Small fiber neuropathy as a complication of SARS-CoV-2 vaccinations

Josef Finsterer

Department of Neurology, Neurology and Neurophysiology Center, Vienna, Austria

ABSTRACT

Generally, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not free of side effects. A rarely reported adverse reaction to SARS-CoV-2 vaccinations is small fiber neuropathy (SFN). Here, we present three patients with SFN after the second dose of messenger ribonucleic acid-based SARS-CoV-2 vaccines. Data for this study were collected via the self-made platform “Pubbly” for reporting side effects of SARS-CoV-2 vaccinations. Three patients with post-SARS-CoV-2 vaccination SFN were identified: a 40 yo Caucasian female (patient 1), a 52 yo Caucasian female (patient 2), and a 32 yo Caucasian female (patient 3). Patient 1 complained about fatigue, dizziness, flushing, palpitations, diarrhea, muscle weakness, and gait disturbance 10 days after the second Pfizer jab. Patient 2 reported dizziness, balance problems, brain fog, palpitations, dysphagia, and sleep problems. Patient 3 complained about profound fatigue, brain fog, vertigo, pre-syncopal sensations, hair loss, chest pain, dyspnea, palpitations, paresthesias, irregular menstrual cycles, muscle weakness, and hives 1 day after the second Moderna dose. All three patients underwent skin biopsy upon which SFN was diagnosed. Patient 1 profited from immunoglobulins, but patient 2 did not require any treatment. Symptoms in patient 3 resolved upon symptomatic treatment. Despite treatment, patient 1 did not completely recover. SFN can be a rare side effect of SARS-CoV-2 vaccinations. Post-SARS-CoV-2 vaccination SFN can be mild or severe and may or may not require treatment. Post-SARS-CoV-2 vaccination SFN is most likely immune-mediated as it responds to intravenous immunoglobulins.

Keywords: Adverse reaction, COVID-19, neuropathy, pain, SARS-CoV-2, side effect, small fibers, vaccination

Introduction

Small fiber neuropathy (SFN) is a disorder of the peripheral nervous system (PNS), characterized by affection of small nerve fibers (myelinated Aδ fibers, non-myelinated C-fibers) which conduct in an anterograde or retrograde manner either sensory (somatic) or autonomic information.[1] Clinically, SFN usually manifests as chronic pain of uncertain origin or autonomic dysfunction.[1,2] Causes of SFN are primary (genetic)[3] or secondary (metabolic, infectious, toxic, immune, paraneoplastic).[3] Although SFN has been occasionally reported as a complication of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [coronavirus disease 19 (COVID-19)][4,5] or as a manifestation of the post-(long)-COVID syndrome,[6,7] SFN has been only rarely reported as an adverse reaction to SARS-CoV-2 vaccinations.[8] Here, we present three patients with SFN following SARS-CoV-2 vaccinations with messenger ribonucleic acid (mRNA)-based vaccines.

Case Report

Patient 1 is a 40 yo Caucasian female with an uneventful previous history and without a current medication who developed side effects 10 days after the second dose of an mRNA-based SARS-CoV-2 vaccine (Pfizer). Her history was negative for COVID-19 prior to the vaccinations. She particularly complained about severe fatigue, dizziness, flushing, palpitations, diarrhea, muscle weakness, and gait disturbance 10 days after the second Pfizer jab. Patient 2 reported dizziness, balance problems, brain fog, vertigo, pre-syncopal sensations, hair loss, chest pain, dyspnea, palpitations, paresthesias, irregular menstrual cycles, muscle weakness, and hives 1 day after the second Moderna dose. All three patients underwent skin biopsy upon which SFN was diagnosed. Patient 1 profited from immunoglobulins, but patient 2 did not require any treatment. Symptoms in patient 3 resolved upon symptomatic treatment. Despite treatment, patient 1 did not completely recover. SFN can be a rare side effect of SARS-CoV-2 vaccinations. Post-SARS-CoV-2 vaccination SFN can be mild or severe and may or may not require treatment. Post-SARS-CoV-2 vaccination SFN is most likely immune-mediated as it responds to intravenous immunoglobulins.

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by the vaccination was suspected why a skin punch biopsy was carried out, which revealed a reduced intra-epidermal nerve fiber density (IENFD), suggesting SFN. Initially, she was treated with clonazepam, diltiazem, loratadine, steroids, and famotidine. Because the clinical manifestations of SFN hardly resolved upon this treatment, intravenous immunoglobulins (IVIGs) were added with a beneficial effect.

Patient 2 is a 52 yo Caucasian female with an uneventful previous history and without taking any current medication who developed dysautonomia 17 days after the second dose of an mRNA-based SARS-CoV-2 vaccine (Moderna). She complained about dizziness, balance problems, brain fog, palpatiations, dysphagia, and sleep problems. Her history was negative for COVID-19 prior to the vaccinations. Ambulatory work-up for dysautonomia by a skin punch biopsy revealed SFN. She did not receive any treatment as her symptoms spontaneously resolved.

Patient 3 is a 32 yo Caucasian female with an uneventful previous history who developed profound fatigue, brain fog, vertigo, pre-syncopal sensations, hair loss, chest pain, dyspnea, palpitations, parasthesias, irregardless menstrual cycles, muscle weakness, and hives 1 day after the second dose of an mRNA-based SARS-CoV-2 vaccine (Pfizer). During hospitalization, SFN was suspected and confirmed upon skin punch biopsy showing reduced IENFD. Upon symptomatic treatment, most of her complaints resolved.

Discussion
This case series shows that SARS-CoV-2 vaccinations can be complicated by SFN. Clinical presentation of post-SARS-CoV-2 vaccination SFN is not at variance from clinical manifestations of SFN because of other causes. Post-SARS-CoV-2 vaccination SFN is presumably immune-mediated as it responds favorably to IVIG. The study is important for the family physician because he needs to take SFN as a complication of the patient and because he needs to take SFN as the first health care professional who sees the patient. Ambulatory work-up for dysautonomia prior to the vaccinations. Ambulatory work-up for dysautonomia by a skin punch biopsy revealed SFN. She did not receive any treatment as her symptoms spontaneously resolved.

Generally, SFN is due to primary (genetic) or secondary causes. Genetic SFN is because of mutations in a number of genes, such as GLA (Fabry disease), TTR (transthyrein-related amyloidosis), or SNCA (alpha-synucleinopathy) and many others. Secondary causes of SFN prevail and include, for example, diabetes, renal failure, thyroid dysfunction, hypovitamins, acute infections (SARS-CoV-2, borreliosis), vaccinations (rubies, varicella, human papillomavirus, Lyme, SARS-CoV-2), auto-immune disease, pure autonomic failure because of alpha-synuclein deposition, sarcoidosis, Sjogren syndrome, Parkinson’s disease, and many others. SFN may go along with or without affection of large motor or sensory fibers. Thus, SFN can be associated with polyneuropathy (neuropathy of nerves built up of large fibers) but usually occurs without it. Length-dependent SFN and non-length-dependent SFN are delineated.

Generally, SFN manifests clinically as chronic focal or regional pain [complex regional pain syndrome (CRPS)] or with autonomic manifestations, such as fatigue, cognitive impairment, over-sensitivity to light, sicca syndrome, postural tachycardia syndrome, syncope, near-syncope, nodo-motor dysfunction (dyshidrosis), reduced heart rate variability, reduced blood pressure variability, disturbed thermo-regulation, urinary retention, constipation, or impotency. The clinical presentation of the three index cases is in line with these clinical manifestations as they had pain or dysautonomia.

Work-up for SFN includes quantitative sensory testing, nerve conduction studies to exclude large fiber neuropathy, micro-neurography, sensory stimulation tests, autonomic testing (deep breathing, Valsalva maneuver, tilt test, cerebral blood flow velocity measurements, quantitative sudomotor axon reflex test, corneal confocal microscopy, pain-related evoked potentials, and proximal or distal skin biopsy). Skin biopsy of the proximal or distal lower limbs is by far the most widely applied technique and the golden standard to diagnose SFN. Skin biopsies of the three index patients were in line with previously reported findings of skin biopsies including reduced IENFD.

Treatment of SFN can be symptomatic, pathogenesis-related, or causal. Causal treatment is available for most of the secondary SFNs. Symptomatic treatment includes systemic pain killers, local analgesics (local anesthetics, capsaicin ointment), transcutaneous electrical nerve stimulation, or sympathectomy. Autonomic disturbance responds favorably to symptomatic treatment. Often, combinations of causal/pathogenesis-related and symptomatic therapies are required.

Post-SARS-CoV-2 vaccination SFN has been previously reported in a single patient, a 57 yo female who presented 1 week after receiving the second dose of the Pfizer SARS-CoV-2 vaccine with sub-acute onset of intense burning dysesthesias in the feet, gradually spreading to the calves and minimally into the hands, unaccompanied by other neurological or constitutional symptoms. There was no known prior COVID-19 exposure. She was not on any medication and denied the use of alcohol.

In conclusion, SFN can be a rare side effect of SARS-CoV-2 vaccinations. Post-SARS-CoV-2 vaccination SFN can be mild or severe and may or may not require treatment. Post-SARS-CoV-2 vaccination SFN is most likely immune-mediated as it responds to IVIG.

Author contribution
JF: Literature search, discussion, first draft, critical comments, final approval.

Declaration of patient consent
Was obtained.
Statement of ethics
The study was approved by the institutional review board.

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Conflicts of interest
There are no conflicts of interest.

References
1. Gibbons CH. Small fiber neuropathies. Continuum (Minneap Minn) 2014;20 (5 Peripheral Nervous System Disorders):1398-412.
2. Contijoch Roqueta C, Izquierdo MF, Arrabal Solano L. Neuropatía de fibras pequeñas: Una revisión small fibre neuropathy: A review. Semergen 2020;46:277-82.
3. Egenolf N, Zu Altenschildesche CM, Kreß L, Eggermann K, Namer B, Gross F, et al. Diagnosing small fiber neuropathy in clinical practice: A deep phenotyping study. Ther Adv Neurol Disord 2021;14:17562864211004318.
4. Consonni M, Telesca A, Grazzi L, Cazzato D, Lauria G. Life with chronic pain during COVID-19 lockdown: The case of patients with small fibre neuropathy and chronic migraine. Neurol Sci 2021;42:389-7.
5. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ, et al. Autonomic dysfunction following COVID-19 infection: An early experience. Clin Auton Res 2021;31:385-94.
6. Hinduja A, Moutairou A, Calvet JH. Sudomotor dysfunction in patients recovered from COVID-19. Neurophysiol Clin 2021;51:193-6.
7. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: A case report. eNeurologicalSci 2020;21:100276.
8. Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, Hijazi N, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 vaccination. Vaccines (Basel) 2021;9:435.
9. Waheed W, Carey ME, Tandan SR, Tandan R. Post COVID-19 vaccine small fiber neuropathy. Muscle Nerve 2021;64:E1-2.
10. Souayah N, Ajroud-Driss S, Sander HW, Brannagan TH, Hays AP, Chin RL. Small fiber neuropathy following vaccination for rabies, varicella or Lyme disease. Vaccine 2009;27:7322-5.
11. Schofield JR, Chemali KR. How we treat autoimmune small fiber polyneuropathy with immunoglobulin therapy. Eur Neurol 2018;80:304-10.
12. Tulbă D, Popescu BO, Manole E, Băicuş C. Immune axonal neuropathies associated with systemic autoimmune rheumatic diseases. Front Pharmacol 2021;12:610585.
13. González-Duarte A, Varma-Doyle A, Freeman R. Pure autonomic failure and the differential diagnosis of autonomic peripheral neuropathies. Curr Opin Neurol 2021;34:675-82.
14. Napolitano M, Patruno C, D’Andrea M, Ferrillo M, Megna M, Fabbrocini G, et al. Cutaneous sarcoidosis small-fiber neuropathy resembling leprosy. Ital J Dermatol Venerol 2021;156:261-3.
15. Pindi Sala T, Villedieu M, Damian L, Crave JC, Pautot V, Stojanovich L, et al. Long-term efficacy of immunoglobulins in small fiber neuropathy related to Sjögren’s syndrome. J Neurol 2020;267:3499-507.
16. Jeziorska M, Atkinson A, Kass-Iliyya L, Kobylecki C, Gosal D, Marshall A, et al. Small fibre neuropathy in Parkinson’s disease: Comparison of skin biopsies from the more affected and less affected sides. J Parkinsons Dis 2019;9:761-5.
17. Kim M, Kim EM, Oh PS, Lim ST, Sohn MH, Song EK, et al. Usefulness of cyclic thermal therapy and red blood cell scintigraphy in patients with chemotherapy-induced peripheral neuropathy. Korean J Pain 2021;34:427-36.
18. Shrestha M, Chen A. Modalities in managing postherpetic neuralgia. Korean J Pain 2018;31:235-43.
19. Gemignani F, Bellanova MF, Saccani E, Pavesi G. Non-length-dependent small fiber neuropathy: Not a matter of stockings and gloves. Muscle Nerve 2022;65:10-28.
20. Farhad K. Current diagnosis and treatment of painful small fiber neuropathy. Curr Neurol Neurosci Rep 2019;19:103.