Miller Fisher syndrome after Pfizer BioNTech vaccine booster responsive to intravenous Ig treatment

Baibing Chen , Sebastian Lopez, Eric Eggenberger

Department of Neurology, Mayo Clinic in Florida, Jacksonville, Florida, USA

Correspondence to
Dr Baibing Chen;
baibingchen.yale@gmail.com

Accepted 28 October 2022

DESCRIPTION

A woman in her 70s received the Pfizer BioNTech (BNT162b2) COVID-19 vaccine booster. Two weeks later, she developed progressive gait imbalance, diplopia and headache without antecedent constitutional or infectious symptoms. Her medical history was significant for hypertension and breast cancer in remission.

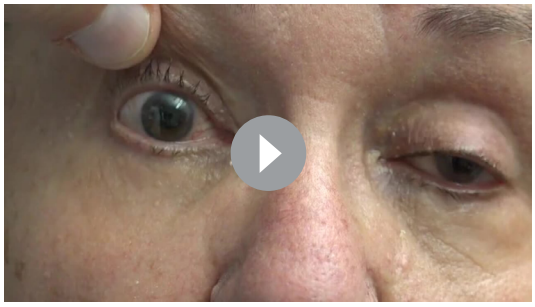
On presentation, the patient was hypertensive, with blood pressure fluctuations between 133/61 mm Hg and 191/79 mm Hg over the 2 days after admission, perhaps reflecting a degree of autonomic dysfunction. The initial examination demonstrated partial global ophthalmoparesis, bilateral ptosis, slowed saccades in restricted range, minimally responsive pupils with a degree of light near dissociation (video 1), bilateral limb ataxia with preserved reflexes, and preserved sensation to light touch, pinprick, vibration, proprioception and temperature in all four limbs. Lumbar puncture showed 0 nucleated cells, glucose of 87 mg/dL and protein of 29 mg/dL. Bacterial and fungal cultures were negative. MRI of the brain with and without contrast showed no abnormalities. Nerve conduction study (NCS) and electromyography showed acute left facial neuropathy, reduced fibular and tibial motor amplitudes, and a mildly prolonged ulnar F wave relative to the F estimate, but no additional abnormalities and no electrophysiological evidence of a neuromuscular junction disorder (table 1). A 5-day course of intravenous Ig 0.4 g/kg resulted in symptom improvement. Serum GQ1b IgG antibodies titres were elevated at 1:12 800 (normal <1:100), supporting the diagnosis of Miller Fisher syndrome (MFS). As for other serum labs, the patient had unremarkable comprehensive metabolic panel, complete blood count with differential, sedimentation rate, C reactive protein, rapid plasma reagin, aquaporin-4-IgG, myelin oligodendrocyte glycoprotein antibody and myasthenia gravis panel.

At the 2-month follow-up visit, the patient had further improvement in symptoms (video 1). She continued to have mild ophthalmoplegia and mild ataxia but was able to ambulate independently and complete her activities of daily living.

MFS is a subtype of Guillain-Barre Syndrome (GBS), a group of immune-mediated acute neuropathies. It is rare, with an incidence of approximately 1 per 1 million. MFS can present after infections or following vaccinations.[1] Postvaccination MFS incidence is unclear in the literature due to its uncommon occurrence. Postvaccination GBS has been reported more frequently, especially in association with the influenza vaccine. The risk of developing GBS is low following vaccination, increasing by one case for every million cases.[2] The prognosis of MFS is generally good, with most patients showing significant improvement or resolution of their symptoms by 6 months.[3] There is some evidence that intravenous Ig therapy may reduce the time to symptom recovery, but plasmapheresis does not appear to affect it. Neither intravenous Ig or plasmapheresis had been shown to affect patient outcomes compared with no immunotherapy.[4] In patients who developed MFS after COVID-19 vaccines, there is currently no long-term data. In the previously reported cases, patients significantly improved 4–6 weeks after immunotherapy.[5]

The Pfizer BioNTech vaccine contains a nucleoside-modified mRNA that encodes the SARS-CoV-2 spike glycoprotein and was designed to elicit B-cell and T-cell responses against the spike protein.[6] MFS had been reported in patients after COVID-19 infection and following the first and second doses of the Pfizer vaccine.[7–10] There also had been multiple cases of GBS reported in patients after receiving COVID-19 vaccination.[11–13] A causal link cannot be established with the very low number of cases compared with the number of vaccines administered, but the timing is supportive. To the best of our knowledge, there has not been a published report of MFS or GBS after the Pfizer vaccine booster.

The classic triad of MFS is ophthalmoplegia, ataxia and areflexia[14]; however, many patients present with incomplete forms. Berlit and Rakicky reported that global ophthalmoplegia was present in 48.9% of patients, and areflexia in 81.6%.[15] Odaka *et al* reported hyporeflexia or areflexia in 53% of MFS patients.[16] The reason for the variability in symptom presentation between individuals is unclear, but it may be secondary to the



Video 1 Neuro-ophthalmological examination in a patient with Miller Fisher syndrome before and after treatment with intravenous immunoglobulin

To cite: Chen B, Lopez S, Eggenberger E. *BMJ Case Rep* 2022;**15**:e251361. doi:10.1136/bcr-2022-251361

Table 1 Nerve conduction study and electromyography

Nerve conduction

		Record	Rep			Normal		Normal	Distal	Normal	F-Wave	F-Wave	Temp
Nerve	Type	Site	Stim	Side	Amp	Amp	CV	CV	Lat	Lat	Lat	Est	(°C)
Fibular	Motor	EDB		L	0.5	(> 2.0)	43	(> 41)	5	(< 6.6)			30.5
Spinal Accessory	Motor	Trapezius	*	L	6.8				2.2				32.7
Facial	Motor	Nasalis	*	L	1.5	(> 1.8)			3	(< 4.1)			33.9
Tibial	Motor	AH		L	1.7	(> 4.0)	41	(> 40)	4.7	(< 6.1)	63	59.8	30.5
Sural	Sensory	Ankle		L	4	(> 0.0)		(> 40)	3.3	(< 4.5)			30.5
Median	Motor	APB		L	9.3	(> 4.0)	49	(> 48)	4.4	(< 4.5)	29.4	31.3	32.3
Ulnar	Motor	ADM	*	L	8.5	(> 6.0)	59	(> 51)	3	(< 3.6)	31	25.4	33
Median	Sensory	Dig II		L	24	(> 15.0)	58	(> 56)	3.3	(< 3.6)			32.6
Ulnar	Sensory	Dig V		L	30	(> 10.0)	63	(> 54)	2.7	(< 3.1)			33.3

Blinks

				R1	R2	R2
	Recording	Stim		Ipsi	Ipsi	Contra
Nerve	Point	Point	Side	Latency	Latency	Latency
Blink supra Orb	Orbicularis oculi	Supra Orb	L	11.4	32.5	35.5
Blink supra Orb	Orbicularis oculi	Supra Orb	R	11.4	31.1	34.7

Needle EMG

		Ins	Spont		MUP		Recruitment		Duration		Amplitude		Phases	
Muscle	Side	Act	Fib	Fasc	Normal	Activ	Reduced	Rapid	Long	Short	High	Low	%	Turns
First dorsal interosseous	L	NL	0	0	NL									
Deltoid	L	NL	0	0	NL									
Triceps brachii	L	NL	0	0	NL									
Trapezius (upper)	L	NL	0	0	NL									
Tensor fasciae latae	L	NL	0	0	NL									
Vastus medialis	L	NL	0	0	NL									
Tibialis anterior	L	NL	0	0	NL									
Frontalis	L	NL	0	0			+/-							
Orbicularis oculi	L	NL	0	0			++							
Orbicularis oris	L	NL	0	0			++		+		+			

*, repetitive nerve stimulation applied; AD, abductor hallucis; ADM, abductor digiti minimi; APB, abductor pollicis brevis; CV, conduction velocity; EDB, extensor digitorum brevis; EMG, electromyography; NL, normal limits.

variation in GQ1b expression sites in the central and peripheral nervous systems. In our case, the patient had ophthalmoplegia and bilateral ataxia with preserved reflexes. There has been much debate regarding whether ataxia in MFS is central or peripheral, or both.[17] In addition to the heavy expression of GQ1b in the ocular motor nerves, GQ1b has also been found in the cerebellum, muscle spindles and large-diameter dorsal root ganglion neurons.[18–20] Berlit and Rakicky reported that in MFS patients that presented with ataxia, 90.1% presented with cerebellar ataxia and only 0.9% presented with sensory ataxia.[15] In MFS patients with evidence of sensory neuropathy on NCS, the sensory NCS can often be incongruent with the level of ataxia and areflexia/hyporeflexia found. Motor and sensory NCS can oftentimes be normal in symptomatic MFS patients and are not reliable for diagnosis or exclusion.[6–9 21]

In conclusion, we describe a case of MFS after the Pfizer COVID-19 vaccine booster. In patients with symptoms involving ophthalmoplegia, ataxia and/or areflexia after receiving the COVID-19 vaccine, MFS should be included in the differential diagnosis. GQ1b antibodies can help confirm diagnosis, and immunotherapy may reduce time to symptom recovery and should be considered. MFS is very rare and should not dissuade people from receiving the vaccine, especially given its favourable risk–benefit ratio.

Patient's perspective

This is a timeline of events that led to my Miller Fisher diagnosis.

A. Received Pfizer COVID-19 vaccines:
   1. First dose (date hidden)
   2. Second dose (date hidden)

B. Booster (date hidden) (3 weeks after the booster vaccine) I noticed my pupils were dilated and walking was difficult and getting worse each day.
   I decided to go to the local hospital emergency room, and I was admitted into the hospital that day.
   The hospital ran a series of tests on me to determine the cause of my condition. Meanwhile they were in contact with (hospital name hidden) because they were baffled by my symptoms. Unable to determine what was causing my symptoms, I was transferred to the (hospital name hidden).
   The physicians there determined that I had Miller Fisher.
   The next day I began 5 days of intravenous Immunoglobulin (IVIG).
   As of today, (date hidden), my eyes aren't normal, but they are better. My legs are weaker than before but seem to be getting stronger.
   In closing I would like to thank (hospital name hidden) and their staff for their care. The commercial for (hospital name hidden) that says if (quote hidden), really fits me. (Name hidden) is the ultimate consummate physician. He is caring and so professional. What is really amazing to me is that he really listened to what I had to say. This seems to be a lost art today with some of our doctors. I am (age hidden) and have been seeing doctors and having surgery since I was (age hidden) and he really stands out among them!

Learning points

- Miller Fisher syndrome (MFS) is a rare event following SARS-CoV-2 vaccination.
- While ataxia, ophthalmoplegia and areflexia constitute the cardinal features of MFS, partial presentations are common.
- SARS-CoV-2 vaccine-associated MFS appears to have a favourable prognosis and may be responsive to immunotherapy.

Contributors BC, SL and EE treated the patient in the report for her condition both in the inpatient and outpatient settings. SL had the initial idea for the article. BC, SL and EE had access to all patient data, met and reviewed the patient's case, and planned to publish an article regarding the novel finding discussed in the report. BC was determined to be the primary author given the most time spent caring for the patient clinically. BC was responsible for discussing with the patient regarding the article and obtaining consent from the patient in written form. BC was responsible for drafting the article, and SL and EE were responsible for revising it critically for important intellectual content. EE was responsible for recording the patient videos before and after treatment. BC, SL and EE agreed on a finalised version of the case report to be submitted for publication once all agreed revisions were made on previous drafts. BC accepts full responsibility for the finished article and controlled the decision to publish. BC, SL and EE agreed to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Baibing Chen http://orcid.org/0000-0002-5713-5518

REFERENCES

1 Lo YL, . Clinical and immunological spectrum of the Miller Fisher syndrome. *Muscle Nerve* 2007;36:615–27.
2 Lasky T, Terracciano GJ, Magder L, *et al*. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med* 1998;339:1797–802.
3 Mori M, Kuwabara S, Fukutake T, *et al*. Clinical features and prognosis of Miller Fisher syndrome. *Neurology* 2001;56:1104–6.
4 Mori M, Kuwabara S, Fukutake T, *et al*. Intravenous immunoglobulin therapy for Miller Fisher syndrome. *Neurology* 2007;68:1144–6.
5 Siddiqi AR, Khan T, Tahir MJ, *et al*. Miller Fisher syndrome after COVID-19 vaccination: case report and review of literature. *Medicine* 2022;101:e29333.
6 Patel R, Kaki M, Potluri VS, *et al*. A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. *Hum Vaccin Immunother* 2022;18:2002083.
7 Michaelson NM, Lam T, Malhotra A, *et al*. Miller Fisher syndrome presenting after a second dose of Pfizer-BioNTech vaccination in a patient with resolved COVID-19: a case report. *J Clin Neuromuscul Dis* 2021;23:113–5.
8 Nishiguchi Y, Matsuyama H, Maeda K, *et al*. Miller Fisher syndrome following BNT162b2 mRNA coronavirus 2019 vaccination. *BMC Neurol* 2021;21:452.
9 Abičić A, Adamec I, Habek M. Miller Fisher syndrome following pfizer COVID-19 vaccine. *Neurol Sci* 2022;43:1495–7.
10 Yamakawa M, Nakahara K, Nakanishi T, *et al*. Miller Fisher syndrome following vaccination against SARS-CoV-2. *Intern Med* 2022;61:1067–9.
11 Razok A, Shams A, Almeer A. Post-COVID-19 vaccine Guillain-Barré syndrome; first reported case from Qatar. *Ann Med Surg*.
12 García-Grimshaw M, Michel-Chávez A, Vera-Zertuche JM. Guillain-Barré syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. *Clin Immunol*.
13 Chun JY, Park S, Jung J, *et al*. Guillain-Barré syndrome after vaccination against COVID-19. *Lancet Neurol* 2022;21:117–9.
14 Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med* 1956;255:57–65.
15 Berlit P, Rakicky J. The Miller Fisher syndrome. review of the literature. *J Clin Neuroophthalmol* 1992;12:57–63.

16 Odaka M, Yuki N, Hirata K. Anti-Gq1B IgG antibody syndrome: clinical and immunological range. *J Neurol Neurosurg Psychiatry* 2001;70:50–5.
17 Sandler RD, Hoggard N, Hadjivassiliou M. Miller-Fisher syndrome: is the ataxia central or peripheral? *Cerebellum Ataxias* 2015;2:3.
18 Kotani M, Kawashima I, Ozawa H, *et al*. Differential distribution of major gangliosides in rat central nervous system detected by specific monoclonal antibodies. *Glycobiology* 1993;3:137–46.
19 Kusunoki S, Chiba A, Kanazawa I. Anti-Gq1B IgG antibody is associated with ataxia as well as ophthalmoplegia. *Muscle Nerve* 1999;22:1071–4.
20 Liu J-X, Willison HJ, Pedrosa-Domellöf F. Immunolocalization of GQ1b and related gangliosides in human extraocular neuromuscular junctions and muscle spindles. *Invest Ophthalmol Vis Sci* 2009;50:3226–32.
21 Arányi Z, Kovács T, Sipos I, *et al*. Miller Fisher syndrome: brief overview and update with a focus on electrophysiological findings. *Eur J Neurol* 2012;19:15–e3.