



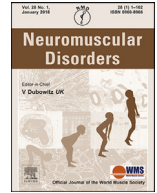
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SARS-CoV-2 vaccination and new-onset myasthenia gravis: A report of 7 cases and review of the literature



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ABSTRACT

Myasthenia gravis (MG) is an antibody-mediated immune disorder of the neuromuscular junction. SARS-CoV-2 is now recognised as a trigger factor for autoimmune diseases and to cause immune-mediated dysregulation, likely due to molecular mimicry induced by viral antigens. SARS-CoV-2 vaccination, similarly, results in exposure to viral antigen. Here we report 7 cases of new-onset myasthenia gravis in timely association with SARS-CoV-2 vaccination, including the first paediatric case identified to date. We also reviewed the literature for other new-onset MG cases reported within 4 weeks of SARS-CoV-2 vaccination and discuss our findings in the context of altered (auto)immunity following SARS-CoV-2 vaccination and/or infection.

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1. Introduction

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease of the neuromuscular junction (NMJ). MG has an incidence of 30 per million/year in adults but is rarer (1–5 per million/year) in children under the age of 18 years [1]. MG is an acquired disease characterised by fatiguable muscle weakness with some risk factors including genetic predisposition and sex bias as well as possible triggers including infection, drugs, and emotional stress [2]. The pathophysiology of MG has been well-studied and

is characterised by predominantly antibody and/or complement-mediated disruption of the neuromuscular junction. Antibodies to the acetylcholine receptor (AChR) are most common, whilst those to muscle specific kinase (MuSK) and low-density lipoprotein (LRP4) occur with lower frequency [3]. In addition, a small proportion of patients with typical MG remain seronegative despite repeated testing, suggesting the presence of other currently unrecognised antibodies.

Viruses are recognised as environmental factors that can trigger autoimmunity in genetically susceptible individuals [4]. The mechanism of such autoimmune activation includes molecular mimicry, B cell clonal activation, epitope spreading, bystander activation and the presence of viral superantigens. There is accumulating evidence to suggest that SARS-CoV-2 virus can activate autoimmunity through a variety of mechanisms including hyperstimulation of the immune system, excess activation of neutrophil-associated cytokine response and neutrophil

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Table 1

Characteristics of the 7 new-onset cases with myasthenia gravis (MG) cases in timely association with SARS-CoV-2 vaccination reported in this study. AChR = Acetylcholine receptor antibody; RNS = Repetitive nerve stimulation; SfEMG = Single fibre EMG; PLEX = plasma exchange.

Patient #	Age at onset (years)	Sex	Vaccine	Vaccine dose	Time to symptom onset (days)	Seropostivity	Neurophysiology	MG subtype	Treatment
Patient 1	13	F	Pfizer-BioNTech®	1st dose	14	Negative	RNS – positive	Generalised	Pyridostigmine Prednisolone
Patient 2	59	M	Oxford-Astra Zeneca®	1st dose	2	AChR positive	No data	Generalised	Pyridostigmine Prednisolone
Patient 3	63	M	Pfizer-BioNTech®	3rd dose	3	AChR positive	No data	Ocular	Pyridostigmine
Patient 4	73	M	Pfizer-BioNTech®	3rd dose	12	AChR positive	SfEMG- increasing jitter	Generalised	Pyridostigmine IVIg Prednisolone
Patient 5	50	M	Pfizer-BioNTech®	1st dose	7	AChR positive	RNS -normal	Ocular	Pyridostigmine
Patient 6	83	F	Pfizer-BioNTech®	1st dose	6	AChR positive	RNS -normal SfEMG- not available	Generalised	Pyridostigmine IVIg Prednisolone
Patient 7	77	M	Oxford-Astra Zeneca®	1st dose	3	AChR positive	RNS and SfEMG – Positive	Generalised	Pyridostigmine PLEX Prednisolone

extracellular traps (NET) as well as molecular mimicry between host and virus, a mechanism that has been previously proposed for other viral antigens [4].

Several vaccines including influenza, hepatitis B, human papilloma virus (HPV), and e Bacillus Calmette-Guérin have been implicated in new onset MG or exacerbation of already established MG [5–13]. Molecular mimicry has been postulated as a possible mechanism with HPV L1 but this does not necessarily explain the mechanisms associated with other vaccination-induced cases [13].

2. Methods

Patients were identified via the British Myology Society (BMS), the North Star Neuromuscular network and the Muscle Interest Group (MIG) of the United Kingdom, dedicated networks of adult and paediatric neurologists with a special interest in neuromuscular disorders.

Members of the above groups were approached electronically via e-mail. We aimed to identify new-onset MG cases with onset within 4 weeks of administration of currently available SARS-CoV-2 vaccines seen in the period between 01.03.21 and 28.02.22 at a neuromuscular centre in the United Kingdom. As a positive control, we also asked for new-onset MG cases with onset within 4 weeks of administration of the seasonal flu vaccine seen in the period between 01.03.21 and 28.02.22 at a neuromuscular centre in the United Kingdom.

All investigations and procedures were conducted as part of routine clinical care. No specific ethical approval was required. All patients and/or their legal guardians gave informed consent to the publication of their anonymised clinical information. Anonymised data were shared in accordance with local hospital procedures, including patient demographics, clinical and treatment details. A literature review was then conducted to identify reported cases of new onset MG following SARS-CoV-2 vaccination.

3. Results

We identified 7 new onset MG patients (see Table 1) with disease-onset within 4 weeks of SARS-CoV-2 vaccination. Of the 7 patients, 5 (71%) were of male sex and 2 of female sex (29%). Six cases (86%) were seropositive with positive serum AChR antibody titres. Median age at MG diagnosis was 63 years (Interquartile Range (IQR) 54.5–75; range 13–83 years); with 6 adult cases (median age 68, IQR 60 to 76, range 50–83) and one case in the paediatric age range (age 13).

Median time from SARS-CoV-2 vaccination to MG symptom onset was 6 days (IQR 3 to 9.5, range 2–14 days). Two patients had symptom onset following the third (booster dose) of the vaccine. Two patients (Patients 3 and 4) had the seasonal influenza vaccine along with the third (booster dose) SARS-CoV-2 vaccine. One patient (Patient 6) had the seasonal influenza vaccine 4 days after first dose of SARS-CoV-2 vaccine and developed symptoms within one week of receiving the first dose of the SARS-CoV-2 vaccine.

All generalised MG patients had significant bulbar symptoms at onset or during the initial disease course. Four patients required initiation of nasogastric (NG) feeds. Median time from symptom onset to initiation of NG feed was 10 weeks (IQR 3.5–18, range 2–24). One patient (Patient 7) also required intensive care support for aspiration pneumonia and respiratory failure. All patients were treated with standard treatments for MG with good response. Two patients required intravenous immunoglobulin (Patients 4 and 6) and one (Patient 7) required plasmapheresis. One patient (Patient 1) had a strong family history of autoimmune disorders, and one patient (Patient 6) had a personal history of thyroid disease.

There were no patients identified that developed MG within 4 weeks of seasonal influenza vaccination in the absence of SARS-CoV-2 vaccination.

An additional literature review identified 7 published cases (see Table 2) of new onset MG following SARS-CoV-2 vaccination [14–19]. All were adults, 5 of male sex (71%) and 2 of female sex (29%). Median age at MG diagnosis was 72 years (IQR 58 to 73, range 33–82). Median time from SARS-CoV-2 vaccination to MG symptom onset was 2 days (IQR 1–7.5, range 1–12). Two patients (Patients 9 and 11) required intensive care support due to bulbar and respiratory failure.

4. Discussion

Here we report 7 patients with new-onset MG within 4 weeks of SARS-CoV-2 vaccination, to our knowledge the largest series of such patients reported to date. Including the cases so far reported in the literature (until May 2022), we discuss findings from a total of 14 patients. A particular strength of the UK cohort is that AChR antibody results were available from all 7 patients (one of them AChR antibody negative), whereas AChR antibody results were available from only 4 out of 7 previously published cases (two of them AChR antibody negative), somewhat limiting the conclusions to be drawn from the latter group. Of the 14 reported

Table 2

Characteristics of the 7 previously reported new-onset cases with myasthenia gravis (MG) cases in timely association with SARS-CoV-2 vaccination. AChR = Acetylcholine receptor antibody; RNS = Repetitive nerve stimulation; SfEMG = Single fibre EMG; PLEX = Plasma exchange.

Patient # + Reference	Age at onset	Sex	Vaccine	Vaccine dose	Time to symptom onset (days)	Antibody	Neurophysiology	MG subtype	Treatment
Patient 8 Maher et al	52	M	Oxford-Astra Zeneca®	1st dose	1	Negative	SfEMG positive	Ocular	Pyridostigmine
Patient 9 Galassi et al	73	M	Oxford-Astra Zeneca®	1st dose	8	AChR positive	RNS positive	Ocular	Pyridostigmine
Patient 10 Lee et al	33	F	Pfizer- BioNTech®	2nd dose	1	Negative	RNS positive	Generalised	Pyridostigmine
Patient 11 Chavez et al	82	M	Pfizer- BioNTech®	2nd dose	2	AChR positive	RNS positive	Generalised	Pyridostigmine IVIG Steroids
Patient 12 Watad et al	72	M	Pfizer- BioNTech®	2nd dose	1	No data	RNS positive	Generalised	Prednisolone PLEX
Patient 13 Watad et al	73	M	Pfizer- BioNTech®	2nd dose	7	No data	RNS positive SfEMG- positive	Generalised	Pyridostigmine PLEX Prednisolone
Patient 14 Sansone et al	64	F	Pfizer- BioNTech®	2nd dose	12	No data	No data	No data	No data

cases, ten (71%) were in patients of male sex. Seven (50%) patients had MG symptom onset after the first dose of SARS-CoV-2, while 5 (35%) had symptom onset after the second dose and 2 (14%) after the third (booster) vaccine dose. Two patients (14%) received the seasonal influenza vaccine at the same time as the SARS-CoV-2 vaccine and 1 (7%) received the influenza vaccine 4 days after the SARS-CoV-2 vaccine.

New onset of autoimmune diseases with systemic, haematological, rheumatological and neurological manifestations are now well-recognised following SARS-CoV-2 infection [20–23]. The proposed mechanisms include molecular mimicry between viral epitopes and human antigens, bystander activation, epitope spreading, complement activation, immune complex formation and SARS-CoV-2 infection which may unmask undiagnosed latent autoimmune disease [21–23]. The latter mechanism, unmasking of a lingering subclinical autoimmune response, seems particularly relevant in the context of our findings, considering the rapid symptom onset after vaccination with a mean of only 4.5 days, and a previously published study predating the SARS-CoV-2 pandemic, suggesting that pathogenic AChR antibodies may already have been present as early as 2 years before symptom onset in MG patients [24].

Infections including viral infections are well recognised triggers for MG exacerbations. SARS-CoV-2 infection has been reported to cause exacerbations of pre-existing MG [25–29] but new-onset of MG has been so far only reported in a small number of cases [30–34]. It is also important to recognise that some early drugs treatments of SARS-CoV-2 infection including azithromycin and hydroxychloroquine are known to exacerbate pre-existing MG.

SARS-CoV-2 vaccination has been reported in association with exacerbations of a range of autoimmune and non-autoimmune disorders including inflammatory arthritis, pericarditis, myocarditis, psoriasis, vasculitis, autoimmune haemolytic anaemia, immune thrombotic thrombocytopenia, Guillain-Barre syndrome (GBS), venous sinus thrombosis (VST) and transverse myelitis [35–38].

The literature so far suggests there may be a 1–15% risk of exacerbation of pre-existing MG following SARS-CoV-2 vaccination, mostly mild and responding well to standard treatment, with the exception of one published case of a patient who suffered a myasthenic crisis one week after the second dose of the Moderna vaccine [18,39–42].

Most MG exacerbations previously reported were seen within 1–20 days of vaccine administration. A UK study noted an increased risk of hospitalisation and death from myasthenic

disorders in a window of 15–21 days after the first dose of the Oxford-Astra Zeneca® vaccine but none following doses of the Pfizer-BioNTech® vaccine [42]. In our cohort of 14 cases (7 new and 7 previously published cases) with new onset MG following SARS-CoV-2 vaccination, the mean interval from receiving the SARS-CoV-2 vaccine to symptom onset was 4.5 days (IQR 2–7.75, range 1–14). This contrasts with a previously published report based on 30-years of data from the United States Vaccine Adverse Event Reporting System of new-onset MG or pre-existing MG exacerbation post vaccination which reported a higher mean time to symptom onset of 10 days [7]. In the US vaccine cohort, 42 cases of new onset MG were reported with myasthenic crisis being the presenting feature in 13 of the cases (31%). In our cohort, 6 (42%) cases had moderate to severe MG symptoms requiring intravenous immunoglobulin and/or plasma exchange, including 3 patients who required intensive care support for myasthenic crisis/respiratory failure between 2 weeks and 6 months from symptom onset.

An interesting finding in our cohort concerns the fact that half of the cases reported only developed MG after the second or third dose of the SARS-CoV-2 vaccination. Moreover, 3 of the 7 cases in the UK cohort received 2 different vaccinations (SARS-CoV-2 and seasonal influenza) within a short time of each other. These observations seem to indicate that repeated and double vaccinations may increase the risk of triggering MG (and, by proxy, other autoimmune diseases) in susceptible individuals, a notion supported by our failure to identify any new-onset MG cases triggered by the seasonal influenza vaccination (where a booster dose is not part of the immunization programme) alone.

Vaccines have been previously implicated in MG exacerbation/new onset MG including influenza, hepatitis B, human papilloma virus and Bacillus Calmette-Guérin [6–14,26–32] but the likely mechanism in these cases remains unclear. Two double-blind randomised controlled trials which evaluated changes in AChR titre and symptom exacerbations in MG patients following influenza vaccination included 109 patients who were followed up between 4 and 12 weeks after influenza vaccination with no statistically significant changes in MG exacerbations and AChR titres noted [43,44].

A recent study explored the relationship between MG and live-attenuated Japanese encephalitis vaccination (LA-JEV) [45], utilizing BALB/c mice which developed MG-like symptoms following exposure to LA-JEV. A strong similarity between LA-JEV peptide and the AChR alpha sub-unit was noted which may explain antibody cross reactivity with AChR, and was postulated as a possible mechanism for MG onset in some patients following

exposure to the LA-JEV subunit. This is of particular interest given higher rates of (ocular) juvenile MG reported in Chinese compared to European cohorts [46], bearing in mind that Japanese encephalitis vaccination is part of the childhood immunisation programme administered in China but not Europe. This association may warrant further investigation.

There are several proposed mechanisms that could explain how vaccines trigger or exacerbate an underlying autoimmune disorder like MG [47–50], including molecular mimicry between vaccine antigens and the AChR resulting in the production of cross-reactive antibodies, a potential bystander effect from inadvertent autoreactive T cell activation, epitope spreading with vaccination-induced immune response resulting in inflammatory cascades, and activation of the toll-like receptor (TLR) pathway. However, these mechanisms are all non-specific and insufficient to explain the observed association between SARS-CoV-2 vaccination and new-onset MG.

Overall, MG remains a rare disease and SARS-CoV-2 related illness continues to have significant morbidity and mortality. Of the 53 million people in the UK vaccinated for SARS-CoV-2 thus far only 7 cases with new-onset MG have been reported, supporting the overall excellent safety record of SARS-CoV-2 vaccines. Furthermore, serious adverse events remain rare following SARS-CoV-2 vaccination and most previously healthy individuals and patients with autoimmune disorders undergo vaccination without adverse events. It is also important to emphasize that whilst neurological complications have been observed in both those who received COVID-19 vaccines and those who have had SARS-CoV2 infection, the risk of such complications appears much higher in the latter group [42].

There are a number of limitations to our study: First, some cases of new onset MG may not have been captured by our methods given that this was not a comprehensive epidemiological study. To mitigate for this, we approached nearly all UK paediatric and adult neurologists with a neuromuscular interest via e-mail through well-established dedicated expert networks. Second, given that a large proportion of the population has received doses of SARS-CoV-2 vaccines the reported cases may be coincidental and mechanistically unrelated to the vaccine. Third, the association suggested in this study is unlikely to be specific, considering the recognition of other autoimmune phenomena post-SARS-CoV-2 vaccination [51]. Fourth, there is also the possibility of false-positive ACHR antibody results [52] and functional neurological symptoms being mis-diagnosed as MG, however, we consider both unlikely, taking into account an overall suggestive clinical context and at least one thorough personal clinical assessment by one of the co-authors.

5. Conclusions

Our study demonstrates a possible temporal association between SARS-CoV-2 vaccination and new-onset MG in a small proportion of susceptible individuals. Further research into possible immunological mechanisms behind this phenomenon, including identifying potential epitopes inducing molecular mimicry, could help establish possible causative links. Consolidating observations from larger epidemiological studies will be required to establish the incidence of MG following SARS-CoV-2 vaccination and to identify patient groups who are at higher risk of experiencing this adverse outcome. Ultimately current evidence suggests that the risks of SARS-CoV-2 infection outweighs the risk of rare vaccine-related adverse events. SARS-CoV-2 vaccines have an excellent safety record, but clinicians ought to be aware of potential autoimmune presentations including MG following SARS-CoV-2 vaccinations in rare cases.

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Informed consent and patient details

All patients gave informed consent to have their semi-anonymised clinical data published in this manuscript.

Ethics approval

No specific ethics approval was required for this study.

Data availability

Data are available upon reasonable request.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Sithara Ramdas: Writing – original draft, Writing – review & editing, Project administration. **Ryan Malcolm Hum:** Writing – original draft, Writing – review & editing, Project administration. **Abigail Price:** Writing – original draft, Writing – review & editing, Project administration. **Anna Paul:** Project administration, Writing – review & editing. **Jeremy Bland:** Project administration, Writing – review & editing. **Georgina Burke:** Project administration, Writing – review & editing. **Maria Farrugia:** Project administration, Writing – review & editing. **Jacqueline Palace:** Project administration, Writing – review & editing. **Alice Storrie:** Project administration, Writing – review & editing. **Pauline Ho:** Project administration, Writing – review & editing. **Emma Standing:** Project administration, Writing – review & editing. **James B. Lilleker:** Project administration, Writing – review & editing. **Heinz Jungbluth:** Writing – original draft, Writing – review & editing.

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