 82% by the third [39]. In contrast, ACD is less frequent in Bickerstaff Brainstem Encephalitis (BBE), with an occurrence rate of 25% during the initial week, escalating to 46% in the second week [20,40].

Atypical forms exhibit an ACD incidence of approximately 30% [15,41]. Cerebrospinal Fluid (CSF) pleocytosis, characterized by an increased number of white blood cells in the CSF, is observed more frequently in BBE (32%) than in MFS (5%) and atypical forms (7%) [20,41].

Thus, while CSF analysis provides supportive data, it cannot reliably differentiate syndrome subtypes [6].

### Anti-GQ1b antibody detection

Serum anti-GQ1b antibodies are a sensitive and specific diagnostic marker, detectable in 85% of MFS and 68% of BBE cases during the first week of symptoms [6,42,43].

The relative incidence of anti-GQ1b antibodies in the various atypical forms of the spectrum varies: ASAN 65%, ataxic GBS 18%, AVS 67%, AO without ataxia 80%, ABP 59%, and GBS with ophthalmoparesis 92% [6,7,10,15]. Other non-GQ1b antibodies may also be identified, which can act as functional equivalents or be associated with symptom worsening, as demonstrated by multiple associative studies [6,43].

### Electroencephalography and neuroimaging

Instrumental investigations such as Electroencephalography (EEG) and neuroimaging provide valuable insights. EEG studies reveal diffuse slowing in the theta or delta range at rest in 57% of BBE patients and 25% of MFS patients, indicating greater Central Nervous System (CNS) involvement in BBE [41].

Advanced imaging techniques, such as Magnetic Resonance Imaging (MRI), can help identify central nervous system involvement, particularly in BBE. MRI scans in MFS are typically normal in 99% of cases, with the rare 1% showing hyperintensity in T2-weighted images in regions such as the brainstem, cerebellum,

middle cerebellar peduncle, and cranial and spinal nerve roots [31,41,44,45]. In contrast, MRI abnormalities are more frequent in BBE, seen in 11% of cases, with hyperintensities in the medulla oblongata, pons, thalamus, cerebellum, superior cerebellar peduncle, or corpus callosum [41]. Some studies suggest that the incidence of MRI abnormalities in BBE could be as high as 30% [20,46,47]. Overlap cases involving MFS/BBE and GBS may show hyperintensities or contrast enhancement of the nerve roots and cauda equina-conus medullaris, similar to findings in several GBS patients [48,49].

Additionally, advanced techniques like Positron Emission Tomography (PET) and Magnetic Resonance Spectroscopy (MRS) have revealed metabolic changes in the brain, indicative of CNS involvement, even in conditions predominantly affecting the peripheral nervous system [6,50,51].

These findings underscore the diverse manifestations of Anti-GQ1b Antibody Syndrome, reinforcing its classification as a continuous spectrum with variable CNS and PNS involvement.

**Neurophysiological assessments**

Neurophysiological assessments typically reveal milder abnormalities in anti-GQ1b syndrome compared to GBS. Unlike GBS, key features of demyelinating polyneuropathy, such as reduced motor conduction velocity, significant temporal dispersion, and conduction blocks, are generally absent in the pure forms of the syndrome. In these cases, motor and sensory nerve conduction studies usually remain within normal ranges. However, a reduced Sensory Nerve Action Potential (SNAP) amplitude, disproportionate to the slowed sensory conduction velocity or prolonged distal latencies, may suggest underlying sensory neuropathy [52,53].

The evaluation of late responses, particularly when assessing the more proximal nerve segments, such as the plexuses and nerve roots, often indicates the absence of the soleus H-reflex, which serves as the neurophysiological correlate of the myotatic reflex [41,53-55]. This abnormality, found in approximately 75% of patients with BBE and 94% of those with MFS, is thought to be related to selective damage to the Ia muscle spindles expressing the GQ1b ganglioside [53,54,56]. Restoration of the H-reflex is closely linked to clinical recovery [57].

Electrophysiological data for atypical forms of the syndrome are less thoroughly documented. In cases of Acute Ophthalmoparesis (AO) and Acute Vestibular Syndrome (AVS), Nerve Conduction Studies (NCSs) are typically normal, though axonal damage, similar to that seen in Acute Motor Axonal Neuropathy (AMAN), has been reported in conditions such as Pharyngeal-Cervical-Brachial (PCB) weakness and Acute Ataxic Neuropathy (AAN) [11,15,16,48,58].

In patients with Acute Bulbar Palsy (ABP), approximately 17% present with abnormal blink reflexes, suggesting facial nerve involvement [59]. Although muscle weakness in ABP is localized to motor cranial nerve territories, subclinical neuropathy affecting the limbs can be detected in over a third of cases. This provides further electrophysiological evidence that ABP is part of the broader spectrum of GQ1b-related syndromes [11,60].

Across both typical and atypical forms, recovery from the disorder is often accompanied by a gradual improvement in SNAP amplitudes, correlating with clinical improvement [33].

Overlap syndromes, such as GBS with MFS or BBE, may present with electrophysiological findings of acute motor axonal neuropathy superimposed on the syndrome [48,49].

Auditory Brainstem Response (ABR) testing, which evaluates neural transmission from the cochlea to the midbrain, may be particularly useful for diagnosing and monitoring BBE. In these patients, reduced evoked potentials without a prolonged I-V latency—likely due to the loss of neural cells expressing anti-GQ1b gangliosides—are frequently observed [38,61].

**Therapy**

Regarding therapy, the rarity of spectrum conditions has precluded randomized, double-blind, placebo-controlled trials on treatment, and retrospective studies yield controversial results. It is inferred that MFS is self-limiting, and therapy is unlikely to affect the patient's outcomes [62,63]. In contrast, BBE often requires more aggressive management due to the higher risk of severe complications, including the need for assisted ventilation in approximately 34% of cases and a mortality rate of 4% [20].

For atypical and overlap forms, treatment responses have shown variability, emphasizing the need for individualized approaches. Intravenous Immunoglobulins (IVIG) and plasmapheresis remain standard treatments, although their efficacy may differ depending on the specific clinical presentation. This necessitates a tailored treatment strategy based on the unique characteristics and biomarkers of each patient, aiming to improve outcomes across the anti-GQ1b spectrum [63,27].

## Conclusion

In summary, this comprehensive overview of anti-GQ1b antibody syndrome underscores the complexity and variability of these autoimmune neuropathies. Shared immune mechanisms suggest a need for a more holistic diagnostic approach, combining clinical evaluation with laboratory testing, particularly focusing on anti-GQ1b antibody detection, which demonstrates high sensitivity and specificity. By recognizing the common pathophysiological mechanism linking MFS, BBE, and their variants, clinicians can improve diagnostic accuracy and offer more personalized treatments. Furthermore, ongoing research into the broader implications of autoimmune neuropathies is crucial, focusing on developing more precise diagnostic tools and novel therapeutic interventions.

**Conflict of interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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