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DATA AVAILABILITY STATEMENT

Anonymized data not published within this article will be made available by request from any qualified investigator.

ETHICS 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.

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Post–COVID-19 vaccine small-fiber neuropathy and tinnitus treated with plasma exchange

Small-fiber neuropathy (SFN) is a known complication of vaccinations, including the coronavirus disease-2019 (COVID-19) mRNA vaccines.[1] A 52-year-old man received the BNT162b2 mRNA COVID-19 vaccine. After two doses, he had paresthesias as well as burning and stabbing pain in the arms, face, and eyes, accompanied by high-pitched right ear tinnitus. He subsequently developed orthostatic intolerance and was unable to stand and walk without syncope. These symptoms progressed for 5 months and cardiac monitoring revealed significant postural tachycardia with heart rate varying from 50 beats per minute (bpm) supine to 180 bpm standing with episodes of supraventricular tachycardia. Neurological examination was normal except diminished sensation to temperature in the feet.

The following laboratory tests were normal or negative: comprehensive metabolic profile, complete blood count, vitamin B12 and B6 levels, thyroid-stimulating hormone, homocysteine, methylmalonic acid, serum protein electrophoresis with immunofixation, paraneoplastic antibody profile, antinuclear antibody, double-stranded DNA, Lyme antibody, C-reactive protein, and erythrocyte sedimentation rate. Hemoglobin A1C was mildly elevated at 5.7%. Electromyography and nerve conduction studies were normal in the upper and lower extremities. Skin biopsy revealed decreased epidermal nerve fiber density of 2.2/mm^2 (normal 13.8) at the distal leg and 7.5/mm^2 at the thigh (normal 21.1). MRI of the brain and internal auditory canals was unremarkable. Expanded antibody testing (CellTrend Laboratories, Luckenwalde, Germany) revealed elevated

Abbreviations: COVID-19, coronavirus disease-2019; PLEx, plasma exchange; POTS, postural orthostatic tachycardia syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SFN, small-fiber neuropathy.

TABLE 1 Autoantibody titers pre- and post-PLEx

Antibody	Pre-PLEx titer (units/mL)	Post-PLEx titer (units/mL)	Reference range (units/mL)
Anti–α1-adrenergic antibodies	21.8	6.8	<7/0
Anti–β1-adrenergic antibodies	41.9	5.0	<15.0
Anti–β2-adrenergic antibodies	39.1	3.5	<8.0
Anti-muscarinic cholinergic receptor-1 antibodies	18.7	3.7	<9.0
Anti–muscarinic cholinergic receptor-2 antibodies	25.5	3.3	<9.0
Anti–ACE2 antibodies	41.5	15.7	<9.8
Anti-Mas antibodies	61.3	30.8	<25.0

ACE2, angiotensin-converting enzyme 2; PLEx, plasma exchange

titers of antibodies to multiple adrenergic receptors along with muscarinic cholinergic receptors and angiotensin-converting enzyme 2 (ACE2) (Table 1).

The patient was treated with nadolol 40 mg/day, with improvement in tachycardia. Gabapentin 600 mg three times daily for 1 month, amitriptyline 50 mg/day for 2 months, and trazodone 50 mg twice daily for 2 months resulted in no improvement in pain. He was then treated with intravenous immunoglobulin 2 g/kg one time, but he developed hemolytic anemia with the second treatment. He was started on subcutaneous immunoglobulin 200 mg/kg per week for three doses, with improvement of his neuropathic pain but significant worsening of tinnitus. A course of prednisone at 0.5 mg/kg per day for 1 month had no effect.

He underwent five plasma exchanges (PLEx) over 10 days without side effects. His neuropathic pain began to improve after the second exchange and resolved after five exchanges. In addition, after the fourth exchange his heart rate and blood pressure remainder stable upon standing, permitting him to ambulate normally. His tinnitus persisted but improved. Subsequent antibody testing showed reduction of all titers (Table 1).

We have identified a case of small-fiber and autonomic neuropathy with tinnitus after COVID-19 vaccination responding to PLEx. There are multiple reports of SFN after various vaccinations, including human papillomavirus, varicella zoster virus, Lyme and rabies,[2] and COVID-19.[1] Post-vaccine neuropathy is likely immune-mediated from either hypersensitivity to the vaccine solvent or to the active components of the vaccine itself. In our patient, the presence of the ACE2 antibody suggests an immune reaction to the vaccine itself as the vaccine mRNA encodes the spike protein that binds to ACE2 receptors. ACE2 antibodies have been described after infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[3]

A distinctive feature of our case was dysautonomia and the postural orthostatic tachycardia syndrome (POTS). POTS has been described following both SARS-CoV-2 infection and COVID-19 vaccination.[4] A subset of patients with POTS have antibodies to beta-adrenergic and muscarinic cholinergic receptors[5]; the presence of these antibodies in our patient and the response to PLEx suggests that his POTS was an immune-mediated response to the COVID-19 vaccination, although the antibody titers may also have represented a monophasic response to the vaccination.

The patient's tinnitus responded partially to PLEx. Interestingly, his anti-ACE2 and anti-Mas antibodies (in the ACE pathway) were the only antibodies to remain elevated when tested after plasma exchange though the titers of both decreased. Recent studies examining tinnitus after infection with SARS-CoV-2 show that the human inner ear expresses the ACE2 receptors and that the virus directly infects inner ear hair and Schwann cells via entry through this receptor.[6] This suggests that the anti-ACE2 antibodies induced by vaccination may have cross-reacted with cochlear ACE2 receptors and contributed to the tinnitus.

To date, PLEx has been used successfully for treatment of thrombotic thrombocytopenia purpura after adenovirus-based COVID-19 vaccination,[7] but not for treatment of neuropathy. Our case indicates a need for further investigation of the immune response to COVID-19 vaccination and possible immunomodulatory treatments of adverse neurological events.

KEYWORDS

COVID-19, dysautonomia, plasma exchange, small-fiber neuropathy, vaccination

CONFLICTS OF INTEREST

T.H.B. has received consulting income from Pfizer, Akcea, Ionis, and Alnylam, and clinical trial funding from Ionis and Alnylam to his institution. The remaining authors have no disclosures.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request." cd_value_code="text

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.

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Diagnosing myasthenia gravis in older patients: Comments and observations

We read with great interest the excellent manuscript published in the latest issue of *Muscle & Nerve* entitled" Validation of myasthenia gravis diagnosis in the older Medicare population" by Lee et al.[1] This study concerns an extremely important issue of myasthenia gravis (MG) epidemiology in patients aged 65 y or older. The authors demonstrated algorithms that, based on the International Classification of Diseases (ICD) codes, enabled them to identify with high accuracy MG patients aged ≥65 y in administrative health data.[1] The issues raised by Lee and colleagues are of special interest as in recent decades a steady increase in MG incidence and prevalence rates has been observed, especially in the elderly.[1,2] Due to comorbidities and the aging process, the diagnostic approach to elderly patients remains a great challenge for clinicians.

Therefore, this study is appealing but raises several points that require discussion. Importantly, some MG symptoms in the elderly may be perceived as age-related, such as ptosis often misdiagnosed as senile ptosis or fatigue commonly attributed to other neurological disorders associated with aging. However, the diagnostic criteria used by the authors did not take into account clinical features of MG, such as fluctuating weakness of ocular and/or extraocular muscles. Noteworthy, the presence of these symptoms justifies further targeted diagnostics.

Interestingly, as many as 38% of patients were classified as ocular MG, despite having a median disease duration of 5 y in 2015, which exceeds the data from other reports. It is widely assumed that the majority of patients with ocular MG experience conversion to generalized disease within 2 y from onset, and up to 20% of them continue to manifest isolated ocular MG.[2,3] Sakai et al. showed that elderly individuals with late onset MG experienced transition to generalized symptoms at a higher frequency than non-elderly ones.[4]

We are surprised that only 19 patients had repetitive nerve stimulation (RNS) tests performed, and 17 patients had single fiber electromyography (SFEMG). Among them, 15 patients had confirmed postsynaptic neuromuscular junction dysfunction in RNS tests and 16 patients in SFEMG. The percentage of patients who underwent electrophysiological studies appears to be particularly low compared to the fact that results of serum antibody testing were available in all subjects. However, false positive acetylcholine receptor (AChR) antibodies results can occur in radioimmunoprecipitation assays in patients without clinical MG symptomatology, and such findings should be confirmed in a live cell-based assay.[5]

Therefore, questions arise as to why the electrophysiological tests and clinical symptomatology were scarcely reported in these patients? Did they complain about less specific symptoms or could electrodiagnostic techniques be too burdensome for them? We are also interested in which methods were used to detect the antibodies against antigens of the neuromuscular junction? Interestingly, despite such a high percentage of patients with ocular MG, only 7.2% of the study participants were seronegative.

When considering the increase in MG prevalence in the elderly, one cannot be certain that the proportion of seronegative patients in

Abbreviations: MG, myasthenia gravis; **ICD**, International Classification of Diseases; **AChR**, acetylcholine receptor; **RNS**, repetitive nerve stimulation; **SFEMG**, single fiber electromyography.