Case Series

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

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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).[2] 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.

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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. On admission, blood pressure was elevated. Immune-mediated dysautonomia triggered

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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, palpitations, 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, paresthesias, irregular 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 is most frequently the first health care professional who sees the patient and because he needs to take SFN as a complication of SARS-CoV-2 vaccinations into consideration as a differential.

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* (transthyretin-related amyloidosis), or *SNCA* (alpha-synucleinopathy) and many others. Secondary causes of SFN prevail and include, for example, diabetes, renal failure, thyroid dysfunction, hypovitaminoses, acute infections (SARS-CoV-2,[8] borreliosis[9]), vaccinations (rabies, varicella, human papillomavirus, lyme, SARS-CoV-2),[8,10] auto-immune disease,[11,12] pure autonomic failure because of alpha-synuclein deposition,[13] sarcoidosis,[14] Sjögren syndrome,[15] Parkinson's disease,[16] and many others.[17] SFN may go along with or without affection of large motor or sensory fibers.[18] 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.[19]

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, sudo-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 sudo-motor axon reflex test, corneal confocal microscopy, pain-related evoked potentials, and proximal or distal skin biopsy.[7,20] 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.[3,7]

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.[9]

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.

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