CASE REPORT

Small fiber neuropathy with normal intra-epidermal nerve fiber density but reduced sweat gland density after third BNT162b2 shot

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ABSTRACT

Small fiber neuropathy (SFN) has not been reported after the third dose of BNT162b2 in a previously healthy vaccinee. A 44-year-old previously healthy female developed pain and sensory disturbances in varying locations after the third BNT162b2 dose. Additionally, she developed recurrent tinnitus, headaches, arthralgia, neck stiffness, and motor dysfunction. A skin biopsy five months after symptom onset revealed normal intra-epidermal nerve fiber density (IENFD) but reduced sweat gland nerve fiber density. She is intended for a first series of intravenous immunoglobulins. SARS-CoV-2 vaccinations may be complicated by SFN; the diagnosis SARS-CoV-2 vaccination SFN may be delayed; IENFD may be normal, but sweat gland nerve fiber density may document SFN; and full recovery after SFN cannot always be achieved quickly.

KEYWORDS: small fiber neuropathy; skin biopsy; sweat gland nerve fiber density; SARS-CoV-2 vaccination; side effect

INTRODUCTION

Small fiber neuropathy (SFN) affects the A-delta and C-fibers either in combination with large fibers or in isolation [1]. The etiology of SFN can be primary (genetic, idiopathic) or secondary (diabetes, renal insufficiency, alcohol, vitamin deficiencies, infections, vaccinations, neoplastic or paraneoplastic) [1]. Clinical manifestations of SFN include neuropathic pain, sensory disturbances, and autonomic dysfunction [1]. In about one third of cases, pain is in an acral distribution, but in about half of the patients, pain and sensory disturbances affect the entire body [2]. Treatment of SFN strongly depends on the underlying etiology and is symptomatic in most cases but can be causative in most of the secondary SFNs [1]. There is increasing evidence from single case reports or small case series that SARS-CoV-2 vaccinations can be occasionally complicated by SFN [3,4]. A previously healthy patient with SFN after the third stitch of the BNT162b2 (Biontech Pfizer vaccine (BPV)) has to our knowledge not been reported.

CASE PRESENTATION

The patient is a 44-year-old female with SFN symptoms starting 74 days following the third shot of the BPV. Her previous history was positive for COVID-19 in March 2020 exclusively. She was not taking any drugs regularly. Individual and the family history were negative for genetic causes of SFN (transthyretin-related amyloidosis, Fabry disease, Wilson's disease, SCN9A-related pain syndromes, and hereditary sensory autonomic neuropathy type-1 (HSAN1). The patient did not report any symptoms after the first and second dose of BPV. The initial complaint was pain in the right big toe followed by right leg weakness and stiffness. She later developed recurrent hypoesthesia, paresthesia, and burning in changing locations. Recurring numbness was reported over the iliotibial bands, buttocks, arms, legs, face, neck, back, and breast (Table 1). Recurrent pain was reported over the buttocks, legs, abdomen, chest, arms, hands, and eyes. Burning paresthesia occurred in the legs, buttocks, abdomen, arms, hands, face, gum, tongue, lower back, and the saddle area. Occasionally, she experienced itching of the lips, jaw, eyes, legs, and belly. There was also recurrent tinnitus in both ears. Between April and June 2022, she experienced recurrent headache. Palpitations and dyspnea were recurrently reported. The patient also suffered recurrent episodes of fatigue and tiredness. Clinical neurologic exam was normal. MRI of the cervical and lumbar spine was non-informative. Cerebral MRI with contrast medium did not disclose any pathology. Nerve conduction studies of the right median (motor and sensory), left ulnar (motor and sensory), right peroneal nerve, and both sural nerves were within normal limits. Skin biopsy of the left distal arm, left calf, and left foot revealed normal intra-epidermal nerve fiber density (IENFD) but reduced sweat gland nerve fiber density

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Table 1. Symptoms the patient reported after third BPV dose.

Day	Sign/Symptom/Event
26/12/2020	COVID positive
04/07/2021	BPV 1st dose
04/28/2021	BPV 2nd dose
11/14/2021	flu shot
11/30/2021	BPV 3rd dose
02/10/2022	first time right side big toe hurt
02/21/2022	foot doctor injects cortisone, hurts more, stiffness, numbness, pain
03/25/2022	pain of right buttock, burning and right legs weakness, tightness on lateral thigh and anterior thigh, numbness over IT bands, pins, and needles under both feet
04/06	burning sensation on left buttock, numbness over left IT bands, left buttock burning every day constantly from 04/06 till mid-May, inner thigh also feels pulling while standing and walking
04/08	staring burning lower back every other morning once a while
05/14	first time tingling in left lower anterior leg, pain in left lateral thigh and left groin feel pulling and burning at beginning only feet pin and needles
05/27	lower abdominal shooting pain
05/28	lower abdominal shooting pain
05/29	heavier breathing because of pain, tiredness, bilateral gluteal numbness, before only IT bands are numbness
05/30	more lower abdominal and pubic pain
05/29/30/31	heavier breathing, weak body because of pain
06/04	numbness of arms and hands, pain. burning sometimes.
06/05	left legs numbness, spreading from buttock to legs, IT bands front thigh down to lower legs and left foot
06/06	right knee weird and behind knee tight
06/18	right legs numbness spread from buttocks and IT bands and front thigh to lower leg and foot
06/19	facial lips jaw itchy tingling numbness both sides
06/24	facial tingling numbness both sides numbness keeps staying there
06/26	upper back spread mid back numbness traps muscle pain, little numbness of neck
06/30	upper back numbness spread to front peck, breast, chest, breathing shallow
07/01	eye surround skin twitching itchy both side facial numbness a little burning
07/04	scalp tingling increased, back of head numbness, face jaw numbness increases, while doing activity
07/06	peck chest breast numbness
07/07	sacrum lower back belly numbness
07/12	both legs getting harder to walk, weaker heavier, whole legs especially knees like tape wrapped around
07/13	pain burning abdominal
07/14	shooting pain and burning abdominal, shooting searing type pain, legs pain worse while standing right leg, weakness after walk, 10 minutes sitting and laying down hurts too
May to June	anus and groin region tingling too
April to June	slight headache, and scalp tingling, scalp tingling a little more this week
07/15	left side arm and breast numbness increased
07/16	legs twitching, eyes itchy
07/17	belly twitching, body itchy, sacral muscle, and tail bone very numb after long sitting
07/18 l	left head numbness, both ears flush sometimes. heart beat raised in a sudden while walking routine lasted 3 minutes, 10 minutes late heart raised again for 20 minutes
07/19	left side calf spasm
07/20	sometimes feel something in throat, tongue a little numb, been a while
07/26	numb legs, heavy pulling, getting more difficult walking gradually it's been a while
7/27	right lower leg (tibialis anterior) pain
7/29	big toe joint pain increased
08/02	ear ring mildly
08/03	tongue burning gum burning head burning
08/09	head burning been a while heart beat raised 1 min
08/10	white colour, tiny pimple on face and body been a while, upper abdominal muscles twitching 40 minutes in morning 30 minutes in afternoon, increased pain behind knee, ear mild ring, neck very stiff
08/12	neck stiff/restriction of rang of motion continue
08/13	tiredness, left sided arm shooting pain, ear still ring, gum burning and mild pain
08/15	tiredness/fatigue mid of the day, ear ring
08/16	tiredness/fatigue mid of the day, ear ring
08/17	tiredness, ringing ear
08/18-08/20	fatigue, ringing ear
08/21-29	fatigue, weak, tired, ear ring sound getting louder
08/30	shooting pain on left hand, armpit
08/31	bottom skin burning and increased pain as well
04/01-08/31	loose stool
09/01	constipation then loose stool
09/02	tired by talking, GI gurgling a lot
09/03	GI gurgling a lot
09/06	diaphragm muscle twitching
09/07	diaphragm muscle twitching
09/10	shooting pain on left chest hands affected burning and pain get more noticeable like bottom of feet
09/11	buttocks pain getting worse and worse, pressure on chest and throat for 1 hour then went away
09/11	big toe moving itself
09/13	brain cognition cannot concentrate been a while
09/12	lightheaded/faint right arms hands feel like feather
09/14	pressure on chest, eyes pain, vision blurry
09/15	extremely tired, eyes pain, vision blurry, chest pressure and pain at night hard breath while lay down
09/16	tired dizziness light headed chest tight and chest pain eyes burning and pain
09/17	eye pain and blurry stays, cannot breathe, dizziness, legs lose gravity light like feather
09/18	cannot breath, faint, legs arms light
09/19-22	cannot breathe, eye pain, blurry fain arms legs are light
09/23	weak arms and legs, dyspnoe
09/24	dyspnoea, airway 90% blocked
09/25	dyspnoea, diarrhea undigested food
09/26	dyspnoea
09/29	4-7pm heart pounding 166-133
09/29-10/01	hospitalized due to tachycardia/autonomic neuropathy heart issue mild lung edema
10/02	discharge from hospital, weak, no energy dizziness, pressure on chest
10/03	sleep disturbance because buttocks are painful along other pain, feel tired after breakfast
10/04-10/16	tired chest discomfort shortness of breath dizziness eyes discomfort
10/17	constipation am and diarrhoea pm
10/27	increased heart rate while on rowing machine
10/28	short concentration span
10/29	pain level increased

Am: ante meridiem, BP: blood pressure, BPV: Biontech Pfizer vaccine, ER: emergency room, GI: gastrointestinal, IT: ilio-tibial, pm: post meridiem

in the distal arm (42.6, normal: 46-46.9) and the left foot (31.4, normal: 34.8-35.9) (Figure 1). Extensive work-up for the causes of SFN were non-informative. Acupuncture provided only temporary relief. The patient is scheduled for a series of intravenous immunoglobulins.

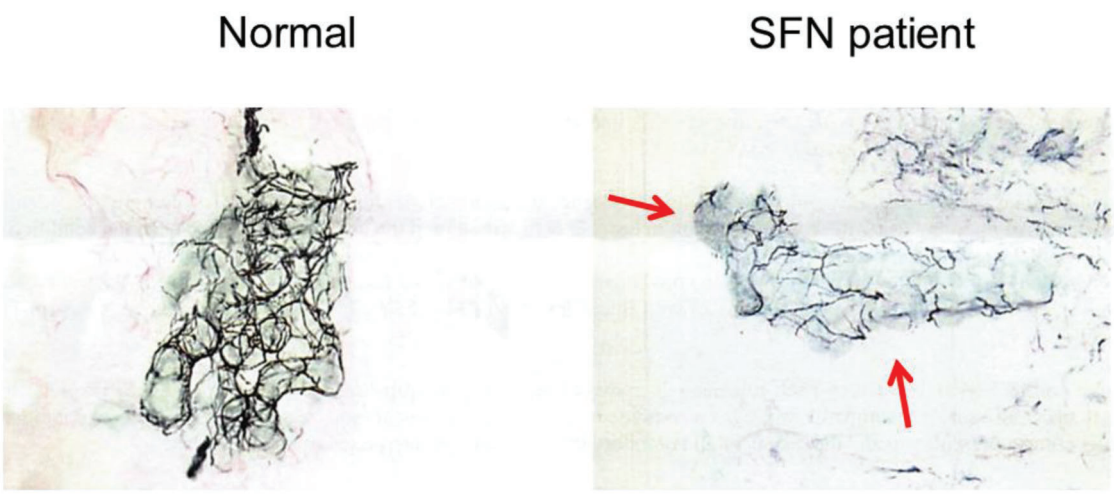

Fig. 1. Skin biopsy showing reduced sweat gland fiber density (PGP 9.5 immunostaining, x50).

DISCUSSION

The study confirms that anti-SARS-CoV-2 vaccinations can be complicated by neurological side effects, including SFN. SARS-CoV-2 vaccination associated SFN is increasingly recognized as a possible complication of SARS-CoV-2 vaccinations. SARS-CoV-2 vaccination associated SFN has been recently reported in a 64 years-old female who developed dull retrosternal pain, palpitations, light-headedness, and tingling in lower limbs three weeks after having received the third dose of the Moderna vaccine [3]. Despite a history of pre-diabetes, positive antinuclear antibodies (ANAs), suspected undifferentiated connective tissue disease, hyper IgE-syndrome, and basal cell cancer, SFN was attributed to the vaccination because she was in her usual health condition prior to the vaccination and because of the temporal relation between vaccination and the development of SFN symptoms [3]. In a study of 23 patients with newly developed neuropathic symptoms within one month after a SARS-CoV-2 vaccination, all reported sensory disturbances and 61% had orthostasis, heat intolerance, or palpitations [4]. Autonomic testing in 12 of these patients revealed distal hypohidrosis in seven patients and positional orthostatic tachycardia syndrome (POTS) in six patients [4]. Among 16 patients undergoing lower-leg skin biopsies, 31% had diagnostic/subthreshold intra-epidermal nerve fiber densities (IENFD), 13% were borderline, and 19% showed axonal swelling [3]. Altogether, definite SFN was diagnosed in 52% of patients and 58% of patients achieved complete or near-complete recovery of symptoms within two weeks of treatment [4]. In patients who did not receive steroids, spontaneous, complete recovery of SFN symptoms occurred within 12 weeks [4]. In three patients who did not recover within 5-9 months after diagnosis, IVIGs resulted in complete recovery within 2 weeks after starting the treatment [4]. In a study of 27 patients (21 of whom had a previously known immunologic or rheumatologic disorder), six developed newly onset immunological disease including neurosarcoidosis with SFN [5]. It was concluded that immunological disorders, including immune SFN, are rare following a SARS-CoV-2 vaccination [5]. There is also a report about three patients with acute onset SFN following vaccination with the Astra Zeneca vaccine [6]. All three patients developed burning pain and dysesthesias of hands and feet within two weeks of vaccination [6]. Clinical exam revealed pinprick and thermal hyposensitivity in the areas of neuropathic pain [6]. Thermal thresholds were abnormal and IENFD was reduced in the lower leg in all three patients [6]. Neuropathic pain persisted in two patients until the last follow-up [6]. SFN may occasionally develop together with other symptoms after a SARS-CoV-2 vaccination [7]. A 52-year-olf male developed paresthesia, burning and stabbing pain in the upper limbs and face, orthostasis, POTS, and high-pitched right ear tinnitus [7]. Sensory disturbances and tinnitus improved upon application of five PLEX cycles [7]. Post-vaccination SFN was also reported in a 57yo female who developed burning dysesthesias of the feet that progressed to the calves and the hands one week after the second dose of the BPV [8]. SFN was diagnosed upon three skin biopsies showing loss of protein gene product 9.5 (PGP-9.5) labelled nerve fibers in the dorsum of left foot over the extensor digitorum brevis muscle, and over the left ischial tuberosity [8]. Differential etiologies of SFN were appropriately ruled out and the patient profited significantly from administration of gabapentin [8].

Despite the long latency between the third shot and onset of SFN in the index patient, vaccination was regarded as causative, because there were no indications for secondary SFN and the individual and family history was negative for primary causes of SFN.

Importantly, SFN in the index patient may explain only some but not all the patient's complaints. Symptoms, which cannot be easily explained with SFN include tinnitus, headache, arthralgia, neck stiffness, and motor dysfunction.

The pathophysiology of post-SARS-CoV-2 vaccination SFN remains elusive but most likely involves a cross-reaction of a vaccine-induced immunologic reaction not only against virus particles but also against components of small fibers. A strong argument in favour of the immunologic hypothesis of SARS-CoV-2 vaccination associated SFN is that most patients so far reported benefit from steroids, IVIG, or PLEX.

CONCLUSION

This case shows that SARS-CoV-2 vaccinations can be complicated by SFN, that the diagnosis SARS-CoV-2 vaccination SFN is established with delay, that IENFD may be normal but sweat gland nerve fiber density may document SFN, and that full recovery may not always be achieved quickly.

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Statement of Ethics: a) The study was approved by the institutional review board (responsible: Finsterer J.) at the 4th November 2022. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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Disclosures

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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