

29. Bedlack RS, Simel DL, Bosworth H, et al. Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. *Neurology*. 2005;64:1968-1970.
30. US Centers for Disease Control and Prevention. Considerations for COVID-19 vaccination in moderately or severely immunocompromised people in interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax-immunocompromised>. Accessed May 31, 2022.
31. Hitti FL, Weissman D. Debunking mRNA vaccine misconceptions—an overview for medical professionals. *Am J Med*. 2021;134:703-704.
32. L'Huillier AG, Posfay-Barbe KM. Live viral vaccines in immunocompromised patients. *Future Virol*. 2014;9:161-171.
33. Papp KA, Haraoui B, Kumar D, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. *J Cutan Med Surg*. 2019;23:50-74.
34. Salemi S, D'Amelio R. Are anti-infectious vaccinations safe and effective in patients with autoimmunity? *Int Rev Immunol*. 2010;29:270-314.
35. Shen C, Risk M, Schioppa E, et al. Efficacy of COVID-19 vaccines in patients taking immunosuppressants. *Ann Rheum Dis*. 2022;81:875-880.
36. Apostolidis SA, Kakara M, Painter MM, et al. Altered cellular and humoral responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. *Nat Med*. 2021;27:1990-2001.
37. Verschuuren JJ, Palace J, Murai H, Tannemaat MR, Kaminski HJ, Brill V. Advances and ongoing research in the treatment of autoimmune neuromuscular junction disorders. *Lancet Neurol*. 2022;21:189-202.
38. Zhou Q, Zhou R, Yang H, Yang H. To be or not to be vaccinated: that is a question in myasthenia gravis. *Front Immunol*. 2021;12:733418.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gamez J, Gamez A, Carmona F. Safety of mRNA COVID-19 vaccines in patients with well-controlled myasthenia gravis. *Muscle & Nerve*. 2022;66(5):612-617. doi:10.1002/mus.27703

COVID-19 infection and vaccination in patients with skeletal muscle channelopathies

Vinojini Vivekanandam MBBS(Hons), FRACP  | Dipa Jayaseelan PhD, FRCP | Michael G. Hanna MD, FRCP(UK), FMedSci

Centre for Neuromuscular Diseases, QS UCL Institute of Neurology, London, UK

Correspondence

Vinojini Vivekanandam, Centre for Neuromuscular Diseases, QS UCL Institute of Neurology, Box 102, London WC1N 3BG, UK. Email: v.vivekanandam@ucl.ac.uk

Funding information

University College London

Abstract

Introduction/Aims: Although we have gained insight into coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome–coronavirus 2 since the beginning of the pandemic, our understanding of the consequences for patients with neuromuscular disorders is evolving. In this study we aimed to study the impact of COVID-19 and COVID-19 vaccination on skeletal muscle channelopathies.

Methods: We conducted a survey of patients with genetically confirmed skeletal muscle channelopathies seen at the UK Nationally Commissioned Channelopathy Service.

Results: Thirty-eight patient responses were received. Six patients had COVID-19 infection leading to exacerbation of their underlying muscle channelopathy. No major complications were reported. Thirty-six patients had received one or two COVID-19 vaccinations and the majority (68%) had no worsening of their underlying channelopathy. Thirty-two percent reported worsening of their usual symptoms of their muscle channelopathy, but all reported recovery to baseline levels. No serious adverse events were reported.

Discussion: The overall rates of COVID-19 infection were low in our study and COVID-19 vaccine uptake rates were high. Our results have been useful to inform patients that a subset of patients have reversible worsening of their channelopathy post-COVID-19 vaccination. Our study provides information for giving advice to patients with skeletal muscle channelopathies regarding COVID-19 infection and vaccination.

KEYWORDS

channelopathies, coronavirus, COVID-19, myotonia, neuromuscular disorders

1 | INTRODUCTION

Our understanding of the impact on coronavirus disease-2019 (COVID-19) infection and vaccination for patients with neuromuscular disorders is evolving.¹ Skeletal muscle channelopathies encompasses a group of rare genetic neuromuscular conditions, including myotonia congenita (MC), sodium channel myotonia (SCM), paramyotonia congenita (PMC), hypokalemic periodic paralysis (hypoPP), hyperkalemic periodic paralysis (hyperPP), and Andersen-Tawil syndrome (ATS). These conditions are characterized by episodic symptoms ranging from myotonia to periodic paralysis caused by the dysfunction of specific ion channels expressed in skeletal muscle.²

Throughout the pandemic, concerns were raised about COVID-19 infection-related electrolyte disturbances on patients with skeletal muscle channelopathies.^{3,4} In addition, the side-effect profile of COVID-19 vaccination in patients with channelopathies is unknown.⁵ Because of concerns over the risk of venous or arterial thromboembolism with some vaccines, the risk profile is unclear in patients with channelopathies who have impaired ambulation or may be more sedentary.^{6,7}

Driven predominantly by the need to practice cautiously in an unknown era, recommendations and guidelines were created to broadly advise patients with neuromuscular disorders.⁸ In channelopathies, patients with ATS who may have cardiac involvement were advised to shield (remain at home and avoid face-to-face contact) in the UK based on the risk of cardiac arrhythmias.

The aim of this study was to better understand the effect of COVID-19 on patients with skeletal muscle channelopathies and the side effects of COVID-19 vaccination in this cohort.

2 | METHODS

Two hundred patients with a genetically confirmed diagnosis of a skeletal muscle channelopathy (with pathogenic variants in *CLCN1*, *SCN4A*, *CACNA1S*, *KCNJ2*, or *RYR1*) seen at the UK Nationally Commissioned Channelopathy Service run at the National Hospital for Neurology and Neurosurgery, Queen Square, were enrolled into a cohort study (Investigation of Human Neurological Ion Channel or Episodic Neurological Disorders, REC 07/Q0512/2) which received

ethics approval from the Joint National Hospital for Neurology and Institute of Neurology research ethics committee. Written informed consent was obtained for collection of retrospective and prospective clinical data.

The questionnaire was developed by the Highly Specialized Service channelopathy service, focusing on symptoms and complications of COVID-19 infection as well as side effects of the COVID-19 vaccine. The survey was reviewed by the University College London Hospital (UCLH) patient experience team. A total of 14 questions were included (see supplementary material). Patients were sent the survey via post and the UCLH e-healthcare system in March 2021 and responses collected over 4 months. A reminder email was sent in April 2021. Patients who reported worsening of their channelopathy from either COVID-19 infection or COVID-19 vaccination and had indicated on the survey that they agreed to be contacted to provide further information were then contacted by phone or email to obtain additional information about clinical features. Clinical and demographic details were collected from the patients' electronic health records. Serious adverse events were defined as side effects or adverse events that required hospitalization. Data are presented descriptively.

3 | RESULTS

A total of 38 (19% response rate) patient responses were received (Table 1). The median age of respondents was 51 (range, 18-77) years, half of whom were female.

Six patients had COVID-19 infection, with all six reporting that the infection-related symptoms lasted 2 weeks. In all cases, their underlying muscle condition was exacerbated by the COVID-19 infection for the full duration of the COVID-19 illness. Three patients with myotonia reported increased cramps and spasms as well as stiffness. Pain was also increased. The other three patients with hypoPP or ATS had increased muscle weakness, predominantly of the lower limbs. Only one patient had weakness severe enough to require assistance with activities of daily living. No patients were hospitalized for weakness or electrolyte disturbances.

COVID-19 vaccination outcomes were available for 37 patients. Thirty-two (86%) patients had received both doses of a COVID-19 vaccination by March 2021. Four (11%) had received their first dose

TABLE 1 Summary of patient data

Diagnosis (n)	Male	Had COVID-19 infection	Worsening of muscle condition with COVID-19 infection	Received one or both COVID-19 vaccination(s)	Worsening of muscle condition after COVID-19 vaccination	Medication for channelopathy ^a
Myotonia---MC, SCM, and PMC (24)	10	3	3	24	10	Mexiletine (15); flecainide (10); acetazolamide (2); magnesium (1)
HypoPP (6)	5	1	1	6	0	Acetazolamide (5); amiloride (2); spironolactone (2); dichlorphenamide (1)
HyperPP (2)	1	0	NA	2	0	Acetazolamide (2); bendroflumethiazide (1)
ATS (6)	3	2	2	4	2	Acetazolamide (3); spironolactone (2)

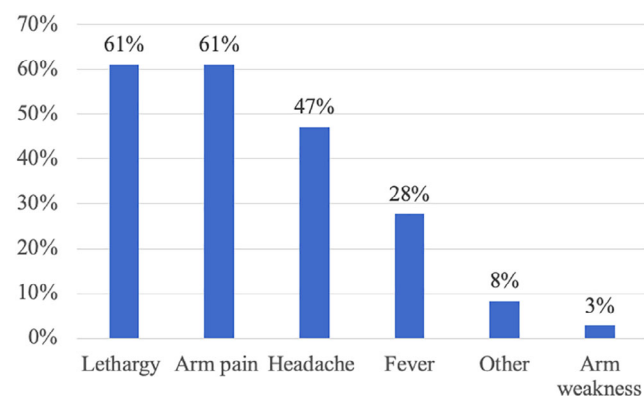
Abbreviations: ATS, Andersen-Tawil syndrome; COVID-19, coronavirus disease-2019; HyperPP, hyperkalemic periodic paralysis; HypoPP, hypokalemic periodic paralysis; MC, myotonia congenita; NA, not applicable; PMC, paramyotonia congenita; SCM, sodium channel myotonia.

^aMay be on more than one medication.

and one had not yet been vaccinated. All patients who had either one or both doses of a COVID-19 vaccine had side effects, the most common being lethargy and arm pain (Figure 1).

Other side effects included chills, nausea and vomiting, palpitations, and joint soreness. There were no serious adverse events reported.

Twelve patients had worsening of their muscle condition after receiving the COVID-19 vaccination (Table 1). Six of 12 patients had increased stiffness; in three patients, this necessitated an increase in the dose of mexiletine. One patient increased the mexiletine dose for 3 days before returning to baseline. The other two patients increased their mexiletine doses for 2 weeks before recovering and returning to their usual dose. One patient with PMC also had episodes of transient weakness, which was not experienced previously; and two patients with MC also described weakness. Four (of 10) patients had increased pain related to myotonia. Patients found it helpful to transiently increase the dose of mexiletine to manage the myotonia after their COVID-19 vaccination.

**FIGURE 1** Coronavirus disease-2019 vaccination-related side effects in patients with a skeletal muscle channelopathy.

The remaining two patients had ATS. One patient had a usual attack of periodic paralysis after the second dose of the vaccine, returning to baseline function after 24 hours. The other patient had reduced exercise tolerance post-COVID-19 vaccination. This persisted for 1 week, with gradual recovery.

Twenty-five (67.6%) patients had no worsening of their underlying skeletal muscle channelopathy and all 12 patients with transient worsening of their skeletal muscle channelopathy had full recovery.

4 | DISCUSSION

In a small cohort of 38 patients with skeletal muscle channelopathies, the incidence of COVID-19 infection was low, which reflects our clinical experience in the Nationally Commissioned Channelopathy Service in the UK. This may be due to cautious behavior and voluntary shielding in our patients as a result of uncertainty about the impact of COVID-19 infection. There may also be a number of patients who had asymptomatic infection of which we are unaware.

COVID-19 vaccination uptake in this study was high and no serious adverse events occurred. The majority of patients did not have worsening of their underlying skeletal muscle channelopathy after COVID-19 vaccination. The incidence of side effects after COVID-19 vaccination was higher in our cohort compared with the UK population. Fatigue occurred in 8% to 21% of the UK community self-reporting side effects compared with 61% in our cohort.⁹ Although arm pain was the most common local side effect in both our cohort and the UK cohort, the incidence was again higher in our cohort (61% vs 19% to 34%).⁹ However when compared with the side effects reported in the phase III clinical trials of the BNT162b2 vaccine, the frequency of arm pain (71% to 83%) was comparable with what we observed in our cohort.¹⁰ Frequency of fatigue was still higher in our cohort compared with the trial (61%

in our cohort vs 34% to 47% in the trial). Given that fatigue is a significant component of the channelopathies,² it may be that this is enhanced or exacerbated after COVID-19 vaccination.

The small sample size of this study is a significant limitation. However, this subgroup is representative of our larger channelopathy cohort. The majority of patients having myotonia, followed by periodic paralysis and then ATS is representative of the prevalence of subtypes within our cohort. The sex distribution is also representative of the demographic in our cohort---greater male representation (6 of 8) in the periodic paralyse and equal sex ratio for MC and ATS. Similarly, the mean age is comparable. We have not seen channelopathy-specific risks associated with COVID-19 infection. In this study, although electrolytes were not measured routinely, given that no patients required hospitalization, it is unlikely that their electrolytes reached severely abnormal ranges that would otherwise result in neuromuscular morbidity necessitating admission.

The study also illustrates the challenges faced with surveys. It is difficult to generalize the results due to the small study size, and ongoing data collection will be needed. Overall, the information is useful by adding to the growing understanding of the interplay between COVID-19 and neuromuscular disorders and is aligned with our clinical experience in channelopathies. Understanding the effects of the COVID-19 vaccination in patients with skeletal muscle channelopathies allows us to plan and provide advice to patients. Transiently increasing medication or planning to work/study from home for a few days after COVID-19 vaccination may be helpful approaches.

ACKNOWLEDGMENTS

Thank you to all patients and family who participated in our survey. We provide the only NHS England-commissioned national diagnostic service and references laboratory for children and adult muscle channelopathies led from University College London NHS Foundation Trust. For further details contact m.hanna@ucl.ac.uk.

FUNDING INFORMATION

International Centre for Genomic Medicine in Neuromuscular Diseases (MRC strategic award to M.G.H.); Highly Specialized Service for Channelopathies, Mission Impossible (Hadi Manji) (to V.V.); The Jon Moulton Charity (to V.V.); UCLH NIHR Biomedical Research Centre

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DISCLOSURE STATEMENT

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Vinojini Vivekanandam  <https://orcid.org/0000-0002-4944-0061>

REFERENCES

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77:683-690. doi:10.1001/jamaneurol.2020.1127
2. Vivekanandam V, Männikkö R, Matthews E, Hanna MG. Improving genetic diagnostics of skeletal muscle channelopathies. *Expert Rev Mol Diagn.* 2020;20:725-736. doi:10.1080/14737159.2020.1782195
3. Mabilard H, Sayer JA. Electrolyte disturbances in SARS-CoV-2 infection. *F1000 Res.* 2020;9:587.
4. Mandal AKJ, Kho J, Metaxa S, Missouri CG. Covid-19 and hypokalaemia---a potential mechanism. *Ann Clin Biochem.* 2021;58:259-260. doi:10.1177/0004563220973497
5. Živković SA, Gruener G, Narayanaswami P. Doctor---Should I get the COVID-19 vaccine? Infection and immunization in individuals with neuromuscular disorders. *Muscle Nerve.* 2021;63:294-303. doi:10.1002/mus.27179
6. Narici M, De Vito G, Franchi M, et al. Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. *Eur J Sport Sci.* 2021;21:614-635. doi:10.1080/17461391.2020.1761076
7. Hippisley-Cox J, Patone M, Mei XW, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. *BMJ.* 2021;374:n1931. doi:10.1136/bmj.n1931
8. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology.* 2020;94:959-969. doi:10.1212/WNL.0000000000009566
9. Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID symptom study app in the UK: a prospective observational study. *Lancet Infect Dis.* 2021;21:939-949. doi:10.1016/s1473-3099(21)00224-3
10. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020;383:2603-2615. doi:10.1056/nejmoa2034577

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Vivekanandam V, Jayaseelan D, Hanna MG. COVID-19 infection and vaccination in patients with skeletal muscle channelopathies. *Muscle & Nerve.* 2022; 66(5):617-620. doi:10.1002/mus.27704