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Case Report

GM1 ganglioside antibody and COVID-19 related Guillain Barre Syndrome – A case report, systemic review and implication for vaccine development

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ABSTRACT

Background: Guillain Barre Syndrome (GBS) and Miller Fisher Syndrome (MFS) are emerging as known consequences of COVID-19 infection. However, there have been no reported cases with positive GM1 or GQ1b antibodies in the literature to date. Although clinically similar, the pathophysiology of COVID-19 related GBS and MFS may be significantly different from cases in the pre-pandemic era.

Case presentation: We present a patient with ascending areflexic weakness consistent with GBS with positive GM1 antibody. The patient had recovered from COVID-19 infection two weeks prior with mild viral illness and symptoms. Her weakness was isolated to the lower extremities and improved after intravenous immunoglobulin treatment. Patient recovered eventually.

Conclusions: – The general lack of reported ganglioside antibodies supports a novel target(s) for molecular mimicry as the underlying etiology, which raises the concern for possible vaccine induced complication. Whether the current GM1 positive case is a sequelae of COVID-19 or a mere coincidence is inconclusive. Further understanding of the disease mechanism of pandemic era GBS and MFS, including antigen target(s) of COVID-19, may be of utmost importance to the development of a safe COVID-19 vaccine.

1. Introduction

GBS and one of its variant MFS are autoimmune diseases that are commonly associated with a preceding infection that can lead to cross-reactions between components of peripheral nerves, leading to inflammatory demyelination. It is not too common, with an incidence of 2–3 per 100,000 cases, however surges and seasonal variation have been observed (Yang and Liu, 2020). Gangliosides are molecular markers expressed on peripheral nerves. They are important in the maintenance and repair of neurons. They also participate in synaptic transmission. They play a central role in the molecular mimicry pathophysiology of GBS and MFS, triggering of immune response against self-peptides due to molecularly similar peptides being expressed by a pathogen. Commonly tested ganglioside antibodies include: GM1, GM2, Asialo GM1, GD1a, GD1b, and GQ1b. GM1 is the most common ganglioside antibody found in patients with GBS while GQ1b is associated with MFV. GM1 is found to be positive in 88% of GBS patients in one study (Basta et al., 2005). Prior to the current COVID-19 pandemic, it was uncommon to have a completely negative ganglioside antibody panel for cases of GBS and MFS. Aside from our current case, a review of available articles yields no

reported cases of COVID-19 related GBS or MFS which tested positive for GM1 or GQ1b. The results of our review are presented, followed by discussion of possible pathophysiology and important implications.

2. Method

A Pub Med literature search was performed on August 28, 2020 which yielded 102 entries related to COVID-19 induced GBS and/or MFV. Searches were performed cross referencing the following key terms “Covid-19”, “Guillain Barre”, “Miller Fisher”, “GM1”, “GQ1b”, and “Ganglioside”. Of the 102 articles found eight were large scale review papers (Abu-Rumeileh et al., 2020; De Sanctis et al., 2020; Galassi and Marchioni, 2020; Caress et al., 2020; Ellul et al., 2020; Guijarro-Castro et al., 2020; Dalakas, 2020; Romoli et al., 2020); the other entries were all case reports. All cases included in the eight review papers and each separate case studies were reviewed. All cases in the review papers were tracked to their primary source to prevent duplication of cases. Laboratory data and ganglioside antibody testing was extracted from the case descriptions. Ganglioside antibody testing was either not reported (NR) or the results were clearly stated. We then included the ganglioside

Abbreviations: ACE2, Angiotensin-Converting Enzyme 2; GBS, Guillain Barre Syndrome; HSP, Heat Shock Protein; MFS, Miller Fisher Syndrome.

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antibody testing information on our case.

3. Case

A 36-year-old woman with obesity presented to Emergency Department (ED) with 3 days of progressive ascending weakness. On day of admission, she was unable to stand and ambulate. Her history is significant for recent recovery from a COVID-19 infection. She was exposed to the virus by her brother. She had a positive nasopharyngeal swab, PCR SARS-CoV-2 testing, 3 weeks prior to presenting to the ED. She experienced loss of smell and taste, generalized malaise and mild shortness of breath. She was released after one day of hospitalization and recuperated at home. She did not receive remdesivir or steroid. She never had muscle weakness or gait difficulty until 3 days prior to the current admission. On examination, she had normal vital signs. General overall examination by the ED was unremarkable. On neurological examination, she was oriented and coherent. Cranial Nerves 1–12 were all intact. Upper extremities strength was 5/5 and lower extremities strength was 3/5. There were no sensory deficits. She had absent deep tendon reflexes. The patient did not have bowel or bladder control problems. She was unable to stand or ambulate at the time of admission. Her upper extremities demonstrated no dysmetria or dysidiadochokinesia. MRI of head and whole spine were negative for demyelination, or infarct. Her blood chemistry, hematology studies, and hepatic function tests were all normal. Her COVID-19 nasopharyngeal swab test was negative at the time of current presentation. Spinal fluid analysis showed 0 WBC, 0 RBC, and protein of 20 mg/dL. Her B12 level was normal at 499 pg/mL. Ganglioside antibody panel was positive for multiple antibodies (see table). Patient deferred electrodiagnostic studies.

The patient's lower extremities strength continued to worsen for 3 days in the hospital. Intravenous immunoglobulin at 400 mg/kg/day was administered for 5 days. After one week of hospitalization, her strength began to improve. She was eventually discharged home after 10 days in the hospital. A follow up phone call after 3 weeks, found that that patient was already ambulating with a walker and even short distances with a cane.

4. Result of literature review

The most recent review paper by Abu-Rumeileh et al. is also the most extensive, which included 73 cases (Abu-Rumeileh et al., 2020). It included most of the cases reviewed in the other seven review papers that were published prior (De Sanctis et al., 2020; Galassi and Marchioni, 2020; Caress et al., 2020; Ellul et al., 2020; Guijarro-Castro et al., 2020; Dalakas, 2020; Romoli et al., 2020). Only two additional cases have been identified by a shorter review paper by Ellul et al. (2020). The 73-case review paper by Abu-Rumeileh et al. included cases published up until 7/20/2020. We reviewed all the cases excluded by Abu-Rumeileh et al. also and found no positive ganglioside antibodies among those excluded patients. We have identified seven more reported individual cases, which have not been included in any case review to date (Berciano and Gallardo, 2020; Garcia-Manzanedo et al., 2020; Abrams et al., 2020; Ray, 2020; Senel et al., 2020; Maideniuc and Memon, 2020; Pelea et al., 2020). Including our current case, there are 83 individual cases of COVID-19 related GBS or MFS being reported to date. Nine cases are MFS and 74 cases are GBS. Forty-seven cases had NR. Among the 36 cases that reported testing results, 31 were negative for the commonly tested antibodies. The five cases that reported positive ganglioside antibody testing are (Table 1):

The case with positive GM2 testing reported by Chan was mistakenly noted as GM1 in the review paper by Abu-Rumeileh et al. (2020). In over half of the cases reported, cerebral spinal fluid analysis was not performed or mentioned. Based on our review, many of the cases lack electrodiagnostic studies. In the case reported with positive GD1a testing, COVID-19 testing was negative and the patient was asymptomatic. COVID-19 diagnosis was made based on the appearance of "ground glass"

Table 1

Three GBS and two MFS patients and their ganglioside antibody panel.

Author:	Disease:	Lab Positive:
Gutierrez (Gutierrez-Ortiz et al., 2020)	MFS	GD1b
Lantos (Lantos and Strauss, 2020)	MFS	Equivocal Asialo GM1
Gigli (Gigli et al., 2020)	GBS	GD1a
Chan (Chan et al., 2020)	GBS	GM2 (not GM1)
Current case	GBS	Asialo GM1: 76, GM1: 58, GD1a: 76, GD1b: 60 and GQ1b: 56

on the patient's chest CT scan. In Lantos' case, the Asialo GM1 was only equivocally positive. Our review shows there is roughly 14% positivity on ganglioside antibody studies in presumed COVID-19 related GBS and MFS cases. There have been no cases positive for GM1 in those with GBS and no MFS cases with positive GQ1b testing prior to our case.

5. Discussion

The patient in our case has clinical presentation, laboratory studies and therapeutic response typical of GBS. Neurophysiological studies usually play an important role in the diagnosis, subtype determination and prognosis estimation. Lacking such is a potential weakness of our case. However, with our current pandemic, such studies are lacking in more than half of the reported cases due to various reasons and availability. With a positive GM1 antibody test, we are confident that GBS is our patient's diagnosis.

Although not essential to the diagnosis of GBS or MFS, positive antibody testing helps guide the clinician, especially when the clinical presentation is mild, atypical or confounded by other factors. Additionally, we commonly see a combination of positive antibodies on the testing panel. The exact role of each antibody is still up for discussion; patients with the same clinical presentation can have very different antibody profiles. Furthermore, the same antibody can have very different clinical presentations. For example, GQ1b is found in both MFS as well as in Bickerstaff encephalitis. With lack of familiar antibodies identified, we do not yet fully understand the true pathological steps (what the immune system is targeting) leading to demyelination of the peripheral nervous system caused by COVID-19 infection.

Since COVID related GBS and MFS cases do respond favorably to IVIG and plasma exchange, molecular mimicry is probably the most likely etiology. Due to the absence of cases reporting GM1 and GQ1b positive testing prior, it appears that COVID-19 induces GBS and MFS through a different target(s). There are many articles citing the pathologic role played by angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is present on neuron and glial cells (Zhou et al., 2020). Other candidate being mentioned is heat shock protein (HSP), in particular HSP 27, 60, 70 and 90 (Lucchese and Floel, 2020). Identifying the true antigen related to COVID-19 induced GBS and MFS may be of paramount importance to improving the safety profile of these new vaccines. This concern is not unfounded as there was a significant increase of GBS cases after the 1976 swine flu vaccine program (Vellozzi et al., 2014). Current vaccine production usually takes an estimated 10–15 years from concept to mass production. This consists of three phases that demonstrate the safety, immunogenicity, and efficacy in a large-scale population. We want to ensure that traditional safeguards are not bypassed to expedite the release of a COVID-19 vaccine (Han, 2015).

Standard GBS and MFS (not associated with COVID-19) is likely still occurring at their usual rates. We have seen a slight decrease in cases recently but this is likely due to social distancing and increased hand hygiene which reduces exposure to the usual germs or viruses that lead to GBS and MFS. Due to the overwhelming majority of negative GM1 or GQ1b in COVID-19 associated GBS and MFS seen so far, our case here can be interpreted as either the very first documented case of GM1 positive COVID-19 related GBS or the first confirmed non-COVID-19 related GBS.

It is likely that any further report citing positive GM1 or GQ1b testing maybe a coincidence rather than a true association.

6. Conclusion

More effort and research are needed to locate the true antigen target(s) in COVID-19 related GBS and MFS. This may be essential in determining the true incidence of COVID-19 related GBS and MFS, as well as in the development of more effective treatment and ultimately a safe vaccine.

Declaration of competing interest

There is no conflict of interest to report. There is no funding involved.

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References

- Abrams, R., Kim, B., Markantone, D., et al., 2020. Severe rapidly progressive Guillain Barre syndrome in the setting of acute COVID-19 disease. *J. Neurovirol.* 1–3. <https://doi.org/10.1007/s13365-020-00884-7>.
- Abu-Rumeileh, S., Abdelhak, A., Foschi, M., et al., 2020. Guillain Barre syndrome spectrum associated with COVID-19: an up-to-date systemic review of 73 cases. *J. Neurol.* <https://doi.org/10.1007/s00415-020-10124-x>. (Accessed 25 August 2020).
- Basta, I., Suturkova, L., Vujic, A., et al., 2005. Antibodies to ganglioside GM1 C jejuni in patients with Guillain Barre syndrome. *Srp Arh Celok Lek.* Mar-Apr 133 (3–4), 123–128. <https://doi.org/10.2298/sarh0504123b>, 2005.
- Berciano, J., Gallardo, E., 2020. Spinal nerve pathology in Guillain Barre syndrome associated with COVID-19 infection. *Muscle Nerve.* <https://doi.org/10.1002/mus.27031>. (Accessed 21 July 2020).
- Caress, J., Castoro, R., Simmons, Z., et al., 2020. COVID-19-associated Guillain Barre syndrome: the early pandemic experience. *Muscle Nerve.* <https://doi.org/10.1002/mus.27024>. (Accessed 17 July 2020).
- Chan, M., Han, S., Kelly, S., et al., 2020. A case series of Guillain Barre Syndrome following COVID-19 infection in New York. *Neurol. Clin. Pract.* <https://doi.org/10.1212/CPJ.0000000000000880>.
- Dalakas, M.C., 2020. Guillain Barre syndrome: the first documented COVID-19 triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol. Neuroimmunol. Neuroinflamm.* 7 (5), e781 <https://doi.org/10.1212/NXI.0000000000000781>. (Accessed 9 June 2020).
- De Sanctis, P., Doneddu, P., Vigano, L., et al., 2020. Guillain Barre Syndrome associated with SARS-CoV-2 infection. A systemic review. *Eur. J. Neurol.* 14462.
- Ellul, M., Benjamin, L., Singh, B., et al., 2020. Neurological associations of COVID-19. *Lancet Neurol.* 19 (9), 767–783. [https://doi.org/10.1016/S1474-4422\(20\)30221-0](https://doi.org/10.1016/S1474-4422(20)30221-0). (Accessed September 2020).
- Galassi, G., Marchioni, A., 2020. Facing acute neuromuscular diseases during COVID-19 pandemic: focus on Guillain Barre syndrome. *Acta Neurol. Belg.* 1–9. <https://doi.org/10.1007/s13760-020-01421-3>. (Accessed 21 July 2020).
- Garcia-Manzanedo, S., Lopez de la Oliva Calvo, L., Ruiz, S., et al., 2020. Guillain Barre syndrome after COVID-19 infection. *Med. Clin.* (20), S0025–S7753. <https://doi.org/10.1016/j.medcli.2020.06.023>. (Accessed 9 July 2020).
- Gigli, G., Bax, F., Marini, A., et al., 2020. Guillain Barre syndrome in the COVID-19 era: just an occasional cluster? *J. Neurol.* 1–3. <https://doi.org/10.1007/s00415-020-09911-3>, 2020 May 19.
- Guijarro-Castro, C., Roson-Gonzalez, M., Abreu, A., et al., 2020. Guillain Barre Syndrome associated with SARS-CoV-2 infection. Comments after 16 published cases. *Neurologia* 35 (6), 412–415. <https://doi.org/10.1016/j.nrl.2020.06.002>. (Accessed July 2020).
- Gutierrez-Ortiz, C., Mendez-Guerrero, A., Rodrigo-Rey, S., et al., 2020. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 95 (5), e601–e605. <https://doi.org/10.1212/WNL.0000000000009619>, 2020 Aug 4.
- Han, Seunghoon, 2015. Clinical vaccine development. *Clin. Exp. Vaccine Res.* 4 (1), 46–53. <https://doi.org/10.7774/cevr.2015.4.1.46>, 2015 Jan.
- Lantos, J., Strauss, Lin E., 2020. COVID-19-associated miller Fisher syndrome: MRI findings. *Am. J. Neuroradiol.* 41 (7), 1184–1186. <https://doi.org/10.3174/ajnr.A6609>, 2020 Jul.
- Lucchese, G., Floel, A., 2020. SARS-XCoV-2 and Guillain-Barre syndrome: molecular mimicry with human heat shock proteins as potential pathogenic mechanism. *Cell Stress Chaperones* 1–5. <https://doi.org/10.1007/s12192-01145-6>, 2020 Jul 29.
- Maideniuc, C., Memon, A., 2020. Acute necrotizing myelitis and acute motor axonal neuropathy in a COVID-19 patient. *J. Neurol.* 1–3. <https://doi.org/10.1007/s00415-020-10145-6>, 2020 Aug 9.
- Pelea, T., Reuter, U., Schmidt, C., et al., 2020. SARS-CoV-2 associated Guillain Barre syndrome. *J. Neurol.* 1–4. <https://doi.org/10.1007/s00415-020-10133-w>, 2020 AUG 8.
- Ray, A., 2020. Miller Fisher syndrome and COVID-19: is there a link? *BMJ Case Rep.* 13 (8), e236419 <https://doi.org/10.1136/bcr-2020-236419>. (Accessed 11 August 2020).
- Romoli, M., Jelcic, I., Bernard-Valnet, R., et al., 2020. A systemic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details. *Eur. J. Neurol.* <https://doi.org/10.1111/ene.14382>, 2020 Jun 5.
- Senel, M., Abu-Rumeileh, S., Michel, D., et al., 2020. Miller-Fisher syndrome after COVID-19: neurochemical markers as an early sign of nervous system involvement. *Eur. J. Neurol.* <https://doi.org/10.1111/ene.14473>.
- Vellozzi, C., Iqbal, S., Broder, K., 2014. Guillain Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence. *Clin. Infect. Dis.* 58 (8), 1149–1155. <https://doi.org/10.1093/cid/ciu005>, 2014 Apr.
- Yang, M., Liu, A., 2020. Surge of Miller Fisher variant and Guillain Barre syndrome in two downtown Los Angeles community teaching hospitals. *Clin. Case Rep.* 1–6. <https://doi.org/10.1002/ccr3.3132>, 2020;00.
- Zhou, Z., Kang, H., Li, S., et al., 2020. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotrophic mechanisms. *J. Neurol.* 267 (8), 2179–2184. <https://doi.org/10.1007/s00415-020-09929-7>.