



Case Report

Amyotrophic lateral sclerosis in a patient who recovered from Miller Fisher Syndrome: The role of GQ1b antibody revisited

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ABSTRACT

Miller Fisher Syndrome (MFS), a variant of Guillain Barre Syndrome (GBS), and amyotrophic lateral sclerosis (ALS) are two rare neuromuscular diseases that are usually unrelated. While ganglioside antibodies have a common relation with MFS and GBS, they have also been found in association, albeit less commonly, with ALS. A patient experiencing MFS and then ALS in tandem has never been documented. We discuss a case demonstrating these findings, with GQ1b elevated on both occasions. The pathophysiologic role of GQ1b is explored.

1. Introduction

ALS and MFS/GBS are two rare neuromuscular diseases. ALS is a relentlessly progressive, motor-specific illness affecting both the upper and lower motor neurons with fatal outcome. In contrast, MFS and GBS are autoimmune diseases usually preceded by an infection that cause lower motor neuron paralysis with recovery potential. Molecular mimicry is thought to be the main pathophysiology. Five percent of GBS patients suffer from MFS, which is characterized by the triad of ataxia, ophthalmoplegia, and areflexia. While MFS and ALS are mainly diagnosed based on the clinical presentation of a patient, the role of ganglioside antibodies in the pathogenesis of these conditions has been studied in recent years. Gangliosides are sialic acid-containing glycosphingolipids that are present abundantly in peripheral nerves (GM1, GM2, GD1a, GD1b, GQ1b and Asialo-GM1). These antibodies are well known to be associated with GBS and MFS, with GQ1b particularly prevalent for MFS (81% prevalence) (Yuki et al., 1993). Ganglioside antibodies have also been reported in some patients with ALS. When an antibody is present, it is usually GM1 (Pestronk et al., 1989, 1998; Lamb and Patten, 1991; Taylor et al., 1996; Sanders et al., 1993; Yuki et al., 2014; Kollwe et al., 2015); GQ1b among ALS is a very rare occurrence (Sawaya, 2019). A review of literature does not review any case where ALS is diagnosed in a patient who recovered from MFS with re-surfing GQ1b levels as the common finding.

1.1. Case

A 68-year-old Hispanic female with past medical history of hypertension, diabetes mellitus, familial hyperlipidemia, and asthma presented to our hospital complaining of dizziness, bilateral external ophthalmoplegia, diplopia, and lower limb ataxia with altered gait that had been present for three days. She had a non-specific upper respiratory tract infection three weeks prior. She did not receive any vaccination in the past 6 months. There was no travel history or sick contact.

On physical examination, she was alert and oriented to person, place, and date. No focal sensory or motor deficit was present. Deep tendon reflexes were found to be absent in all extremities and she had an unsteady gait without any lateralization. Rapid alternating movement was mildly impaired, though the patient did not have evidence of hand tremor, shuffling gait, or slurred speech. Her pupils were round and equal with sluggish pupillary light reflex.

Complete blood count, comprehensive metabolic panel, thyroid function, liver function and cardiac markers were unremarkable. The urine toxicology for common substances, alcohol level, and serum anti-cholinesterase antibody test were negative.

MRI of the brain was unremarkable. Cerebral spinal fluid analysis showed WBC 2/μl, RBC 0/dl, glucose level of 63 mg/dl, and protein level of 33mg/dl with negative gram stain and cultures. Hepatitis B surface antigen, HIV, and RPR were negative. Serum ganglioside antibodies against GD1b, GM1, and GQ1b were sent to ARUP Laboratories. The patient's GD1b antibody was 146 and GQ1b antibody was 478 (normal

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range 0–50). The rest of the ganglioside antibody panel was negative. Electrodiagnostic studies were not performed.

Her symptoms progressed over 1 week. At the worst, she had complete ophthalmoplegia in all directions and severe bilateral ptosis. She had moderate dysarthria and dysphagia. She was able to protect her airway and no mechanical ventilation was needed. Arriving at the diagnosis of Miller Fisher Syndrome, intravenous immunoglobulin (octagam 5% 400mg/kg/day x 5 days) was started. Due to the rapid improvement of debilitating symptoms, our patient was discharged and instructed to follow up with outpatient neurology. She was seen at a follow-up appointment six weeks post discharge, with complete resolution of initial symptoms and was completely asymptomatic. A repeat GQ1b antibody level was 135 on that outpatient visit, the rest of the antibody panel was negative. She had no deep tendon reflex on that visit.

Interestingly, this patient's MFS was among a "surge" of cases described by Liu et al., in 2015 (Liu and Yang, 2020). During that year, there was a surge in both GBS and MFS cases with seasonal difference. MFS was particularly prevalent accounting for 52% of the total cases.

Fifteen months after the initial hospitalization, she returned to the hospital with progressive weakness, dysphagia, slurred speech, and great difficulty standing with increasingly frequent falls. Physical examination showed normal mentation, severe dysphagia, and dysarthria. Eye examination was completely normal with no ophthalmoplegia. Motor examination was significant for generalized muscle atrophy with fasciculation most obviously seen in right upper extremity. There was a positive Hoffman's sign, hyperreflexia in knee jerks, sustained clonus in the ankle, as well as bilateral positive Babinski sign. There were no signs of bowel or bladder incontinence and her lower motor strength was 4-/5 throughout. Sensation examination was normal for light touch, proprioception, ice sensation, and noxious stimuli.

Cervical spine MRI results were negative, with no evidence of signal abnormalities within the central cord. Vitamin B12 and thyroid function measurements were both within normal limits. The serum anticholinesterase antibody test was repeated and was again found to be negative.

After electromyography studies, a diagnosis of clinically definite spinal ALS was made based on the El Escorial Criteria. Riluzole was started. GQ1b antibody level was elevated in isolation at 376; the rest of the ganglioside panel was negative. No pathologic mutations were detected by massive parallel sequencing of the coding regions and intron-exon boundaries or by deletion/duplication analysis of the 11 target genes associated with familial ALS by ARUP Laboratories. No immunotherapy was administered.

Patient experienced a rapid deterioration and was bedridden within 9 months of ALS confirmation. She developed terminal dysphagia and received a gastric tube placement. Despite respiratory difficulty, she refused mechanical ventilation. She went into Hospice Care after a tracheostomy and passed away 1 year after ALS diagnosis.

2. Discussion

This patient was first affected by MFS. She displayed a classic presentation, response to treatment, as well as typical recovery course of MFS. Her GQ1b was strongly positive and had been declining on follow up exam and testing. Following recovery from MFS, the patient experienced an asymptomatic period for a year until she began to display signs of ALS. Accompanying the symptomatology of ALS, it was noted that the GQ1b level had become strongly positive again. Her ALS course was also typical as her extraocular movement was completely spared and she developed pathologic hyperreflexia, which are expected in ALS. Bowel and bladder control remained intact. For those ALS patients with positive ganglioside antibody, only one study has observed the presence of IgG GQ1b antibody in one subject among the patient cohort (Sawaya, 2019). The correlation between the antibody titers and clinical presentation of ALS has not been fully elucidated, as some studies report a higher titer in patients with significantly more severe lower motor neuron deficit

(Pestronk et al., 1998; Lamb and Patten, 1991).

A point of interest in this report is that we have demonstrated GQ1b as the ganglioside antibody that is involved in both illnesses in tandem. The fact that its level dropped during MFS recovery but again became elevated during ALS manifestation raised the question of the role of GQ1b in various diseases. A study shows that the level of GQ1b can fluctuate and even increase in the months after MFS recovery (Sawaya, 2019), but no one has documented a rise in a separate disease entity (ALS) 18 months after recovery from MFS.

Generally believed to be a consequence of molecular mimicry, our understanding of the exact role of GQ1b in the pathophysiology of MFS remains incomplete. The relation between the presence of anti GQ1b antibody and various disease presentations is poorly understood. In the peripheral neuromuscular system, GQ1b is found in extraocular neuromuscular junctions and muscle spindles (Liu et al., 2009). In the central nervous system, GQ1b is associated with Bickerstaff's brainstem encephalitis (BBE) with implied involvement of this ganglioside in the brainstem (Saito et al., 2013). GQ1b positive sera from both MFS and BBE were studied and only sera from the latter were demonstrated to destroy the blood brain barrier. This finding has led to the consideration that the clinical manifestation of the antibody in question may be dependent upon the presence or absence of blood brain barrier disruption. GQ1b appears to be only part of the disease mechanism, its presence does not dictate the manifestation.

Even less is known about the association between ALS and GQ1b. It is known that GM1, GD1 and GD1b are found in certain locations within the central nervous system (Liu et al., 2009), and GQ1b is found to be less abundant than the other gangliosides in brain regions other than the motor cortex in ALS brain postmortem study (Rapport et al., 1985). In an otherwise normal brain, GQ1b is found to be less prevalent in white matter to begin with, indicating that the presence of elevated levels on laboratory testing may hold significance (Marconi et al., 2005). No study or article has addressed GQ1b presence in neurons and glial cells of the motor track. Together with the fact that GQ1b is rarely found in ALS patients, a simple molecular mimicry is not the answer. For a possible explanation, we turn to the cellular function disruption aspect of MFS and ALS. GQ1b antibody is known to inhibit voltage-gated calcium channel (VGCC) current in cerebellar granule cells (Nakatani et al., 2009). The mechanism of damage to the cells can be calcium current abnormality and/or complement activation in nature (Smith et al., 1995). For ALS, it is known that abnormal calcium channel kinetics as well as intracellular calcium influx are associated features (Appel et al., 1995; Boylu et al., 2010). Sporadic ALS patients have antibodies that bind to certain subtypes of VGCC. Studying the cytotoxicity of such has led some to believe it is responsible for motor neuron cell death (Smith et al., 1994). The question of whether GQ1b and calcium abnormality can be the link between these 2 diseases is yet to be fully explored.

Knowledge of GQ1b's role in MFS and ALS still do not explain the reason why MFS and ALS occurred in tandem for this patient. It is not a common occurrence. ALS is probably not a uniform disease. There are probably different subtypes or etiologies leading to the motor neuron's demise. Researchers have found an immune component of ALS. Besides developing vaccines/immunotherapy that have shown to slow down motor neuron's death (Zhao et al., 2019; Urushitani et al., 2019), there is also a case of a young girl who developed ALS after Human Papilloma virus vaccine (Hikiyami et al., 2018). The idea of ALS being triggered by a vaccination was brought up. In our current patient, the possibility that an infection/environmental exposure could trigger both the MFS (manifested within weeks) and the pathologic cascade of ALS is considered. As mentioned, this patient's MFS was among a surge of GBS and MFS cases observed by the author reported in a previous article (Liu and Yang, 2020). GQ1b antibody was positive for 50% of these MFS patients. A seasonal difference was observed between the GBS and MFS cases. This yet to be identified trigger may have started both diseases with GQ1b as a common link.

GQ1b antibody may have a potential association with the onset and

development of ALS clinical presentation in the case discussed. This correlation demonstrates a potential clinical implication for the utility of GQ1b in detecting and following the progression of ALS. Further study is needed to understand the relationship between ALS and the role of ganglioside antibodies, particularly GQ1b. Furthermore, since immunotherapy has been studied in ALS, vaccine development and immunomodulation (plasma exchange and IVIG) should be studied in future cases of ALS with a positive ganglioside antibody panel.

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Consent form

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Declaration of competing interest

The authors have no financial or other conflicting interests to declare.

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