From: Fritz, Craig (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=79148D8C0CEE49689FD637304BB82B42-b6]
Sent: 4/28/2021 4:41:56 PM
To: Collins, Francis (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=410e1ca313f44ced9938e50d2ff0b6c2-b6 ; Tabak, Lawrence (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=02e22836b5ff4e9988e3770cfc7ee770-b6 ; Aklin, Courtney (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c77a5e1631f44bb8abe376bc81d01065-b6 ; Burklow, John (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2e57f267323b43c08be856acb5b964ca-b6 ; Jorgenson, Lyric (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3bbde7d361374981a4d336b6eeb17521-b6
CC: Myles, Renate (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7d317f5626934585b3692a1823c1b522-b6 ; Fine, Amanda (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=61290b74aa9a44358954c45439ffdeb6-b6 ; Wojtowicz, Emma (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=45c6610aca6e44a08d497630425e5ecd-b6
Subject: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.
Attachments: Z__Barbara_Manuscript_2021_New_England_Journal_of_Medicine_Neuropathic_symptoms_post_covid_vaccine_4-17-21.pdf

Importance: High

Good afternoon,

We are flagging for your awareness the attached manuscript from Dr. Avi Nath and colleagues. The manuscript has been rejected by NEJM and we are not sure if he will submit it to another journal. NINDS has not yet determined if they will do any proactive press materials on this paper, if accepted. Please let me know if you have any questions. For your reference, below is additional information provided by NINDS.

Thank you,
Craig

COVID manuscript: Neuropathy following COVID vaccine
NINDS
Researchers from Dr. Avi Nath's lab report cases of neuropathic symptoms following the COVID vaccine. The symptoms included paresthesia, tremor, and dysautonomia. Some patients experienced relief following treatment with oral corticosteroids. The letter will be submitted to NEJM. (Since rejected)
4/26/2021
5/31/2021
Manuscript
N/A - Not Media

Craig M. Fritz
Public Affairs Specialist
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Neuropathic symptoms following vaccination for SARS-CoV-2

Short author list for print version

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Long author list for online version

Farinaz Safavi MD, PhD[1], Lindsey Gustafson NP[1], Anita Fletcher MD[1], Tanya Lehky[1], Mark Hallett MD[1], Amanda Wiebold RN[1], Susan Shin MD[2], Avindra Nath MD[1]

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Text: 388 words

To the Editor: We report a series of patients with acute neuropathic and autonomic symptoms post-vaccination for SARS-CoV-2. Thirty-two patients contacted us between January 11 to March 31, 2021 seeking advice about neurological symptoms that started post-vaccination. All patients were enrolled in an IRB approved study and evaluated by televisit or an in-person visit, and medical records were reviewed. We excluded 8 patients because their complaints were non-neurologic or limited to worsening or recrudescence of underlying neurological symptoms. 9/24 (37%) patients developed skin-flushing, tachycardia and increased blood pressure following vaccination lasting less than 30 minutes.

All patients developed new onset of neuropathic symptoms within 14 days and median time of two days from vaccination (Figure S1). Median age of the patients was 39 years (range: 27-70 years). Twenty-one were women. One received the vaccine manufactured by b6 8 by b6 and 15 by b6 16/24 (66%) developed neurological symptoms following the first dose (Table S1). All patients reported paresthesia and/or burning sensation in either or both upper and lower limbs and in seven patients it involved the face, mouth, and scalp (Table 1). Two patients had severe unilateral paresthesia in the distribution of the V1 branch of the trigeminal nerve with intermittent tearing and burning in the eye suggestive of trigeminal neuralgia. 9/24 (37%) described a moderate to severe intermittent internal tremor in the head and throughout the body that interfered with daily activities and sleep. 8/24 (33%) patients had dysautonomia (Table S2; Figure S2). 13/24 had brain and/or spinal cord MRI with unremarkable findings. 3/24 patients had symptoms of brachial plexopathy confirmed by EMG. Brachial plexus MRI showed nerve enhancement in one patient. Six patients treated with oral corticosteroid, completely (n=4) or partially (n=2) improved after one or two weeks (Table S2). Untreated patients had either no recovery (n=7), partial (n=9) or complete recovery (n=2) at a median of 10 weeks.

This report describes symptoms suggestive of a neuropathy following vaccination for SARS-CoV-2 from three different manufactures that is distinct from the acute allergic reaction. These vaccines have in common the gene encoding the spike protein[4] suggesting that the symptoms may be driven by an immune response to it. Response to treatment with corticosteroids supports that possibility. While further investigations are needed to determine the underlying pathophysiology of these symptoms, treatment with corticosteroids may be considered in these patients.

Acknowledgments: Funded in part by intramural funds from NINDS (NS003031 and NS 003130). We thank Dr. Walter Koroshetz for helpful comments.

References

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2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403-416. (In eng). DOI: 10.1056/NEJMoa2035389.
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603-2615. (In eng). DOI: 10.1056/NEJMoa2034577.
4. Fergie J, Srivastava A. Immunity to SARS-CoV-2: Lessons Learned. Front Immunol 2021;12:654165. (In eng). DOI: 10.3389/fimmu.2021.654165.

Table: Neurological manifestations post-SARS-CoV-2 vaccination

Case#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Onset of symptoms		2h	5h	3d	10h	4d	6d	3h	10h	1d	14d	2d	7d	2h	10d	7d	10h	2h	2d	2d	10m	2d	6d	5d	8d
Sensory																									
	Paresthesia	+++	+++	+	+++	++	++	++	++	++	+	+	++	++	+	++	+	++	++	+	+	++	+	++	++
	Burning	+	+	-	-	+	-	+	-	-	-	-	-	+	-	+	-	-	+	+	-	+	-	-	+
	Back pain	+	++	++	+	+	-	-	++	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Motor					-																				
	Weakness	+	-	+	-	+	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	+	+	-	+
	Fasciculations	-	-	+	-	-	-	-	-	-	-	-	-	++	-	-	-	-	-	+	-	-	++	-	+
Dysautonomia																									
	Orthostatic Tachycardia	++	-	-	-	-	-	-	-	-	+	++	-	-	++	-	-	-	-	-	+	-	-	-	-
	presyncope	+	-	-	-	-	-	-	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	+	-
	Blood pressure variability	+	-	-	+	+	-	-	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	-	-
Corticosteroid treatment		-	-	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	+	-	-	-	-	+	-
Recovery																									
	Complete						+				+	+	+		+		+								
	Partial	+	+	+	+									+		+			+	+	+	+		+	
	None					+		+	+	+								+					+		+

+mild; ++moderate; +++severe

Table S1: Demographic characteristics

Demographic Information	Case# 1	2	3	4	5	6	7	8	9	10	11	12
Age	b6											
Sex												
Type of vaccine												
Dose	1st	1st	2nd	1st	1st	2nd	1st	1st	1st	1st	2nd	1st
History of COVID-19	Probable*	no	Probable	no	no	no	no	no	unknown	no	no	no
Past Medical History	Tinnitus, cholestoma	Hypertension, Crohn's disease	None	None	None	None	no	Hypothyroidism, polycystic ovarian syndrome	no	no	seasonal allergy, Migraine headaches	hyperlipidemia
Family history of autoimmune diseases	no	no	unknown	SLE	no	no	no	no	no	no	psoriasis	no

Demographic Information	13	14	15	16	17	18	19	20	21	22	23	24
Age	b6											
Sex												
Type of vaccine												
Dose	1st	2nd	2nd	1st	1st	1st	2nd	1st	1st	1st	2nd	2nd
History of COVID-19	no	no	no	no	no	no	no	no	no	no	no	no
Past Medical History	Chiari syndrome, L5 radiculopathy	migraine headaches, supra ventricular tachycardia	no	asthma and eczema	migraine headaches with aura, hashimoto thyroiditis	asthma	none	none	Anxiety dx	no	Hypothyroidism	no
Family history of autoimmune diseases	no	rheumatoid arthritis	no	no	no	no	no	unknown	no	no	no	RA

*Probable: History of upper respiratory tract infection but not confirmed with SARS-COV2 PCR or Antibody testing

Table S2: Clinical characteristics and course of illness

Symptom characteristics	9	10	11	12	13	14	15	16
Time from vaccination to any symptoms	24 hours	8 days	8 hours	2 days	2 hours	30 minutes	2 days	10 hours
Symptom at onset	fever, chills, and fatigue	lymphadenopathy in neck and axillary area	flu like symptoms, fever muscle pain	right scapular muscle spasm with constant pain and discomfort	formication in scalp and lower limbs, severe fatigue	flushing, tachycardia, positional dizziness	feet paresthesia	intermittent cognitive changes, paresthesia in both hands
Onset of neurological symptoms	1 day	14 days	2 days	7 days	2 hours	10 days	7 days	10 hours
Neurological symptoms	intermittent paresthesia in all limbs. Right ulnar distribution numbness, cramping in right hand fingers and difficulty with fine movements in right hand	numbness in left shin and right hand; progress to cold sensation in left leg and intermittent paresthesia in all limbs; Raynaud's phenomenon in left leg	orthostasis, fluctuation in heart rate, blood pressure fluctuation, nausea, diarrhea, band like tightness in T2-T3 level; Paresthesia in face, upper and lower limbs; internal tremor	paresthesia in right arm ulnar distribution progressed to weakness in right hand for fine movements	severe paresthesia and severe fasciculations in lower limbs	severe orthostatic tachycardia, pallor, flushing, diarrhea, fluctuation in blood pressure	progressive paresthesia in upper and lower limbs	paresthesia in ulnar distribution of both arms, numbness in feet
Neurological examination	decreased light touch and pin prick sensation on right ulnar distribution, mild weakness in right arm	normal	normal	finger abduction and wrist/hand dorsiflexion weakness	decreased vibration in right foot, Hyperesthesia in left leg; fasciculations in both legs	normal	normal	ND
MRI	consistent with brachial plexopathy	normal brain and cervical spinal cord	ND	normal brachial plexus and cervical spinal cord	ND	ND	normal brain and total spinal cord	ND
EMG-NCV	ND	ND	ND	Brachial plexopathy lower trunk	ND	normal	mild peripheral neuropathy	ND
Other tests	ND	ND	tilt table test fulfilled clinical criteria for POTS	ND	ND	tilt table test fulfilled clinical criteria for POTS, skin biopsy showed small fiber neuropathy	ND	ND
Corticosteroid treatment	ND	Prednisone 20 mg two times a day for 5 days	Prednisone 30 mg/day with weekly taper	Prednisone 60 mg/day for 3 days, tapered every 3 days	ND	Prednisone 40 mg/day, tapered every 3 days	ND	ND
Course of Disease	no improvement after 3-4 weeks	improvement started 1-2 weeks after corticosteroid treatment. Complete improvement after 10-12 weeks.	improvement started 1-2 weeks after corticosteroid treatment. Complete improvement after 8 weeks.	improvement started at1-2 weeks after corticosteroid treatment. Complete recovery after 6-8 weeks.	partial improvement after 6 weeks	Improvement started 1-2 weeks after corticosteroid treatment. complete improvement after 8-10 weeks,	partial improvement after 8-10 weeks	complete improvement after 2 weeks

Symptom characteristics	17	18	19	20	21	22	23	24
Time from vaccination to any symptoms	4 minutes	20 minutes	5 hours	10 minutes	2 hours	1 day	3 hours	15 minutes
Symptom at onset	sensation of tremor from head to toe	dizziness, presyncope	severe tingling in all limbs	numbness in both arms	transient right side face numbness	fatigue, headache, loss of appetite	intermittent cognitive changes, headache, dizziness	transient burning and tingling in mouth
Onset of neurological symptoms	2.5 hours	2 days	5 hours	10 min	2 days	6 days	5 days	7 days
Neurological symptoms	distal paresthesia and numbness in all limbs	formication in V1 distribution of trigeminal nerve progressed to severe paresthesia and burning sensation with tearing and burning in eyes	tingling and burning sensation followed by fasciculations in both thighs and forearms	Internal tremor, paresthesia and numbness in all limbs. Variable tachycardia.	Intermittent face, hands and feet paresthesia, burning and numbness. Mild right-hand weakness and paresthesia in right ulnar distribution	both legs weakness; fasciculations in all limbs; internal tremor, facial paresthesia; band like tightness in ribcage	photophobia, paresthesia and burning sensation in V1 distribution of trigeminal nerves	paresthesia and burning sensation in upper and lower limbs; fasciculations in limbs
Neurological examination	normal	normal	normal	ND	normal	normal	normal	normal
MRI	ND	normal brain	ND	ND	normal brain, cervical and thoracic spinal cord	ND	ND	normal brain
EMG-NCV	ND	ND	ND	ND	right lower trunk brachial plexopathy with no active denervation	ND	ND	normal
Other tests	ND	ND	ND	ND	ND	ND	ND	ND
Corticosteroid treatment	ND	Prednisone 40 mg/day, tapered every 3 days	ND	ND	ND	ND	Prednisone 50 mg/day, tapered every 2 days	ND
Course of Disease	no improvement after 4 weeks	Improvement started 1-2 weeks after corticosteroid treatment. Partial improvement after 4 weeks	partial improvement after 8 weeks	partial improvement after one week	partial improvement after 10-12 weeks	no improvement after 4 weeks	Improvement started 1-2 weeks after corticosteroid treatment. Partial improvement after 8-10 weeks	no improvement after 7 weeks

*Clinical Criteria for Positional Orthostatic Tachycardia Syndrome (POTS): Increase in heart rate more than 30 beats per minutes with tilt table test

AchR = Acetylcholine receptor; ND = not done; MRI = magnetic resonance imaging; EMG-NCV = electromyography and nerve conduction velocities

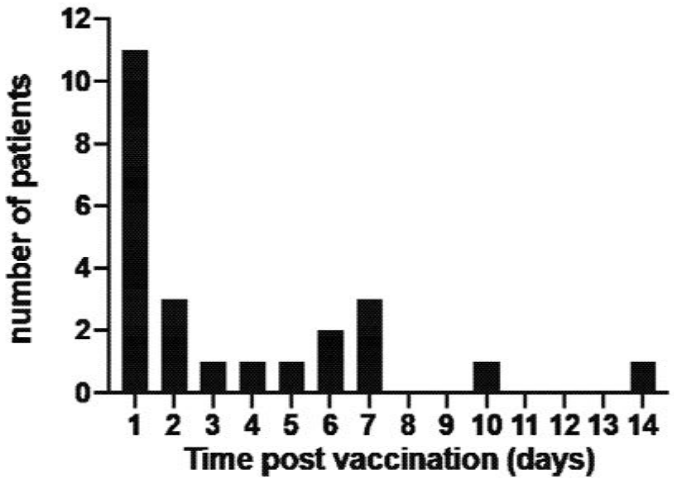

Figure S1: Onset of neurological symptoms from time of receiving the vaccine. Except for two patients, all patients developed symptoms within the first week following vaccination

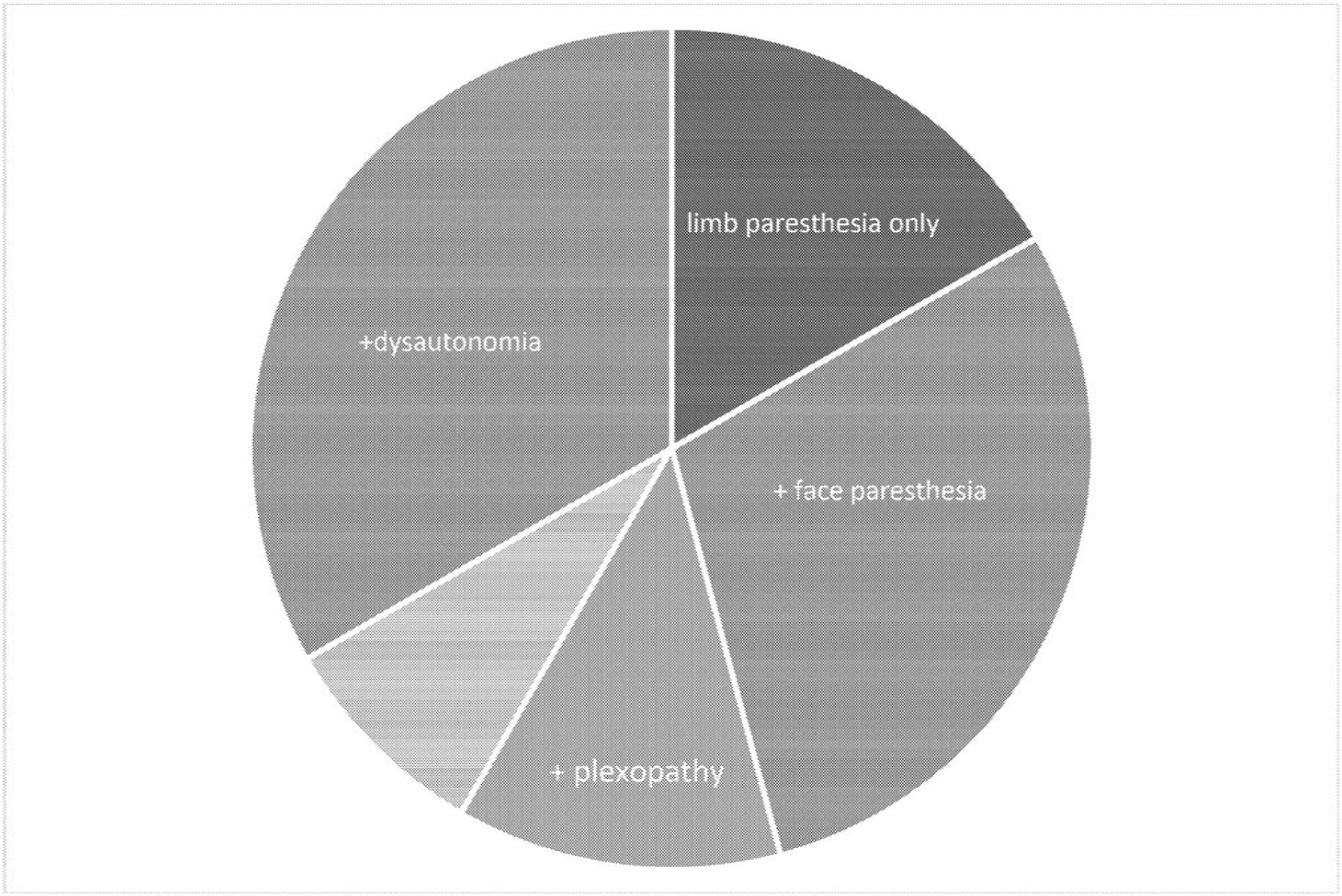

Figure S2: Neuropathic symptoms post-SARS-CoV-2 vaccination: All patients had parasthesia. Some patients had additional symptoms of parasthesia in face, brachial plexopathy, trigeminal neuralgia or dysautonomia.

From: Tabak, Lawrence (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=02E22836B5FF4E9988E3770CFC7EE770 b6
Sent: 4/29/2021 10:11:45 AM
To: Collins, Francis (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=410e1ca313f44ced9938e50d2ff0b6c2 b6
Subject: Re: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.

I thought it was me. I don't understand why Walter does not shut this down.

From: Francis Collins b6
Date: Thursday, April 29, 2021 at 5:16 AM
To: "Koroshetz, Walter (NIH/NINDS) [E]" b6
Cc: "Tabak, Lawrence (NIH/OD) [E]" b6 "Burklow, John (NIH/OD) [E]" b6
Subject: RE: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.

Hi Walter,

I find this approach very troubling. If there is truly the risk of a cause and effect serious adverse neurologic event, that's important to discover. But collecting anecdotes and then trying to build a case isn't scientifically compelling – and will have the main consequence of feeding vaccine hesitancy and social media overreaction.

I don't think enrolling NIH staff in a study would fly with OMS – they are very concerned about not mixing medical care and research.

FC

From: Koroshetz, Walter (NIH/NINDS) [E] b6
Sent: Wednesday, April 28, 2021 10:03 PM
To: Collins, Francis (NIH/OD) [E] b6
Cc: Tabak, Lawrence (NIH/OD) [E] b6 ; Burklow, John (NIH/OD) [E] b6
Subject: RE: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.

Yes, have talked to Avi at length. I sent paper to Tony for head's up. Previously Avi and colleagues from American Neurol Assoc did search the VAERS and lots of reports but can't say not due to chance. But have to be wary. (report attached). Good news is nothing is very common. After the ANA report I think Avi has turned into a magnet for docs with patients complaining of neuro troubles after the vaccine So the cases in this new paper are referred to him from all over..

Causality is purely based on temporal relationship but these have been trickling in from the beginning of the vaccination. His report only includes symptoms so will be hard to publish. What I have heard are isolated cases suggestive of brachial plexitis, mononeuritis multiplex, tinnitus + hearing loss, POTS-like symptoms. Avi knows of one transverse myelitis case with positive MRI. Two cases in last week admitted to hospitals.

Tinnitus:
I talked to a NINDS staff member who developed temporary tinnitus after first shot, then got really loud tinnitus after second shot which has not gone away. Avi has case of tinnitus with hearing loss.

From British Tinnitus Association: Do the coronavirus vaccines cause tinnitus or make it worse? https://www.tinnitus.org.uk/coronavirus-vaccines-and-tinnitus

In the trials prior to release, no mention was made of the onset of tinnitus or worsening tinnitus for either vaccine[3] [4].

The safety update report of 5 March 2021 from the MHRA estimates that 31.6 million first doses of the vaccines had been given, and around 5.5 million second doses [5].

A total of 176,439 Yellow Cards reporting adverse effects have been received[6].

A total of 1545 reports of tinnitus were made.

This means that fewer than 1 in 24,000 people are affected which classifies this side effect as 'very rare'[7].

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American Tinnitus Association.-- In response to the many inquiries we are receiving about tinnitus and possible connections to the coronavirus and vaccines, please note the following:
https://www.ata.org/tinnitus-and-coronavirus

https://www.thesun.ie/news/6909139/new-side-effect-covid-vaccine-tinnitus/

How to study. Would it be possible to post a survey for NIH folks who were vaccinated and volunteer to fill it out to get some incidence data? It's a matter of time before reports start to come out from neurologists.

From: Collins, Francis (NIH/OD) [E] b6
Sent: Wednesday, April 28, 2021 8:36 PM

To: Koroshetz, Walter (NIH/NINDS) [E] b6
Cc: Tabak, Lawrence (NIH/OD) [E] b6 Burklow, John (NIH/OD) [E] b6
Subject: FW: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.
Importance: High

Walter, what do you make of this? The draft letter doesn't explain how these 32 patients were referred – leaving one to wonder whether this is common or rare. What does VAERS have to say about this?

FC

From: Fritz, Craig (NIH/OD) [E] b6
Sent: Wednesday, April 28, 2021 12:42 PM
To: Collins, Francis (NIH/OD) [E] b6 abak, Lawrence (NIH/OD) [E] b6 Aklin, Courtney (NIH/OD) [E] b6 Burklow, John (NIH/OD) [E] b6 ; Jorgenson, Lyric (NIH/OD) [E] b6
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Sent: 4/29/2021 11:45:23 AM
To: Fauci, Anthony (NIH/NIAID) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=df38103d75134f658ae2d356f0396b94-b6
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I gather Walter has also shared this work of Avi Nath with you? Obviously we need to have the facts about adverse events, but this approach seems ill-conceived.

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https://www.ata.org/tinnitus-and-coronavirus

https://www.thesun.ie/news/6909139/new-side-effect-covid-vaccine-tinnitus/

How to study. Would it be possible to post a survey for NIH folks who were vaccinated and volunteer to fill it out to get some incidence data? It's a matter of time before reports start to come out from neurologists.

From: Collins, Francis (NIH/OD) [E] <b6>
Sent: Wednesday, April 28, 2021 8:36 PM

To: Koroshetz, Walter (NIH/NINDS) [E] b6
Cc: Tabak, Lawrence (NIH/OD) [E] <b6> Burklow, John (NIH/OD) [E] b6
Subject: FW: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.
Importance: High

Walter, what do you make of this? The draft letter doesn't explain how these 32 patients were referred – leaving one to wonder whether this is common or rare. What does VAERS have to say about this?

FC

From: Fritz, Craig (NIH/OD) [E] b6
Sent: Wednesday, April 28, 2021 12:42 PM
To: Collins, Francis (NIH/OD) [E] <b6> Tabak, Lawrence (NIH/OD) [E] <b6> Aklin, Courtney (NIH/OD) [E] <b6> Burklow, John (NIH/OD) [E] <b6> Jorgenson, Lyric (NIH/OD) [E] b6
Cc: Myles, Renate (NIH/OD) [E] b6 Fine, Amanda (NIH/OD) [E] <b6>; Wojtowicz, Emma (NIH/OD) [E] b6
Subject: FOR AWARENESS: Dr. Avi Nath manuscript on cases of neuropathy after COVID vaccine.
Importance: High

Good afternoon,

We are flagging for your awareness the attached manuscript from Dr. Avi Nath and colleagues. The manuscript has been rejected by NEJM and we are not sure if he will submit it to another journal. NINDS has not yet determined if they will do any proactive press materials on this paper, if accepted. Please let me know if you have any questions. For your reference, below is additional information provided by NINDS.

Thank you,
Craig

COVID manuscript: Neuropathy following COVID vaccine
NINDS
Researchers from Dr. Avi Nath's lab report cases of neuropathic symptoms following the COVID vaccine. The symptoms included paresthesia, tremor, and dysautonomia. Some patients experienced relief following treatment with oral corticosteroids. The letter will be submitted to NEJM. (Since rejected)
4/26/2021
5/31/2021
Manuscript
N/A - Not Media

Craig M. Fritz
Public Affairs Specialist
Office of the Director
Office of Communications and Public Liaison
National Institutes of Health
Building 1, Room 336
ph: b6
b6

From: Hutter, Julia (NIH/NIAID) [E] via Cpn3004.safety [b6]
Sent: [b4]
To: [b6]@novavax.com]; [b6]@iconplc.com]; [b6] [b6]
CC: [b6]@iconplc.com]; [b6] [b6]@iconplc.com]; [b6]@Novavax.com]; [b6]@Novavax.com]; [b6]@Novavax.com]
Subject: RE: Novavax_Protocol-2019nCoV-301_PSRT Reports Review [b4]
Attachments: RE: Novavax_Protocol-2019nCoV-301_PSRT Reports Review

Hi All,

I have reviewed this Novavax PSRT reports with cut-off [b4]

Please find attached my questions from last week regarding the neuropathy/neuroinflammatory disorder.

There are now three thyroid disorders (hyperthyroidism, Hashimotos, Grave's/hyperthyroidism), only one (Grave's - [b6]) assessed as [b6]. The latest participant [b6] has thyroiditis in combination with myocarditis. This is also noteworthy as myocarditis as AESI was seen in the UK study as mentioned during the presentation last weekly. It would be helpful to get more details and understanding of the causality assessment for those conditions and related circumstances.

There are now also two AESIs with panuveitis [b6] and anterior uveitis [b6] both assessed as severe, and both assessed as [b6]. Is there a Med-Watch report for these cases yet?

Others thoughts on these events are greatly appreciated. I am happy to be available for the call, if we decide to go with email communication a more detailed summary would be helpful.

Thank you, and best regards,
Julia

[b6] (Hutter, Julia (NIH/NIAID) [E])

Julia Hutter, MD, MPH
CDR, USPHS
Medical Officer Team Lead, Vaccine Clinical Research Branch, DAIDS, NIAID, NIH
[b6]
[b6] (c)
[b6] (t)
[b6] (f)
5601 Fishers Lane, Rm 9D11A
Rockville, MD 20852

"For there is always light, if only we're brave enough to see it. If only we're brave enough to be it." Amanda Gorman

From: [redacted]novavax.com>
Sent: [redacted]
To: [redacted]@iconplc.com>; [redacted]
[redacted]
Cc: [redacted]@iconplc.com>; [redacted]
[redacted]@iconplc.com>; [redacted]@Novavax.com>; [redacted]@Novavax.com>; [redacted]
[redacted]@Novavax.com>
Subject: RE: Novavax_Protocol-2019nCoV-301_PSRT Reports Review _[redacted]

Hi – I reviewed the MMR – it's okay and signed

[redacted]

Novavax, Inc
Cell: [redacted]

From: [redacted]@iconplc.com>
Sent: Thursday, March 25, 2021 3:08 AM
To: [redacted] <[redacted]
Cc: [redacted]@iconplc.com>; [redacted]
[redacted]@iconplc.com>; [redacted]@Novavax.com>; [redacted]@Novavax.com>; [redacted]
[redacted]@novavax.com>; [redacted]@Novavax.com>
Subject: RE: Novavax_Protocol-2019nCoV-301_PSRT Reports Review _[redacted]

[SENDER IS EXTERNAL TO NOVAVAX]

Hello PSRT,

The Medical Monitoring Report have been now posted & are ready for your review. Here is the location of the Medical Monitoring Report and listings: [redacted].

Note : Data listings have been posted yesterday in the same location as per the trail mail.

Thanks & Regards,

[redacted]

Tel: [redacted]
Mobile: [redacted]
[redacted]@iconplc.com
www.ICONplc.com

From: [b6]@iconplc.com>
Sent: [b4]
To: [b6] <[b6]
Cc: [b6]@iconplc.com>; [b6]@iconplc.com>; [b6]@Novavax.com>; [b6]@Novavax.com' <[b6]@Novavax.com>; [b6]@novavax.com' <[b6]@novavax.com>; [b6]@Novavax.com' <[b6]@Novavax.com>
Subject: Novavax_Protocol-2019nCoV-301_PSRT Reports Review _[b4]

Hello PSRT,

The data listings have been posted & are ready for your review. After reviewing the reports, please let the Medical Review Unit know by replying to ALL if you 1) would like any additional information on any of the participants, 2) have an item to discuss via email, and 3) if you think a PSRT call is needed.

The next PSRT reports will be posted on [b4]

Here is the location of the Medical Monitoring Report and listings: [b6]
Please contact ICON Medical Review Unit at: [b6] if you have any problems accessing the Box link.

Note : MMR shall be posted tomorrow on [b4] in the same folder as discussed. Intimation will be given after posting the MMR.

Thanks & Regards,

[b6]

Tel: [b6]
Mobile: [b6]
[b6]@iconplc.com
www.ICONplc.com

Thank You,

ICON plc
South County Business Park
Leopardstown
Dublin 18
Ireland
Registered number: 145835

From: Hutter, Julia (NIH/NIAID) [E] [b6]
Sent: [b4]
To: [b6]@iconplc.com]; [b6] [b6] [b6]@Novavax.com]; [b6]@Novavax.com' [b6]@Novavax.com]; [b6]@novavax.com' [b6]@novavax.com]; [b6]@Novavax.com' [b6]@Novavax.com]
CC: [b6]@iconplc.com]; [b6] [b6]@iconplc.com]
Subject: RE: Novavax_Protocol-2019nCoV-301_PSRT Reports Review _[b4]

Hi All,

I have reviewed this week's Novavax PSRT reports, and have a few follow up questions regarding the new related SAE of neuropathy, neuroinflammatory disorder.

[b6]

ACUTE LEFT FOOT DROP, UNILATERAL DISTAL PERIPHERAL NEUROPATHY & NEUROINFLAMMATORY DISORDER.

[b6] randomized on [b6] had multiple SAEs on [b6] a day after [b6] vaccination. Subject has ongoing medical history of Neuropathy. These severe events were considered [b6] to the study vaccine. Subject came for acute illness visit at trial site on [b6], followed by referral to local hospital on same day, where left foot was placed in a walking boot. Subject was on oral Gabapentin for neuropathy. Scheduled doses of study vaccination was completed before the start of the event.

1) Did the participant have prior history of neuropathy, or did symptoms only commence for the first time after vaccination? Above states "ongoing medical history", but I was not sure if this was ongoing since [b6] or prior history.
2) Did the participant get any specialty consult and testing to define the diagnosis?
3) Is the condition resolving/improving?

It is noteworthy that there are now two thyroid autoimmune diseases on trial – Hashimoto's – [b6] and Grave's – [b6]
Is there further rationale of why the Grave's disease was [b6]?

Thank you,
Julia

From: [b6]
Sent: [b4]
To: [b6] [b6] N [b6]@Novavax.com>; [b6]@Novavax.com' [b6]@Novavax.com>; [b6]@novavax.com' [b6]@novavax.com>; [b6]@Novavax.com' [b6]@Novavax.com>
Cc: [b6]@iconplc.com>; [b6] [b6]@iconplc.com>
Subject: RE: Novavax_Protocol-2019nCoV-301_PSRT Reports Review _[b4]

Hello PSRT,

The Medical Monitoring Report have been now posted & are ready for your review. Here is the location of the Medical Monitoring Report and listings: [b6].

Note : Data listings have been posted yesterday in the same location as per the trail mail.

Thanks & Regards,

b6

External Tel: b6
Mobile: b6
Email: b6 @iconplc.com
Web: www.ICONplc.com

ICON
A Symbol of Excellence

From: b6 @iconplc.com>
Sent: b4
To: b6 <b6 ; b6 @Novavax.com>; b6 @Novavax.com' <b6 @Novavax.com>; b6 @novavax.com' <b6 @novavax.com>; b6 @Novavax.com' <b6 @Novavax.com>
Cc: b6 @iconplc.com>; b6 b6 @iconplc.com>
Subject: Novavax_Protocol-2019nCoV-301_PSRT Reports Review _b4

Hello PSRT,

The data listings have been posted & are ready for your review. After reviewing the reports, please let the Medical Review Unit know by replying to ALL if you 1) would like any additional information on any of the participants, 2) have an item to discuss via email, and 3) if you think a PSRT call is needed.

The next PSRT reports will be posted on b4

Here is the location of the Medical Monitoring Report and listings: [b6]. Please contact ICON Medical Review Unit at: b6 @iconplc.com if you have any problems accessing the Box link.

Note : MMR shall be posted tomorrow on b4) in the same folder as discussed. Intimation will be given after posting the MMR.

Thanks & Regards,

b6

External Tel: b6
Mobile: b6
Email: b6 @iconplc.com
Web: b6

ICON plc made the following annotations.

From: Schor, Nina (NIH/NINDS) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2D11AC3973BF453DB49D9BA16C2B66FD-b6]
Sent: 4/22/2021 2:07:07 PM
To: Koroshetz, Walter (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8338dd7cdcd432e986961f1548c5ec6-b6]
Subject: RE: f/u to your AAN talk

Right you are!

From: Koroshetz, Walter (NIH/NINDS) [E] b6
Sent: Thursday, April 22, 2021 10:05 AM
To: Schor, Nina (NIH/NINDS) [E] b6
Subject: RE: f/u to your AAN talk

Speaking of forces of nature..
walter

From: Schor, Nina (NIH/NINDS) [E] b6
Sent: Thursday, April 22, 2021 10:04 AM
To: Koroshetz, Walter (NIH/NINDS) [E] b6
Subject: RE: f/u to your AAN talk

Thanks, Walter. As always with Anne Louise, really interesting. Why does a collaboration among Anne Louise, Marinos Dalakas, and Avi give me pause? Wouldn't want to disagree with a consensus among them! Strong personalities!

Nina

From: Koroshetz, Walter (NIH/NINDS) [E] b6
Sent: Thursday, April 22, 2021 9:57 AM
To: Schor, Nina (NIH/NINDS) [E] b6
Subject: FW: f/u to your AAN talk

Dear Nina—as instructed by our mutual friend please see her poster.
Best,
walter

From: Oaklander, Anne Louise,M.D.,Ph.D. b6
Sent: Thursday, April 22, 2021 9:31 AM
To: Koroshetz, Walter (NIH/NINDS) [E] b6
Subject: f/u to your AAN talk

Dear Walter,
Such a pleasure to see you at the AAN! And as I'm collaborating on a post-COVID neuropathy study with Avi Nath and Marinos Dalakas, useful to hear the very latest information on neuro complications COVID. Keep me in mind if you hear of post-COVID patients being evaluated for distal sensory predominant neuropathy. Our study is exploratory and includes all qualifying cases; we're just aggregating results of evaluations and outcomes to inform neurologists.

I agree that some symptoms of post-COVID resemble CF/CME. So, you might be interested in our just-appearing paper on CF/CME with David Systrom from Brigham. It not only links about 1/3 of patients in this 160-patient sample to SFN, but I'm excited that it identifies 2 independent small-fiber mediated cardiovascular pathophysiologies that appear to explicate fatigue symptoms in many in this cohort.. Hoping this might be useful background for post-COVID.

And I wanted to add for Nina as well our attached AAN poster funded by our R01 on pediatric small-fiber neuropathy.
We've been productive during COVID and will expand in 2021.
Hope to see you in person soon, best regards, Anne Louise

Anne Louise Oaklander, MD PhD, FAAN, FANA
*~
Director, MGH Nerve Unit & Neuropathology Skin Biopsy Service
Associate Professor of Neurology, Harvard Medical School
Assistant in Pathology (Neuropathology), Massachusetts General Hospital
Lab phone: b6 *(Heather Downs)*
Mail: Mass General Hospital, 275 Charles St./Warren 310, Boston, MA 02114
Internet: https://www.NeuropathyCommons.org https://www.youtube.com/watch?v=s66LvWQ5Qso

From: Schor, Nina (NIH/NINDS) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2D11AC3973BF453DB49D9BA16C2B66FD b6
Sent: 4/22/2021 2:52:58 PM
To: Koroshetz, Walter (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8338dd7cdcd432e986961f1548c5ec6 b6
Subject: RE: f/u to your AAN talk

Yes, but my experience with the team b6 had to support him was that they were nothing like the amazing team b6 had behind her. Rachael, Liza, Christine K-P, etc. might be what b6 needs to be effective. Not sure but worth considering.

Nina

From: Koroshetz, Walter (NIH/NINDS) [E] b6
Sent: Thursday, April 22, 2021 10:21 AM
To: Schor, Nina (NIH/NINDS) [E] b6
Subject: RE: f/u to your AAN talk

Good point. Makes for great scientist. Maybe not SD. b6 was like that in some sense.
w

From: Schor, Nina (NIH/NINDS) [E] < b6
Sent: Thursday, April 22, 2021 10:19 AM
To: Koroshetz, Walter (NIH/NINDS) [E] b6
Subject: RE: f/u to your AAN talk

Interesting idea. I worked with him a little on the Intramural Strategic Planning Taskforce. He is delightful and very sensitive to "hot button" issues and such, but it was b6 who kept him organized, on-task, and realistic in his expectations. I mean this is the most complimentary way, but he is a bit of a "space cadet" and needed to be brought back to concrete tasks. Perhaps with Rachael et al., he could be good for it.

Nina

From: Koroshetz, Walter (NIH/NINDS) [E] b6
Sent: Thursday, April 22, 2021 10:08 AM
To: Schor, Nina (NIH/NINDS) [E] b6
Subject: RE: f/u to your AAN talk

Wanted to mention that in speaking to Avi last night he brought up b6 as a potential SD candidate. Hadn't thought of him as he doesn't seem to seek the limelight but that is probably a great attribute. Have no idea if he would do it but he has excelled at almost every turn, including b6

Walter

From: Schor, Nina (NIH/NINDS) [E] < b6
Sent: Thursday, April 22, 2021 10:04 AM
To: Koroshetz, Walter (NIH/NINDS) [E] b6
Subject: RE: f/u to your AAN talk

Thanks, Walter. As always with Anne Louise, really interesting. Why does a collaboration among Anne Louise, Marinos Dalakas, and Avi give me pause? Wouldn't want to disagree with a consensus among them! Strong personalities!

Nina

From: Koroshetz, Walter (NIH/NINDS) [E] [b6]
Sent: Thursday, April 22, 2021 9:57 AM
To: Schor, Nina (NIH/NINDS) [E] [b6]
Subject: FW: f/u to your AAN talk

Dear Nina—as instructed by our mutual friend please see her poster.
Best,
walter

From: Oaklander, Anne Louise,M.D.,Ph.D. [b6]
Sent: Thursday, April 22, 2021 9:31 AM
To: Koroshetz, Walter (NIH/NINDS) [E] [b6]
Subject: f/u to your AAN talk

Dear Walter,
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I agree that some symptoms of post-COVID resemble CF/CME. So, you might be interested in our just-appearing paper on CF/CME with David Systrom from Brigham. It not only links about 1/3 of patients in this 160-patient sample to SFN, but I'm excited that it identifies 2 independent small-fiber mediated cardiovascular pathophysiologies that appear to explicate fatigue symptoms in many in this cohort.. Hoping this might be useful background for post-COVID.

And I wanted to add for Nina as well our attached AAN poster funded by our R01 on pediatric small-fiber neuropathy. We've been productive during COVID and will expand in 2021.
Hope to see you in person soon, best regards, Anne Louise

Anne Louise Oaklander, MD PhD, FAAN, FANA
*~
Director, MGH Nerve Unit & Neuropathology Skin Biopsy Service
Associate Professor of Neurology, Harvard Medical School
Assistant in Pathology (Neuropathology), Massachusetts General Hospital
Lab phone: [b6] *(Heather Downs)*
Mail: Mass General Hospital, 275 Charles St./Warren 310, Boston, MA 02114
Internet: https://www.NeuropathyCommons.org https://www.youtube.com/watch?v=s66LvWQ5Qso

this message means you understand and accept this risk and wish to continue to communicate over unencrypted e-mail.

From: Nath, Avindra (NIH/NINDS) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B81CA051950B4D458D74037A6A86EAD6 b6
Sent: 4/12/2021 8:57:43 PM
To: Tuttle, Alex (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7432a60a668d465780f7faed4ea86a56 b6
CC: Koroshetz, Walter (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8338dd7cdcd432e986961f1548c5ec6 b6
Subject: Re: Neuropathic symptoms with COVID vaccines

Dear Alex,
I want to first extend a warm welcome to you in your new position. I look forward to working with you.

I am sorry to hear of the effects of the vaccine b6 experienced. I would be glad to contact her to learn more about it.

With best wishes.
Avi

From: Tuttle, Alex (NIH/NINDS) [E] b6
Date: Monday, April 12, 2021 at 4:34 PM
To: Nath, Avindra (NIH/NINDS) [E] b6
Cc: Koroshetz, Walter (NIH/NINDS) [E] b6
Subject: FW: Neuropathic symptoms with COVID vaccines

Dear Dr. Nath,
I wanted to let you know that as Walter's new CoS, I had the privilege to see your manuscript come across Walter's desk concerning post-COVID vaccine peripheral neuropathy. I asked b6 permission (b6 another employee in NINDS Division of Neuroscience) about sharing her story. She experienced transient brachial plexopathy (intense shooting pain from injection site down to fingertips) for about 18 hours after receiving a second dose of the Pfizer vaccine on March 25. She has also had a lingering tingling sensation in her in the injected limb for a good deal longer, although I believe it has now gone away. If you would like to follow up with her about her experience, you can reach her at b6

Good luck with the publication process,
~Alex

Alexander H. Tuttle, Ph.D.
Chief of Staff (Acting)
National Institute of Neurological Disorders and Stroke

From: Tuttle, Alex (NIH/NINDS) [E] **On Behalf Of** Koroshetz, Walter (NIH/NINDS) [E]
Sent: Monday, April 12, 2021 4:28 PM
To: Tuttle, Alex (NIH/NINDS) [E] b6
Subject: FW: Neuropathic symptoms with COVID vaccines

Alexander H. Tuttle, Ph.D.
Chief of Staff (Acting)
National Institute of Neurological Disorders and Stroke

From: Nath, Avindra (NIH/NINDS) [E] b6
Sent: Saturday, April 10, 2021 12:27 AM
To: Koroshetz, Walter (NIH/NINDS) [E] b6
Subject: Neuropathic symptoms with COVID vaccines

Dear Walter,
Please see attached manuscript formatted as a letter for NEJM based on our experience of neuropathy like symptoms in 24 patients following SARS-CoV-2 vaccine. The main message is that early recognition and treatment with corticosteroids can reverse the symptoms, although some will spontaneously get better over several weeks. Please let me know your thoughts.
Thanks.
Avi

From: Nath, Avindra (NIH/NINDS) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B81CA051950B4D458D74037A6A86EAD6 b6
Sent: 4/20/2021 2:29:59 AM
To: Koroshetz, Walter (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8338dd7cdcd432e986961f1548c5ec6 b6
Subject: FW: Post Covid-19 Vaccine Small Fiber Neuropathy

This is coming out in Muscle and Nerve

Avi

From: Safavi, Farinaz (NIH/NINDS) [E] b6
Date: Monday, April 19, 2021 at 9:39 PM
To: Nath, Avindra (NIH/NINDS) [E] b6
Subject: Post Covid-19 Vaccine Small Fiber Neuropathy

https://onlinelibrary.wiley.com/doi/epdf/10.1002/mus.27251

well,people started publishing!

Farinaz

From: Tuttle, Alex (NIH/NINDS) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7432A60A668D465780F7FAED4EA86A5[b6]
Sent: 4/12/2021 8:34:54 PM
To: Nath, Avindra (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b81ca051950b4d458d74037a6a86ead6[b6]
CC: Koroshetz, Walter (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8338dd7cdcd432e986961f1548c5ec6[b6]
Subject: FW: Neuropathic symptoms with COVID vaccines
Attachments: Acute neuropathic symptoms post covid vaccine 4-9-21.docx; main table 4-9-21.docx; Supplement.docx

Dear Dr. Nath,
I wanted to let you know that as Walter's new CoS, I had the privilege to see your manuscript come across Walter's desk concerning post-COVID vaccine peripheral neuropathy. I asked [b6]s permission ([b6] another employee in NINDS Division of Neuroscience) about sharing her story. She experienced transient brachial plexopathy (intense shooting pain from injection site down to fingertips) for about 18 hours after receiving a second dose of the Pfizer vaccine on March 25. She has also had a lingering tingling sensation in her in the injected limb for a good deal longer, although I believe it has now gone away. If you would like to follow up with her about her experience, you can reach her at [b6]

Good luck with the publication process,
~Alex

Alexander H. Tuttle, Ph.D.
Chief of Staff (Acting)
National Institute of Neurological Disorders and Stroke

From: Tuttle, Alex (NIH/NINDS) [E] **On Behalf Of** Koroshetz, Walter (NIH/NINDS) [E]
Sent: Monday, April 12, 2021 4:28 PM
To: Tuttle, Alex (NIH/NINDS) [E] [b6]
Subject: FW: Neuropathic symptoms with COVID vaccines

Alexander H. Tuttle, Ph.D.
Chief of Staff (Acting)
National Institute of Neurological Disorders and Stroke

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To: Koroshetz, Walter (NIH/NINDS) [E] [b6]
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Thanks.
Avi

Neuropathic symptoms post vaccination for SARS-CoV-2

Short author list for print version

Farinaz Safavi MD, PhD[1], Susan Shin MD[2], Avindra Nath MD[1]

[1]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

[2]Icahn School of Medicine at Mt Sinai, New York, NY

Corresponding author: Avindra Nath MD; Bldg 10; Room 7C-103; 10 Center Drive, Bethesda, MD 20892

e-mail: b6

Long author list for online version

Farinaz Safavi MD, PhD[1], Lindsey Gustafson NP[1], Anita Fletcher MD[1], Tanya Lehky[1], Mark Hallett MD[1], Amanda Wiebold RN[1], Susan Shin MD[2], Avindra Nath MD[1]

[1]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

[2]Icahn School of Medicine at Mt Sinai, New York, NY

Correspondence:

Avindra Nath MD

Bldg 10; Room 7C-103

10 Center Drive

Bethesda, MD 20892

Email: b6

Text: 392 words

To the Editor: We report a series of patients with acute neuropathic and autonomic symptoms post-vaccination for SARS-CoV-2. Thirty-two patients contacted us between January 11 to March 31, 2021 seeking advice about neurological symptoms that started post-vaccination. All patients were evaluated by televisit or an in-person visit, and medical records were reviewed. We excluded 8 patients because their complaints were non-neurologic or limited to worsening or recrudescence of underlying neurological symptoms. 9/24 (37%) patients developed transient symptoms within 30 minutes following vaccination including skin-flushing, tachycardia and increased blood pressure.

Median age of the patients was 39 years (range: 27-70 years). Twenty-one were women. One received the vaccine manufactured by b6, 8 by b6 and 15 b b6. 16/24 (66%) developed neurological symptoms following the first dose (Table S1). In 21/24 patients' onset of neurological symptoms was within the first week. All patients reported paresthesia and/or burning sensation in either or both upper and lower limbs and in seven patients it involved the face, mouth and scalp (Table 1). Two patients had severe unilateral paresthesia in the distribution of the V1 branch of the trigeminal nerve with intermittent tearing and burning in the eye suggestive of trigeminal neuralgia. 9/24 (37%) described a moderate to severe intermittent internal tremor in the head and throughout their body that interfered with daily activities and sleep. 8/24 (33%) patients had dysautonomia (Table S2; Figure S1). 12/24 had brain and/or spinal cord MRI with unremarkable findings. 3/24 patients had symptoms of brachial plexopathy confirmed by EMG. Brachial plexus MRI showed nerve enhancement in one patient. Six patients treated with oral corticosteroid, completely (n=4) or partially (n=2) improved after one or two weeks (Table S2). Untreated patients had either no recovery (n=7), partial (n=9) or complete recovery (n=2) at a median of 10 weeks.

This report describes symptoms suggestive of a neuropathy following vaccination for SARS-CoV-2 from three different manufactures. These vaccines have in common the gene encoding the spike protein[4] suggesting that the symptoms may be driven by an immune response it. The response to treatment with corticosteroids supports that possibility. Alternatively, lipid nanoparticles or solvents used in the vaccines may induce release of Inflammatory mediators causing activation of sensory signals in nociceptive nerve terminals and dorsal root ganglia[5]. While further investigations are needed to determine the underlying pathophysiology of these symptoms, treatment with corticosteroids may be considered in these patients.

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Table: Neurological manifestations post-SARS-CoV-2 vaccination

Case#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Onset of symptoms		2h	5h	3d	10h	4d	6d	3h	10h	1d	14d	2d	7d	2h	10d	7d	10h	2h	2d	2d	10m	2d	6d	5d	8d
Sensory																									
	Paresthesia	+++	+++	+	+++	++	++	++	++	++	+	+	++	++	+	++	+	++	++	+	+	++	+	++	++
	Burning	+	+	-	-	+	-	+	-	-	-	-	-	+	-	+	-	-	+	+	-	+	-	-	+
	Back pain	+	++	++	+	+	-	-	++	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Motor					-																				
	Weakness	+	-	+	-	+	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	+	+	-	+
	Fasciculations	-	-	+	-	-	-	-	-	-	-	-	-	++	-	-	-	-	-	+	-	-	++	-	+
Dysautonomia																									
	Orthostatic Tachycardia	++	-	-	-	-	-	-	-	-	+	++	-	-	++	-	-	-	-	-	+	-	-	-	-
	presyncope	+	-	-	-	-	-	-	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	+	-
	Blood pressure variability	+	-	-	+	+	-	-	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	-	-
Corticosteroid treatment		-	-	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	+	-	-	-	-	+	-
Recovery																									
	Complete						+				+	+	+		+		+								
	Partial	+	+	+	+									+		+			+	+	+	+		+	
	None					+		+	+	+								+					+		+

+mild; ++moderate; +++severe

Table S1: Demographic characteristics

Demographic Information	Case# 1	2	3	4	5	6	7	8	9	10	11	12
Age	b6											
Sex												
Type of vaccine												
Dose	1st	1st	2nd	1st	1st	2nd	1st	1st	1st	1st	2nd	1st
History of COVID-19	Probable*	no	Probable	no	no	no	no	no	unknown	no	no	no
Past Medical History	Tinnitus, cholestoma	Hypertension, Crohn's disease	None	None	None	None	no	Hypothyroidism, polycystic ovarian syndrome	no	no	seasonal allergy, Migraine headaches	hyperlipidemia
Family history of autoimmune diseases	no	no	unknown	SLE	no	no	no	no	no	no	psoriasis	no

Demographic Information	13	14	15	16	17	18	19	20	21	22	23	24
Age	b6											
Sex												
Type of vaccine												
Dose	1st	2nd	2nd	1st	1st	1st	2nd	1st	1st	1st	2nd	2nd
History of COVID-19	no	no	no	no	no	no	no	no	no	no	no	no
Past Medical History	Chiari syndrome, L5 radiculopathy	migraine headaches, supra ventricular tachycardia	no	asthma and eczema	migraine headaches with aura, hashimoto thyroiditis	asthma	none	none	Anxiety dx	no	Hypothyroidism	no
Family history of autoimmune diseases	no	rheumatoid arthritis	no	no	no	no	no	unknown	no	no	no	RA

*Probable: History of upper respiratory tract infection but not confirmed with SARS-COV2 PCR or Antibody testing

Table S2: Clinical characteristics and course of illness

Symptom characteristics	9	10	11	12	13	14	15	16
Time from vaccination to any symptoms	24 hours	8 days	8 hours	2 days	2 hours	30 minutes	2 days	10 hours
Symptom at onset	fever, chills, and fatigue	Lymphadenopathy in neck and axillary area	flu like symptoms, fever muscle pain	right scapular muscle spasm with constant pain and discomfort	formication in scalp and lower limbs, severe fatigue	flashing, tachycardia, positional dizziness	feet paresthesia	intermittent cognitive changes, paresthesia in both hands
Onset of neurological symptoms	1 day	14 days	2 days	7 days	2 hours	10 days	7 days	10 hours
Neurological symptoms	intermittent paresthesia in all limbs. Right ulnar distribution numbness, cramping in right hand fingers and difficulty with fine movements in right hand	numbness in left shin and right hand; progress to cold sensation in left leg and intermittent paresthesia in all limbs; Raynaud's phenomenon in left leg	orthostasis, fluctuation in heart rate, blood pressure fluctuation, nausea, diarrhea, band like tightness in T2-T3 level; Paresthesia in face, upper and lower limbs; internal tremor	paresthesia in right arm ulnar distribution progressed to weakness in right hand fine movements	severe paresthesia and severe fasciculations in both lower limbs	severe orthostatic tachycardia, paler, flashing, diarrhea, fluctuation in blood pressure	progressive paresthesia in upper and lower limbs	paresthesia in ulnar distribution of both arms, numbness in feet
Neurological examination	decreased light touch and pin prick sensation on right ulnar distribution, mild weakness in right arm	normal	normal	finger abduction and wrist/hand dorsiflexion weakness	decreased vibration in right foot, enhanced light touch and vibration on left side; fasciculations in both legs	normal	normal	ND
MRI	consistent with brachial plexopathy	normal brain and cervical spinal cord	ND	normal brachial plexus and cervical spinal cord	ND	ND	normal brain and total spinal cord	ND
EMG-NCV	ND	ND	ND	Brachial plexopathy lower trunk	ND	normal	mild peripheral neuropathy	ND
Other tests	ND	ND	tilt table test fulfills clinical criteria for POTS	ND	ND	tilt table test fulfils clinical criteria for POTS	ND	ND
Corticosteroid treatment	ND	Prednisone 20 mg two times a day for 5 days	Prednisone 30 mg/day with weekly taper	Prednisone 60 mg/day for 3 days, tapered every 3 days	ND	Prednisone 40 mg/day, tapered every 3 days	ND	ND
Course of Disease	no improvement after 3-4 weeks	improvement started 1-2 weeks after corticosteroid treatment. Complete improvement after 10-12 weeks.	improvement started 1-2 weeks after corticosteroid treatment. Complete improvement after 8 weeks.	improvement started at1-2 weeks after corticosteroid treatment. Complete recovery after 6-8 weeks.	partial improvement after 6 weeks	Improvement started 1-2 weeks after corticosteroid treatment. complete improvement after 8-10 weeks,	partial improvement after 8-10 weeks	complete improvement after 2 weeks

Symptom characteristics	17	18	19	20	21	22	23	24
Time from vaccination to any symptoms	4 minutes	20 minutes	5 hours	10 minutes	2 hours	1 day	3 hours	15 minutes
Symptom at onset	sensation of tremor from head to toe	dizziness, presyncope	severe tingling in all limbs	numbness in both arms	transient right side face numbness	fatigue, headache, loss of appetite	intermittent cognitive changes, headache, dizziness	transient burning and tingling in mouth
Onset of neurological symptoms	2.5 hours	2 days	5 hours	10 min	2 days	6 days	5 days	8 days
Neurological symptoms	distal paresthesia and numbness in all limbs	formication in V1 distribution of trigeminal nerve progress to severe paresthesia and burning sensations, eye tearing and burning	tingling and burning sensation followed by fasciculations in both thighs and forearms	Internal tremor, Paresthesia and numbness in all limbs. Variable tachycardia.	Intermittent face, hands and feet paresthesia, burning and numbness. Mild right-hand weakness with fine movements and paresthesia in right ulnar distribution	both legs weakness; fasciculations in all limbs; internal tremor, facial paresthesia; band like tightness in ribcage	photophobia, paresthesia and burning sensation in V1 distribution of trigeminal nerves	paresthesia and burning sensation in upper and lower limbs; intermittent redness in both hands; lips and mouth tingling fasciculations in limbs
Neurological examination	normal	normal	normal	ND	normal	normal	normal	normal
MRI	ND	normal brain	ND	ND	normal brain, cervical and thoracic spinal cord	ND	ND	normal brain
EMG-NCV	ND	ND	ND	ND	right lower trunk brachial plexopathy with no active denervation	ND	ND	normal
Other tests	ND	ND	ND	ND	ND	ND	ND	ND
Corticosteroid treatment	ND	Prednisone 40 mg/day, tapered every 3 days	ND	ND	ND	ND	Prednisone 50 mg/day, tapered every 2 days	ND
Course of Disease	no improvement after 4 weeks	Improvement started 1-2 weeks after corticosteroid treatment. Partial improvement after 4 weeks	partial improvement after 8 weeks	partial improvement after one week	partial improvement after 10-12 weeks	no improvement after 4 weeks	Improvement started 1-2 weeks after corticosteroid treatment. Partial improvement after 8-10 weeks	no improvement after 7 weeks

*Clinical Criteria for Positional Orthostatic Tachycardia Syndrome (POTS): Increase in heart rate more than 30 beats per minutes with tilt table test

AchR = Acetylcholine receptor; ND = not done; MRI = magnetic resonance imaging; EMG-NCV = electromyography and nerve conduction velocities

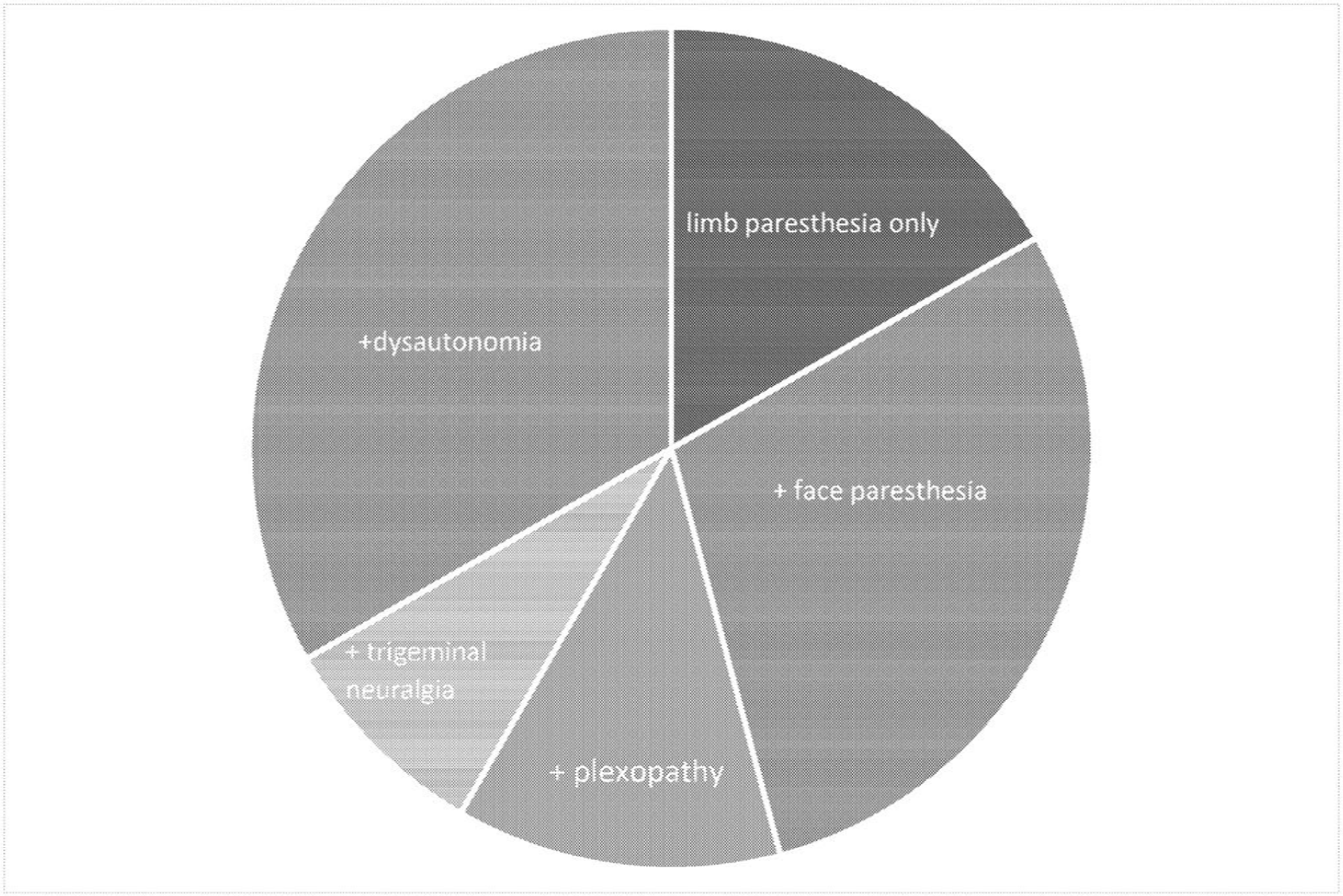

Figure S1: Neuropathic symptoms post-SARS-CoV-2 vaccination: All patients had parasthesia. Some patients had additional symptoms of parasthesia in face, brachial plexopathy, trigeminal neuralgia or dysautonomia.

From: Oaklander, Anne Louise,M.D.,Ph.D. b6
Sent: 4/22/2021 1:30:35 PM
To: Koroshetz, Walter (NIH/NINDS) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8338dd7cdcd432e986961f1548c5ec6 b6
Subject: f/u to your AAN talk
Attachments: 2021 Insights from CPET.pdf; AAN 2021 poster.pdf

Dear Walter,
Such a pleasure to see you at the AAN! And as I'm collaborating on a post-COVID neuropathy study with Avi Nath and Marinos Dalakas, useful to hear the very latest information on neuro complications COVID. Keep me in mind if you hear of post-COVID patients being evaluated for distal sensory predominant neuropathy. Our study is exploratory and includes all qualifying cases; we're just aggregating results of evaluations and outcomes to inform neurologists.

I agree that some symptoms of post-COVID resemble CF/CME. So, you might be interested in our just-appearing paper on CF/CME with David Systrom from Brigham. It not only links about 1/3 of patients in this 160-patient sample to SFN, but I'm excited that it identifies 2 independent small-fiber mediated cardiovascular pathophysiologies that appear to explicate fatigue symptoms in many in this cohort.. Hoping this might be useful background for post-COVID.

And I wanted to add for Nina as well our attached AAN poster funded by our R01 on pediatric small-fiber neuropathy. We've been productive during COVID and will expand in 2021.
Hope to see you in person soon, best regards, Anne Louise

Anne Louise Oaklander, MD PhD, FAAN, FANA
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Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Phillip Joseph, MD; Carlo Arevalo, MD; Rudolf K. F. Oliveira, MD, PhD; Mariana Faria-Urbina, MD; Donna Felsenstein, MD; Anne Louise Oaklander, MD, PhD; and David M. Systrom, MD

BACKGROUND: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) affects tens of millions worldwide; the causes of exertional intolerance are poorly understood. The ME/CFS label overlaps with postural orthostatic tachycardia (POTS) and fibromyalgia, and objective evidence of small fiber neuropathy (SFN) is reported in approximately 50% of POTS and fibromyalgia patients.

RESEARCH QUESTION: Can invasive cardiopulmonary exercise testing (iCPET) and PGP9.5-immunolabeled lower-leg skin biopsies inform the pathophysiology of ME/CFS exertional intolerance and potential relationships with SFN?

STUDY DESIGN AND METHODS: We analyzed 1,516 upright invasive iCPETs performed to investigate exertional intolerance. After excluding patients with intrinsic heart or lung disease and selecting those with right atrial pressures (RAP) <6.5 mm Hg, results from 160 patients meeting ME/CFS criteria who had skin biopsy test results were compared with 36 control subjects. Rest-to-peak changes in cardiac output (Qc) were compared with oxygen uptake (Qc/VO_2 slope) to identify participants with low, normal, or high pulmonary blood flow by Qc/VO_2 tertiles.

RESULTS: During exercise, the 160 ME/CFS patients averaged lower RAP (1.9 ± 2 vs 8.3 ± 1.5; $P < .0001$) and peak VO_2 (80% ± 21% vs 101.4% ± 17%; $P < .0001$) than control subjects. The low-flow tertile had lower peak Qc than the normal and high-flow tertiles (88.4% ± 19% vs 99.5% ± 23.8% vs 99.9% ± 19.5% predicted; $P < .01$). In contrast, systemic oxygen extraction was impaired in high-flow vs low- and normal-flow participants (0.74% ± 0.1% vs 0.88 ± 0.11 vs 0.86 ± 0.1; $P < .0001$) in association with peripheral left-to-right shunting. Among the 160 ME/CFS patient biopsies, 31% were consistent with SFN (epidermal innervation ≤5.0% of predicted; $P < .0001$). Denervation severity did not correlate with exertional measures.

INTERPRETATION: These results identify two types of peripheral neurovascular dysregulation that are biologically plausible contributors to ME/CFS exertional intolerance—depressed Qc from impaired venous return, and impaired peripheral oxygen extraction. In patients with small-fiber pathology, neuropathic dysregulation causing microvascular dilation may limit exertion by shunting oxygenated blood from capillary beds and reducing cardiac return.

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KEY WORDS: dysatonomia; dyspnea; exercise testing; physiology

ABBREVIATIONS: iCPET = invasive cardiopulmonary exercise test; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; MM = mitochondrial myopathy; PAWP = pulmonary arterial wedge pressure; PLF = preload failure; POTS = postural orthostatic tachycardia syndrome; Qc = cardiac output; RAP = right atrial pressure; SFN = small fiber neuropathy; VO_2 = oxygen uptake

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Take-home Point

Study Question: Can invasive cardiopulmonary exercise testing (iCPET) and skin biopsies inform the pathophysiology of exertional intolerance in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and potential relationships to small fiber neuropathy (SFN)?

Results: During exercise, ME/CFS patients averaged lower right atrial pressures (RAP) and peak oxygen uptake (VO_2) compared with control subjects. Rest-to-peak changes in in cardiac output were compared with VO_2 (Qc/VO_2 slope) to identify low, normal, and high pulmonary blood flow tertiles. The low-flow tertile had lower peak Qc than the normal and high-flow tertiles. In contrast, systemic oxygen extraction was impaired in the high-flow group vs the low- and normal-flow tertiles. Thirty-one percent of skin biopsies were consistent with SFN.

Interpretation: Two types of neurovascular dysregulation contribute to ME/CFS exertional intolerance—depressed Qc from impaired venous return and impaired peripheral oxygen extraction. Small fiber pathology may cause neuropathic dysregulation by shunting of oxygenated blood from capillary beds and reducing cardiac return.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating and common disorder that affects up to 2.5 million Americans. Its causes are unknown, but infections, especially viruses, and immunologic and endocrine disorders have been proposed. The National Academy of Medicine (formerly the Institute of Medicine) requires three major criteria for diagnosis; substantial impairment from fatigue for >6 months, post-exertional malaise, and unrefreshing sleep, plus either cognitive impairment or orthostatic intolerance.[1]

ME/CFS overlaps extensively with two other syndromic labels—postural orthostatic tachycardia syndrome (POTS) and fibromyalgia.[2-4] Increasing evidence implicates small fiber neuropathy (SFN) in approximately 50% of adult and juvenile fibromyalgia[5-8] and 38% of POTS patients,[9] generating suggestions of neuropathic and non-neuropathic subtypes in these syndromes.[9,10]

To elucidate potential mechanisms underlying ME/CFS symptoms, we had used invasive cardiopulmonary exercise testing (iCPET) to demonstrate that up to 20% of patients with unexplained exertional intolerance have low aerobic capacity attributable solely to low biventricular filling pressures, or "preload failure" (PLF).[11,12] In accord, most PLF patients report chronic fatigue, and 20% have documented peripheral dysautonomia.[11]

Given the data suggesting hemodynamic phenotypes in POTS[13] and neurovascular dysregulation in fibromyalgia,[14] we hypothesized that the abnormal exercise phenotypes of ME/CFS can, in some patients, reflect SFN. We are not aware of prior iCPET or skin biopsy studies in ME/CFS despite their potential to identify mechanisms underlying exercise intolerance. The goal of this study was to use them to gain insights into contributors to acute exertional intolerance in ME/CFS, and to gather initial data on associations with SFN.

Study Design and Methods

The Partners Human Research Committee approved the review of clinical data (Protocol 2018P001903) and the telephone questionnaire (Protocol 2019P000039) containing the ME/CFS symptoms required for research diagnosis. Patients were given 2 weeks to decline telephone participation.

Study Population

Data from 1,516 clinically indicated iCPETs performed between 2011 to 2018 at the Brigham and Women's Hospital Dyspnea Clinic (Boston, MA) were analyzed. To eliminate potentially confounding submaximal effort and intrinsic heart and lung disease, we excluded the following:

1. Submaximal testing: Maximum heart rate achieved <80% predicted for age or a peak respiratory exchange ratio < 1.05
2. Primary pulmonary mechanical limitation to exercise: Minute ventilation/maximum voluntary ventilation >0.7 at the anaerobic threshold
3. Resting or exercise precapillary pulmonary hypertension: Patients ≤50 years of age: mean pulmonary artery pressure >30 mm Hg and pulmonary vascular resistance >1.34 Woods Units; patients >50 years of age: mean pulmonary artery pressure >33 mm Hg and pulmonary vascular resistance >2.10 Woods Units[15]

Department of Medicine (M. Faria Urbina and D. M. Systrom), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and the Infectious Diseases Unit, Department of Medicine (D. Felsenstein), the Department of Neurology (A. L. Oaklander), and the Department of Pathology (Neuropathology) (A. L. Oaklander), Massachusetts General Hospital, Boston, MA.

Part of this article has been presented at the American Thoracic Society International Conference, May 2019, Dallas, TX.

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4. Resting or exercise postcapillary pulmonary hypertension: Patients ≤50 years of age: pulmonary arterial wedge pressure (PAWP) >19 mm Hg; patients >50 years of age: PAWP >17 mm Hg[15]
5. RAP ≥6.5 mm Hg, which defines our lower limit of normal[11]
6. Incomplete data including lack of skin biopsy results

All then underwent additional medical record review to confirm presence of ME/CFS, using the NAM requirement of documentation of three major criteria (ie, chronic fatigue for ≥6 months, post-exertional malaise, unrefreshing sleep) plus one minor criteria (ie, either cognitive impairment, orthostatic intolerance).[1] For those with uncertain documentation on medical record review, a short telephone questionnaire was used to finalize inclusion or exclusion.

A control cohort assembled for comparison purposes comprised 36 patients who had undergone iCPET for exertional intolerance but who had normal results. Specifically, there was no exercise or resting pulmonary hypertension, heart failure, or decreased aerobic capacity, defined as oxygen uptake (VO_2), cardiac output (Qc), and arterial-mixed venous oxygen content difference ($Ca\text{-}vO_2/[Hb]$) >80% of predicted, along with a $Qc\text{-}VO_2$ percent predicted difference <10% of population-predicted.[16,17]

Invasive Cardiopulmonary Exercise Testing Protocol

Protocols for iCPET, hemodynamic measurements, and gas exchange measurements have been described previously.[18,19] Briefly, the pulmonary and radial arteries are catheterized with ultrasound and fluoroscopic guidance, then standard right-heart catheterization performed with oxygen saturation measurements to assess for intracardiac shunting.[20] Patients are then transported to the cardiopulmonary stress laboratory for incrementally increasing upright exercise to maximum on a cycle ergometer as ventilation and pulmonary gas exchange is measured (MGC Diagnostics). Hemodynamics, including right atrial pressure (RAP), mean pulmonary artery pressure, and mean arterial pressure are continuously recorded (Koninklijke Philips N.V., Amsterdam, Netherlands). PAWP and arterial and mixed-venous blood gases and pH are measured once per 60 seconds, and Qc calculated using the direct Fick principle. Carboxyhemoglobin levels are also returned from both compartments, and none were elevated (data not shown).

Skin Biopsy Measurements of SFN

At the discretion of the referring physician, 3-mm punch biopsy specimens were removed from lidocaine-anesthetized skin 10 cm proximal to the lateral malleolus using standard clinical methods, overnight fixed (Zamboni's), and transported to the Massachusetts General Hospital clinical diagnostic laboratory for standard processing and assessment.[21] Vertical sections were immunolabeled against PGP9.5, then epidermal neurite density was measured by skilled morphologists unaware of patient designations. The standard diagnostic cutoff (≤5% of the laboratory's sex-, age-, and race-adjusted normal distribution) was applied to interpret biopsy normality.[21,22]

Data Analysis

piPredicted values for peak oxygen uptake (VO_2) were derived from the Wasserman-Hansen equation.[15] Based on the rest-to-peak change of cardiac output in relation to oxygen uptake (Qc/VO_2 slope), participants were categorized as low, normal, or high pulmonary blood flow according to Qc/VO_2 tertiles. Statistical analyses were performed with GraphPad Prism (v8.0.0 for Windows, GraphPad Software). Normally distributed data were reported as mean ± SD; non-normally distributed data as median ± interquartile range. Multiple group comparisons used one-way analysis of variance with Tukey post hoc test. Correlations between variables were calculated using the Pearson correlation coefficient or the Spearman rank correlation coefficient according to data distribution. Two-tailed P values < .05 were considered significant.

Results

Among 1,516 patients whose iCPET reports were screened for inclusion, 223 met criteria for PLF and had skin biopsy data. The 72% (160/223) meeting the ME/CFS diagnostic criteria yielded a 160-patient study sample (Fig 1) that was 78% female. Significant associated conditions were POTS, fibromyalgia, mast cell activation syndrome, and history of preceding infection (Table 1). Few patients used diuretics or vasoactive medications.

The mean peak VO_2 was decreased for all ME/CFS patients as compared with control subjects (Table 2). Analyzing incremental exercise Qc/VO_2 slopes revealed low (4 [3.2-4.4]), normal (5.6 [5.3-6]), and high (7.5 [7-8.3]) pulmonary blood flow based on Qc/VO_2 tertiles. The tertile with low-flow had disproportionately low Qc at peak exercise as compared with those with normal- and high-flow. At peak exercise, the high-flow tertile had significantly less oxygen extraction and higher venous oxygen tension than the others. The low- and normal-flow tertiles had oxygen extraction and venous oxygen tension values in the normal range, albeit lower than control subjects (Table 2, Fig 3). No participants had evidence of *intracardiac* left-to-right shunting during resting right heart catheterization, defined as oximetric step-up >9% between superior vena cava and pulmonary artery.[20] Thirty one percent (49/160) had skin biopsies that pathologically confirmed SFN (Table 1). Figure 2 demonstrates that within the entire ME/CFS cohort and the tertiles, there were no correlations between epidermal neurite density and peak VO_2 and Qc as a percentage of predicted, systemic oxygen extraction corrected for hemoglobin concentration, and peak RAPs.

Discussion

ME/CFS is a common and often disabling disorder of unknown pathogenesis reported to affect 10% to 25% of patients in primary care practices,[23] 75 to 267/100,000 people,[24] or 836,000 to 2.5 million people in the United States.[1] Annual productivity losses are estimated at $20,000 per patient, or $9.1 billion

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overall.[25] Because nonspecific symptoms affecting multiple organ systems lead to evaluations by disparate medical specialties, this number is proposed to be an underestimate, with direct and indirect US costs actually approaching $23 billion per year.[26] Hence, insights into pathogenesis are urgently needed because these can translate into improving diagnosis and identifying evidence-based treatment options to ameliorate symptom causes.

ME/CFS has significant overlap with the POTS and fibromyalgia syndrome labels[2-4] where skin biopsy and other biomarker studies report high prevalence of abnormalities consistent with SFN.[5-7,9] SFN is a common disorder caused by excess firing or axonal degeneration in the thinly myelinated and unmyelinated sensory/trophic/autonomic peripheral neurons. Common symptoms include distal-predominant sensory disturbances, including pain, exertional intolerance, nausea, postural orthostatic tachycardia, and hypotension.[21] The SFN diagnosis is confirmed by abnormally low densities of PGP9.5-immunolabeled epidermal neurites in lower-leg skin biopsies (≤5% of predicted), which is recommended for research inclusion.[27]

Given the personal disability and high medical and societal costs of ME/CFS, the identification of potential pathophysiological contributors is of major importance.[26] Studies of varying quality link ME/CFS to preceding infections, immune system disorders, adrenal insufficiency, and various causes of autonomic nervous system function. Noninvasive CPET has been previously used in the evaluation and investigation of ME/CFS,[28,29] but this is the first direct measurement of patient hemodynamics and pulmonary and systemic gas exchange, and the first objective testing for SFN in ME/CFS patients.

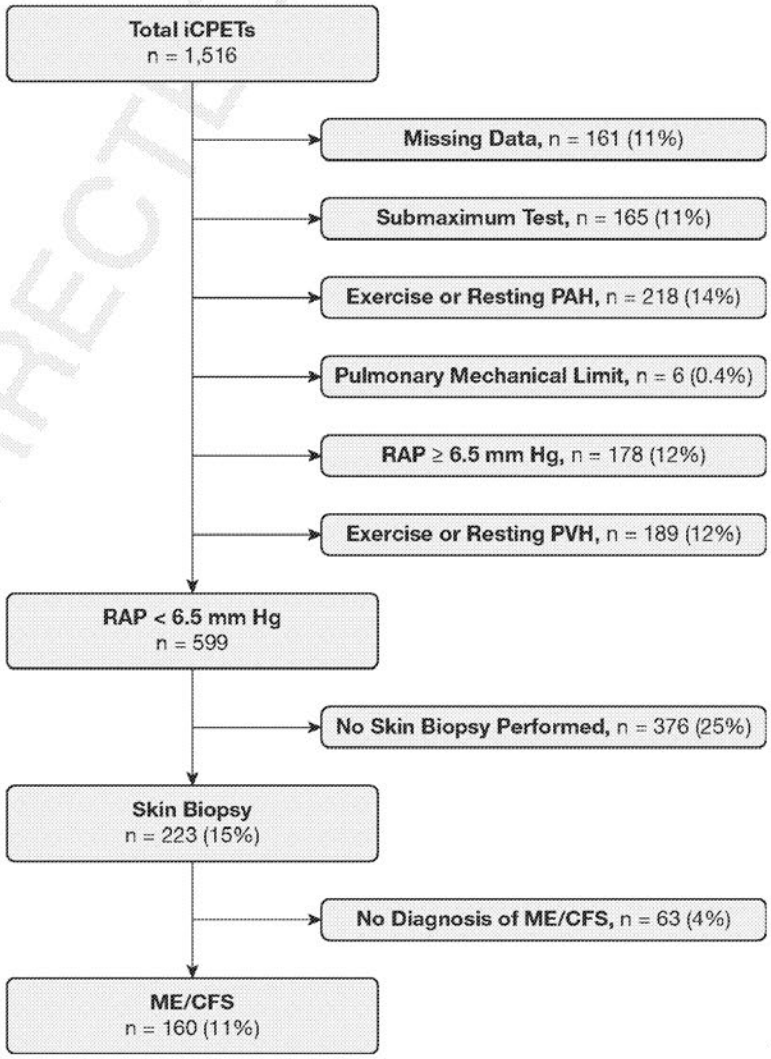

Figure 1 – *Participant case selection.*

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TABLE 1] Baseline Characteristics of ME/CFS Participants

	Subjects	Control Subjects	*P*
No.	160	36	…
Age, y	47 ± 16	56 ± 12	**.0001**
Female (%)	125 (78)	16 (44)	**.0001**
White race (%)	149 (93)	34 (94)	.78
Weight, kg	73 ± 17	85 ± 22	**.0007**
Height, cm	167 ± 9	170 ± 9	.08
BMI, kg.m^2	25.6 ± 5.3	28 ± 6	**.0001**
Hb, g/dL	14.1 ± 1.4	15.3 ± 1.5	**.0001**
Comorbidities (%)			
Hypertension	33 (21)	15 (41)	**.002**
Dyslipidemia	33 (21)	10 (28)	.25
Obesity	28 (18)	10 (28)	.09
CV family history	10 (6)	5 (14)	.06
Diabetes mellitus	6 (4)	2 (5)	.06
Previous myocardial infarction	5 (3)	0 (0)	.08
Coronary artery disease	3 (2)	0 (0)	.15
Medications (%)			
Statins	26 (16)	11 (30)	**.02**
Beta blockers	25 (16)	5 (14)	.69
ASA	25 (16)	7 (19)	.58
Calcium channel blockers	14 (9)	3 (8)	.8
Diuretics	14 (9)	5 (14)	.27
ACE inhibitors	11 (7)	5 (14)	.52
Associated conditions (%)			
Small fiber neuropathy	50 (31)	0 (0)	**<.0001**
POTS	52 (33)	3 (8)	**.0001**
Fibromyalgia	35 (22)	2 (6)	**.001**
MCAS	11 (22)	0 (0)	**<.0001**
Preceding infection	39 (24)	0 (0)	**<.0001**

ACE = angiotensin-converting enzyme; ASA = ; CV = cardiovascular; MCAS = mast cell activation syndrome; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; POTS = postural orthostatic tachycardia syndrome.

ME/CFS Exercise Phenotypes

A major finding was the strong association of impaired aerobic capacity in ME/CFS with two types of systemic vascular dysregulation during upright cycling. Our methods and analyses, which metabolically correct Qc (the Qc/VO_2 slope), identified two groups with abnormally low and high Qc during exercise.

In *low-flow* patients, there was no evidence that depressed peak VO_2 and low Qc were attributable to intrinsic heart disease (eg, heart failure) or pulmonary hypertension. Rather, the sole causal mechanism identified was low biventricular filling pressures during upright cycling, as reported in undifferentiated exertional intolerance.[11]

In *high-flow* patients, low peak VO_2 was associated with impaired systemic oxygen extraction. During exercise, high pulmonary blood flow plus impaired systemic oxygen extraction implicates either left-to-right blood shunting or mitochondrial myopathy (MM), where blood is delivered but muscle use impaired.[30,31] It has been hypothesized that MM underlies exercise intolerance in a subset of patients with ME/CFS,[32,33] whose hallmark during incremental exercise is an increased Qc/VO_2 slope.[31] Possibly the inclusion criteria of PLF undermined our ability to detect patients with MM and an increased Qc/VO2 slope. There was no evidence of *intracardiac* left-to-right shunting at the time of the resting right heart catheterization. Together

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TABLE 2] Exercise Variables and Skin Biopsy Results in ME/CFS

	Control Subjects	Low Flow	Normal Flow	High Flow	ANOVA
$\Delta Qc/\Delta VO_2$	5.1 [4.6-5.5]	4 [3.2-4.4][a]	5.6 [5.3-6.0][b]	7.5 [7-8.3][a,b,c]	**<.0001**
Peak VO_2 % predicated, %	101.4 ± 17	80.4 ± 20.9[a]	86.1 ± 21[a]	7.3 ± 16.7[a,c]	**<.0001**
Peak Qc % predicted, %	98.5 ± 13.3	88.4 ± 19	99.5 ± 23.8[b]	99.9 ± 19.5[b]	**<.01**
Peak (Ca-vO2)/[Hb]	0.95 ± 0.08	0.88 ± 0.11[a]	0.86 ± 0.1[a]	0.74 ± 0.1[a,b,c]	**<.0001**
Rest SBP, mm Hg	147 ± 23	141 ± 23	141 ± 21	135 ± 19	.10
Rest DBP, mm Hg	85 ± 12	78 ± 11[a]	80 ± 11	76 ± 10[a]	**<.005**
Rest MAP, mm Hg	106 ± 15	99 ± 14	100 ± 13	96 ± 12[a]	**<.013**
Peak SBP, mm Hg	200 ± 32	177 ± 37[a]	186 ± 28.5	176 ± 28[a]	**<.0021**
Peak DBP, mm Hg	91 ± 16	82 ± 14[a]	86 ± 14.4	85 ±12	**<.03**
Peak MAP, mm Hg	127 ± 20	113 ± 20[a]	119 ± 17	115 ± 16[a]	**<.01**
Peak SVR, dyn·s·cm^{-5}	731 ± 182	838 ± 228	119 ± 17	115 ± 16	**<.01**
Peak vPO_2, mm Hg	25 [24-28]	27 [25-28]	28 [25-30][a]	30 [28-31][a,b,c]	**<.0001**
Peak SaO_2, %	97 ± 1.3	97 ± 1.2	98 ± 1	98 ± 1.5[a]	**<.0356**
Peak SvO_2, %	30 ± 7	35 ± 7[a]	37 ± 8[a]	44 ± 7[a,b,c]	**<.0001**
Peak RAP, mm Hg	9 [7-9.8]	2 [0-3][a]	1 [0-4][a]	2 [0-3][a]	**<.0001**
Peak PAWP, mm Hg	14 [11-16]	7 [4-10][a]	8 [5-11][a]	8 [5-10][a]	**<.0001**
Rest lactate, mmol/L	1 ± 0.3	0.9 ± 0.4	0.9 ± 0.5	08 ± 0.4	.2
Peak lactate, mmol/L	7 ± 2.2	6.2 ± 2.2	6.5 ± 2.4	5.5 ± 2[b]	**<.05**
Rest A-a gradient, mm Hg	12 ± 16	5.2 ± 17	2.2 ± 12[a]	0.6 ± 13[a]	**<.001**
Peak A-a gradient, mm Hg	23 ± 11	13.2 ± 17[a]	7.7 ± 14[a]	5.3 ± 9.3[a,b]	**<.0001**
Epidermal neurite density, centile	…	21 [1.2-5.0]	25 [2.4-7.6]	26 [0-64]	.52
≤5th centile	…	18 (35.3%)	15 (28.8%)	16 (31.4%)	.61
5th < centile ≤ 15th centile	…	6 (11.8%)	8 (15.4%)	6 (11.8%)	.68
>15th centile	…	27 (52.9%)	29 (55.8%)	29 (56.9%)	.84

ANOVA = analysis of variance; DBP = diastolic BP; Hb = hemoglobin; MAP = mean arterial pressure; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; PAWP = pulmonary arterial wedge pressure; Qc = cardiac output; RAP = right arterial pressure; SaO_2 = oxygen saturation; SvO_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance; VO_2 = oxygen uptake; VPO_2 = venous oxygen tension.

[a] $P < .05$ compared with control subjects.

[b] $P < .05$ compared with low flow.

[c] $P < .05$ compared with normal flow.

these exclusions leave systemic microcirculatory dysfunction (impaired oxygen delivery to muscles) as the presumptive mechanism. Indeed, skin biopsies from patients with focal and small-fiber neuropathies and fibromyalgia reveal arteriovenous blood flow dysregulation, including abnormal innervation and cross-sectional area of arterio-venous shunts.[14,34]

Future studies of the high-flow phenotype are needed to determine how pulmonary blood flow can be exaggerated in the face of low biventricular filling pressures. The current conclusions are also consistent with those from noninvasive exercise studies in ME/CFS patients that also yielded low estimated systemic oxygen extraction.[35] High-flow and low-flow phenotypes have previously been described for POTS,[13] supporting the current results in ME/CFS. In both conditions, the high-flow profile features high Qc and low systemic vascular resistance, and the low-flow phenotype the opposite.

ME/CFS and SFN

The second major finding was very high prevalence of small fiber neuropathology; in one third of ME/CFS patients, slightly lower than the approximately 50% prevalences reported in fibromyalgia and POTS.[5,9,36] Our iCPET data associate SFN with both *low-flow* and *high-flow* ME/CFS profiles. Immunohistochemical studies show that small fibers regulate microvascular tone, primarily by sympathetic and parasympathetic cholinergic synapses on perivascular myocytes.[37] Distal degeneration (axonopathy) can impair venoconstriction with resultant peripheral blood pooling decreasing cardiac return,

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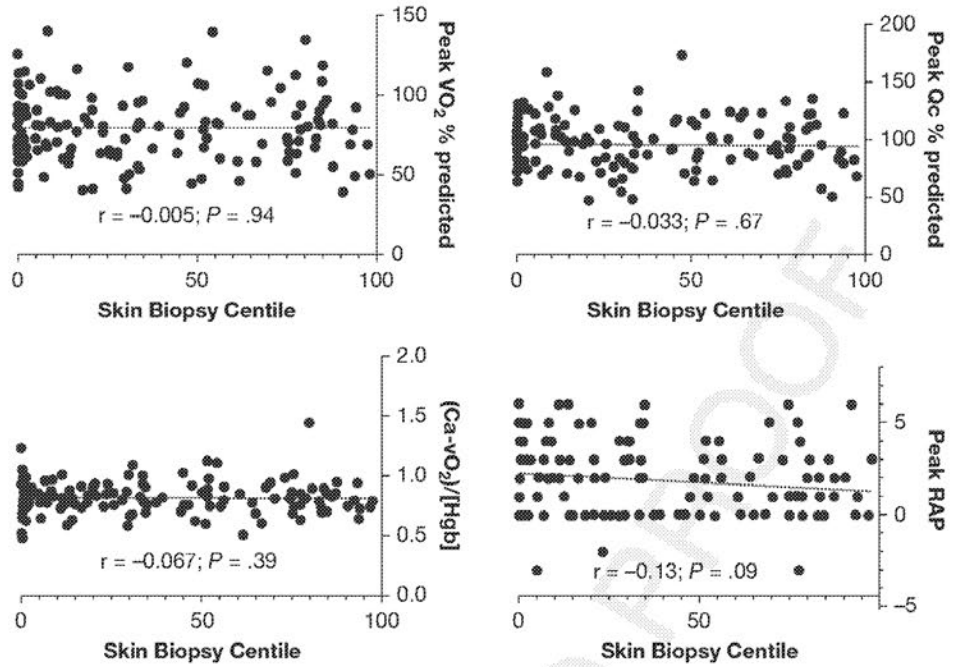

Figure 2 – *Correlations between small fiber neurite density and exercise variables in patients with*

consistent with the "low-flow preload failure" we identified. Abnormal venous pooling in the legs on standing is demonstrated in POTS,[38] and the excess peripheral venoconstriction to experimentally infused norepinephrine or phenylephrine documented is consistent with classic post-denervation adrenergic receptor upregulation.[39,40] This is further supported by low norepinephrine release after sympathetic nervous system stimulation in POTS patients.[41] Thus, we propose SFN as the major cause of preload failure in a substantial, not yet fully measured, proportion of ME/CFS patients.

In the "high-flow" group (high Qc/poor systemic oxygen extraction), SFN-associated tissue-level left-to-right shunting is biologically plausible, as demonstrated by pathological examination of cutaneous microvasculature in chronic regional pain syndrome,[34] a regional small-fiber neuropathy.[42] In fibromyalgia, there is similar evidence of abnormally innervated dilated cutaneous arteriole-venule shunts that permit oxygenated arteriolar blood to bypass capillary beds, returning unextracted to the venous circulation.[34] In exercising muscles, such blood shunting and impaired exercise-associated vasodilation can cause premature anaerobic metabolism with lactic acidosis, premature muscle fatigue, and exertional intolerance. Neurogenic AV shunting in splanchnic microvessels is proposed to also contribute to SFN's characteristic postprandial abdominal discomfort, dysmotility, and nausea in addition to denervation of enteric smooth muscles.[23]

Limitations

A common question is whether exertional intolerance in ME/CFS includes potentially confounding effects of deconditioning. However, aerobic capacity is lower in ME/CFS patients than in sedentary control subjects,[29] and the longer CPET protocol of Keller et al[29] documented significant decrease of peak VO_2 only on day 2, both inconsistent with deconditioning.[29] The current study definitively eliminates this possibility, because the hallmark of deconditioning is low peak-exercise Qc[43] rather than the increased Qc discovered here, plus we saw abnormally low biventricular filling pressures rather than the higher pressures seen in detrained individuals attributable to cardiac atrophy and decreased ventricular compliance.[44,45] Although training can increase arterial-venous oxygen content difference at peak exercise, deconditioning causes little or no change in maximum exercise systemic oxygen extraction.[43,46] Although deconditioning does not explain the exertional intolerance in ME/CFS, many patients become deconditioned secondarily, adding disability. We address this in the clinic by encouraging fitness with a careful, graded exercise program to help compensate for disease-associated cardiovascular limitations.

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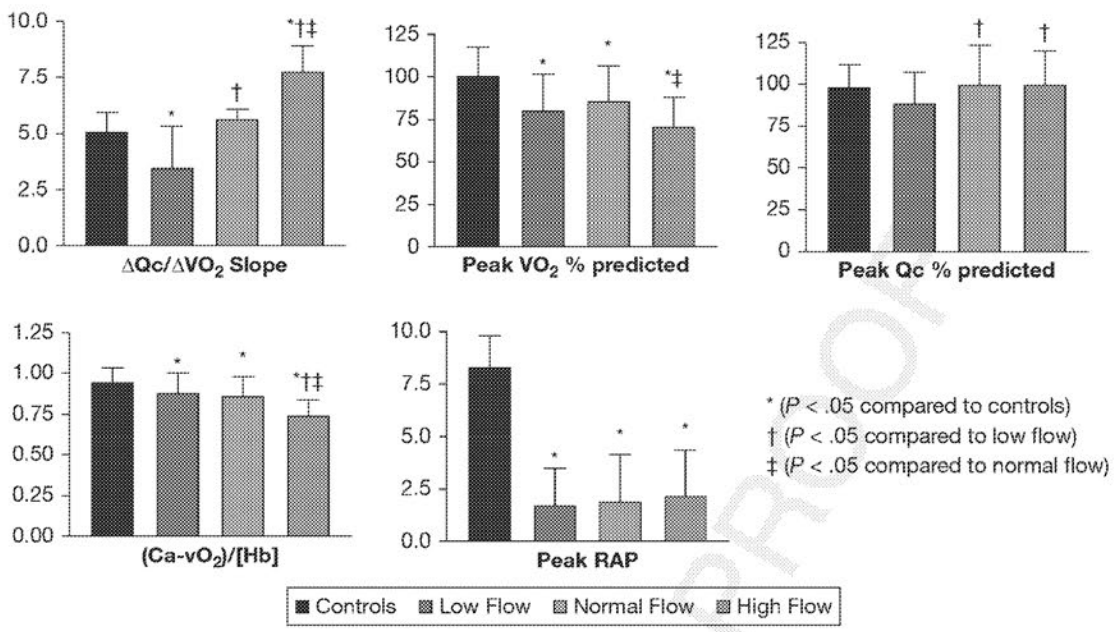

Figure 3 – *Comparison of exercise variables among control subjects and tertiles of Qc/VO2 slopes.*

Regarding study participants, because of the invasive nature of iCPET, this was a retrospective study cohort assembled by careful elimination of intrinsic cardiac and pulmonary disease. Peak RAP <6.5 was used as an inclusion criterion based on previous work showing low biventricular filling pressures depressed peak VO_2 in the absence of intrinsic heart or lung disease.[11] Many of these patients met clinical criteria for ME/CFS. However, this may have eliminated some ME/CFS patients with peak RAP >6.5. If so, this could have limited our ability to detect patients with MM and its characteristic increased Qc/VO_2 slope. Similarly, because the risk-benefit ratio, ethical, and logistic concerns largely preclude recruiting healthy control subjects for iCPET, we used subjects who, despite referral for potential exertional intolerance, had no corroborating iCPET evidence of physiologic abnormality. Finally, the largely white study population, which reflects our institution's referral patterns, limits applicability to other racial groups.

An important assumption underlying our conclusions is that the Fick principle variables are independent of each other at maximum exercise. If not, it would be possible for low Qc to be compensated for by increased systemic extraction and the reverse, as is known to happen during *submaximum* exercise. We have therefore chosen to look at tertiles of Qc/VO_2 slopes, which represent the behavior of the Fick principle variables throughout the entire exercise epoch and are not limited to peak exercise.

Regarding small-fiber metrics, we used the very small single-site distal skin biopsies recommended as required for SFN research, given 91% sensitivity, ease of performance, and widespread accessibility to mail-in pathology interpretation.[47] However, tradeoffs include lower sensitivity (58%)[47] than more comprehensive testing such as autonomic function testing, which is not endorsed because of lower specificity, higher complexity of administration and interpretation, and limited availability.[27] Another reason for low sensitivity is that axonal degeneration is an end-stage change, whereas earlier small fiber malfunction also contributes but is harder to quantify.[48] Lower leg biopsies are less sensitive for patchy, proximal, or non-length-dependent SFN, and in fibromyalgia, wider areas used in biopsies identified proximal denervation as more prevalent (46% in upper-thigh biopsy specimens vs 32% in distal-leg biopsies).[7] Although referral bias of ME/CFS patients referred for skin biopsy might skew our sample to inflate prevalence of SFN, the 32% to 50% prevalence widely reported in fibromyalgia corroborate our data.[6-8] Our distal-only biopsies also may have contributed to lack of correlation between epidermal neurite density and exercise test physiologic variables, given the fibromyalgia study correlation between severity of cutaneous denervation and sensory symptoms.[7] Although measuring SFN symptoms and signs is most important, future ME/CFS studies could consider expanded testing as well.[49] We viewed it as unnecessary for our iCPET control subjects to have skin biopsies because our laboratory has far more comprehensive age-, sex-, and

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race-adjusted same-laboratory norms from more than 450 healthy control subjects.[22]

Interpretation

The findings of the first study to directly measure pulmonary and systemic blood flow and gas exchange and small-fiber metrics in ME/CFS generate the hypothesis that peripheral vascular dysregulation causes ME/CFS's major symptom—exertional intolerance. As in POTS, there appear to be low and high pulmonary blood flow physiological subtypes, the latter associated with impaired peripheral oxygen extraction. We also report the first association of small-fiber pathology with ME/CFS, corresponding to reports in fibromyalgia and POTS, other syndromes that include exertional intolerance. More comprehensive evaluation is recommended to fully address SFN contribution to ME/CFS. Although neither ME/CFS nor any symptom-based syndrome is caused by only one single disease or pathophysiology, diagnosing established diseases when present shifts at least these patients to more effective clinical frameworks and facilitates detection of remaining contributors. This approach may become important given reports of ME/CFS-like syndrome after coronavirus disease 2019 infection, with questions of associated SFN.[50]

Acknowledgments

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Pediatric Small-Fiber Neuropathy: Towards a Case Definition

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OBJECTIVE: To characterize initial presentation of confirmed cases of pediatric small-fiber neuropathy (pSFN) to inform care and research

BACKGROUND

Adult SFN was characterized in the mid-90's as skin-biopsy testing developed with pediatric case reports beginning around 2005. The prevalence of pSFN is unstudied, but diagnoses are increasing. Still today, most pediatric cases remain undiagnosed.

Undiagnosed, untreated childhood neuropathy can cause life-long developmental and educational harm and reduce family saving and income.

Causes in the young differ greatly, with negligible diabetes, cancer-associated, lifestyle, nutritional, occupational and toxic risks.

We reported 53% prevalence of SFN-diagnostic skin biopsies in juvenile fibromyalgia,[1] similar to adult prevalences.[2]

Given high prevalence of fibromyalgia and lack of disease-modifying treatments, better diagnosis and treatment of pSFN and adult SFN could have widespread impact.

In adult SFN, ectopic firing then degeneration of small-diameter peripheral axons is the cause of sensory and autonomic symptoms including widespread neuropathic pain/paresthesias/itch, exertional intolerance, orthostatic hypotension, and gastrointestinal distress.[3]

A first formal case definition and diagnostic recommendations for adult SFN appeared in 2020.[4]

SFN pathophysiology is virtually unstudied in children, but high capacity for axonal regeneration implies high efficacy of definitive treatments.

DESIGN/METHODS

- With IRB approval, we reviewed records of all children <18y at time of 2-3mm skin biopsies from the standard lower leg (5-10cm above the lateral malleolus) PGP9.5 immunolabeled lower-leg skin-biopsy. Data were collected through 12/31/20.
- Biopsy neurite counts were analyzed using MGH's age/gender/race-based algorithms that include 47 screened healthy children age 8.1-17.9y.
- Standard clinical methods and interpretations were applied and only those with diagnostic epidermal neurite densities (≤5% of predicted) were included, yielding 154 participants.
- Patients/parents completed the validated MGH SSS (Small-fiber Symptom Survey), rating 33 symptoms in 5 categories.[5]
- Neuromuscular specialists completed the MAGNET (Mass General Neuropathy Exam Tool) to capture standard neuropathy exam findings.[6]
- AFTs were performed at MGH using clinical equipment and interpretations. Metrics comprised heart-rate and blood-pressure variability during deep inspiration, Valsalva and tilt-table testing, and 4-site sudomotor axon reflex testing (QSART).
- To minimize treatment/recovery influences, only screening blood tests from <1y of earliest SFN test were included.
- Genomic sequencing from all certified clinical diagnostic labs at any time was included; GeneDx, Invitae, and MGH/Broad performed most.

ACKNOWLEDGEMENTS Supported in part by the U.S. National Institutes of Health (NINDS R01NS093653) and private foundations including The MAYDAY Fund. We are grateful for the generous participation of children and families in our research, and for the contributions of other clinicians.

RESULTS

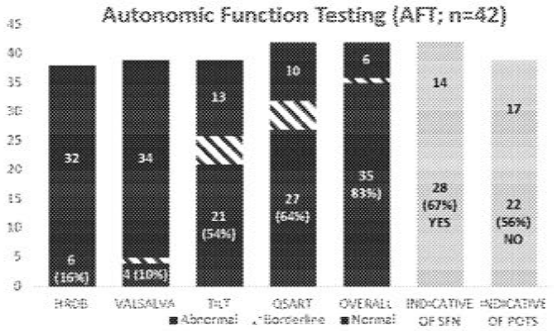
Age at first biopsy (range) (n=154)	
14.3±3.3y (3.73-17.92y)	
Sex	
Female	76.7%
Race/Ethnicity	
Caucasian	91.6%
Asian	1.3%
Black/African American	1.9%
Multiracial/other/unknown	5.2%
Hispanic	2.6%

MAGNET Average Score/Maximum	
Vital signs	0.3/2
Pupils	0/4
Appearance of lower legs, feet, toes	1.2/8
Strength - Great toe extension	0.5/4
Joint Position - Great toe	0.4/4
128 Hz Vibration - Great toe	0.4/4
Light touch in legs, feet	1.0/12
Pin sharpness in legs, feet	2.8/12
Ankle reflexes	0.3/4
Total Score	**6.9/54**

Test (definition of abnormal)	Prevalence in sample (ratio)	Prevalence in healthy adults
ANA (≥ 1:160)	48.1% (13/27)	8.9%
Ig deficiency (G, M, A, E)	30.4% (7/23)	unreported
C3 (low)	16.7% (4/24)	2.7%
Lyme	16.7% (3/18)	variable
CRP (high)	12% (3/25)	7.1%
Vitamin B12 (high or low)	12% (3/25)	3.8%
AST/ALT (high)	10.3% (3/29)	10.0%
Light chain kappa/lambda spike	10% (1/10)	0.8% (over 50y)
SPEP/IFIX (spike)	8.7% (2/23)	3.2%
C4 (low)	8.3% (2/24)	10.4%
ESR (high)	6.7% (2/30)	5.0%
TSH (low or high)	3.8% (1/26)	0.5%
SS-A/SS-B	3.7% (1/27)	0.7-3.9%
Hemoglobin A1c (diabetes/prediabetes)	0% (0/16)	44.9%
Hepatitis C	0% (0/10)	1.6%
TTG IgA (high)	0% (0/20)	0.5-1.0%

[Healthy population data not available from children.[7]
0/10 subjects had anti-dsDNA or anti-Smith antibodies.

Small-Fiber Symptom Survey Category	Weighted Avg. Score
Sensation	35.4%
Circulation	33.6%
GI	41.1%
Pelvic	16.6%
Miscellaneous	42.7%
Total Score (49/136)	**36.0%**



CONCLUSIONS

- Childhood SFN patients are predominantly female, like adult patients.
- Age of onset averaged 9.1 years, with 5-year interval to skin biopsy confirmation.
- Most prevalent SSS symptoms were physical and/or mental fatigue, headaches, orthostatic intolerance, sleep difficulties, and sensory disturbances.
- Most children with confirmed-SFN presented with normal neurologic exams, with hyperemic lower legs/feet most common abnormality (41.7%), so objective tests may be more important for confirming diagnosis than exam.
- Autonomic Function Testing frequently revealed orthostatic intolerances and reduced distal sweat responses in 64%.
- Strongest medical associations so far are with dysimmune diagnoses and markers; consider immunotherapy.
- Blood screening is required to highlight potential causes and exclude others, but adult recommendations[9] can be curtailed e.g., don't test children for diabetes, hepatitis, HIV.
- As ~10% of cases appeared genetic despite non-universal testing, consider early comprehensive genomic sequencing; particularly if pre-adolescent onset and strong family history, as precision treatments are increasingly available.

These results suggest value of age-specific case definitions, SSS, MAGNET, AFT and screening recommendations that include genomics for pediatric SFN.

FUTURE RESEARCH PRIORITIES

- To adapt and validate adult SFN metrics for childhood use
- To develop evidence-based recommendations for parsimonious blood testing
- To more comprehensively prospectively collect standardized SFN data
- To recruit more healthy children under 10y for skin biopsy and AFT norms
- To characterize more common causes of pSFN for clinician use
- To track outcomes in children and prepare for clinical trials

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From: Koroshetz, Walter (NIH/NINDS) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=E8338DD7CDCD432E986961F1548C5EC6 b6
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Subject: 2 things
Attachments: Z__Barbara_Manuscript_2021_New_England_Journal_of_Medicine_Neuropathic_symptoms_post_covid_vaccine_4-17-21 (1).pdf; small fiber neuropahty Vermont.pdf

Dear Tony,

1) Thanks for the Academy of Neurology panel taping. Over 2300 watched it "live" and many more since.
2) FYI--There have been steady slow stream of reports to me of post vaccination neurologic conditions, seem to be mostly peripheral nerve disorders- single nerve, brachial plexus, distal axonal neuropathy (attached report), maybe an occasional spinal cord issue. Avi has been collecting a bunch. He has a report sent out to publish. Hard to know not due to chance but are timed to the vaccination.

Best,

Walter J. Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke

Neuropathic symptoms following vaccination for SARS-CoV-2

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To the Editor: We report a series of patients with acute neuropathic and autonomic symptoms post-vaccination for SARS-CoV-2. Thirty-two patients contacted us between January 11 to March 31, 2021 seeking advice about neurological symptoms that started post-vaccination. All patients were enrolled in an IRB approved study and evaluated by televisit or an in-person visit, and medical records were reviewed. We excluded 8 patients because their complaints were non-neurologic or limited to worsening or recrudescence of underlying neurological symptoms. 9/24 (37%) patients developed skin-flushing, tachycardia and increased blood pressure following vaccination lasting less than 30 minutes.

All patients developed new onset of neuropathic symptoms within 14 days and median time of two days from vaccination (Figure S1). Median age of the patients was 39 years (range: 27-70 years). Twenty-one were women. One received the vaccine manufactured by b6 8 by b6 and 15 by b6 16/24 (66%) developed neurological symptoms following the first dose (Table S1). All patients reported paresthesia and/or burning sensation in either or both upper and lower limbs and in seven patients it involved the face, mouth, and scalp (Table 1). Two patients had severe unilateral paresthesia in the distribution of the V1 branch of the trigeminal nerve with intermittent tearing and burning in the eye suggestive of trigeminal neuralgia. 9/24 (37%) described a moderate to severe intermittent internal tremor in the head and throughout the body that interfered with daily activities and sleep. 8/24 (33%) patients had dysautonomia (Table S2; Figure S2). 13/24 had brain and/or spinal cord MRI with unremarkable findings. 3/24 patients had symptoms of brachial plexopathy confirmed by EMG. Brachial plexus MRI showed nerve enhancement in one patient. Six patients treated with oral corticosteroid, completely (n=4) or partially (n=2) improved after one or two weeks (Table S2). Untreated patients had either no recovery (n=7), partial (n=9) or complete recovery (n=2) at a median of 10 weeks.

This report describes symptoms suggestive of a neuropathy following vaccination for SARS-CoV-2 from three different manufactures that is distinct from the acute allergic reaction. These vaccines have in common the gene encoding the spike protein[4] suggesting that the symptoms may be driven by an immune response to it. Response to treatment with corticosteroids supports that possibility. While further investigations are needed to determine the underlying pathophysiology of these symptoms, treatment with corticosteroids may be considered in these patients.

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Table: Neurological manifestations post-SARS-CoV-2 vaccination

Case#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Onset of symptoms		2h	5h	3d	10h	4d	6d	3h	10h	1d	14d	2d	7d	2h	10d	7d	10h	2h	2d	2d	10m	2d	6d	5d	8d
Sensory																									
	Paresthesia	+++	+++	+	+++	++	++	++	++	++	+	+	++	++	+	++	+	++	++	+	+	++	+	++	++
	Burning	+	+	-	-	+	-	+	-	-	-	-	-	+	-	+	-	-	+	+	-	+	-	-	+
	Back pain	+	++	++	+	+	-	-	++	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Motor					-																				
	Weakness	+	-	+	-	+	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	+	+	-	+
	Fasciculations	-	-	+	-	-	-	-	-	-	-	-	-	++	-	-	-	-	-	+	-	-	++	-	+
Dysautonomia																									
	Orthostatic Tachycardia	++	-	-	-	-	-	-	-	-	+	++	-	-	++	-	-	-	-	-	+	-	-	-	-
	presyncope	+	-	-	-	-	-	-	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	+	-
	Blood pressure variability	+	-	-	+	+	-	-	-	-	+	+	-	-	++	-	-	-	-	-	-	-	-	-	-
Corticosteroid treatment		-	-	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	+	-	-	-	-	+	-
Recovery																									
	Complete						+				+	+	+		+		+								
	Partial	+	+	+	+									+		+			+	+	+	+		+	
	None					+		+	+	+								+					+		+

+mild; ++moderate; +++severe

Table S1: Demographic characteristics

Demographic Information	Case# 1	2	3	4	5	6	7	8	9	10	11	12
Age	b6											
Sex												
Type of vaccine												
Dose	1st	1st	2nd	1st	1st	2nd	1st	1st	1st	1st	2nd	1st
History of COVID-19	Probable*	no	Probable	no	no	no	no	no	unknown	no	no	no
Past Medical History	Tinnitus, cholestoma	Hypertension, Crohn's disease	None	None	None	None	no	Hypothyroidism, polycystic ovarian syndrome	no	no	seasonal allergy, Migraine headaches	hyperlipidemia
Family history of autoimmune diseases	no	no	unknown	SLE	no	no	no	no	no	no	psoriasis	no

Demographic Information	13	14	15	16	17	18	19	20	21	22	23	24
Age	b6											
Sex												
Type of vaccine												
Dose	1st	2nd	2nd	1st	1st	1st	2nd	1st	1st	1st	2nd	2nd
History of COVID-19	no	no	no	no	no	no	no	no	no	no	no	no
Past Medical History	Chiari syndrome, L5 radiculopathy	migraine headaches, supra ventricular tachycardia	no	asthma and eczema	migraine headaches with aura, hashimoto thyroiditis	asthma	none	none	Anxiety dx	no	Hypothyroidism	no
Family history of autoimmune diseases	no	rheumatoid arthritis	no	no	no	no	no	unknown	no	no	no	RA

*Probable: History of upper respiratory tract infection but not confirmed with SARS-COV2 PCR or Antibody testing

Table S2: Clinical characteristics and course of illness

Symptom characteristics	9	10	11	12	13	14	15	16
Time from vaccination to any symptoms	24 hours	8 days	8 hours	2 days	2 hours	30 minutes	2 days	10 hours
Symptom at onset	fever, chills, and fatigue	lymphadenopathy in neck and axillary area	flu like symptoms, fever muscle pain	right scapular muscle spasm with constant pain and discomfort	formication in scalp and lower limbs, severe fatigue	flushing, tachycardia, positional dizziness	feet paresthesia	intermittent cognitive changes, paresthesia in both hands
Onset of neurological symptoms	1 day	14 days	2 days	7 days	2 hours	10 days	7 days	10 hours
Neurological symptoms	intermittent paresthesia in all limbs. Right ulnar distribution numbness, cramping in right hand fingers and difficulty with fine movements in right hand	numbness in left shin and right hand; progress to cold sensation in left leg and intermittent paresthesia in all limbs; Raynaud's phenomenon in left leg	orthostasis, fluctuation in heart rate, blood pressure fluctuation, nausea, diarrhea, band like tightness in T2-T3 level; Paresthesia in face, upper and lower limbs; internal tremor	paresthesia in right arm ulnar distribution progressed to weakness in right hand for fine movements	severe paresthesia and severe fasciculations in lower limbs	severe orthostatic tachycardia, pallor, flushing, diarrhea, fluctuation in blood pressure	progressive paresthesia in upper and lower limbs	paresthesia in ulnar distribution of both arms, numbness in feet
Neurological examination	decreased light touch and pin prick sensation on right ulnar distribution, mild weakness in right arm	normal	normal	finger abduction and wrist/hand dorsiflexion weakness	decreased vibration in right foot, Hyperesthesia in left leg; fasciculations in both legs	normal	normal	ND
MRI	consistent with brachial plexopathy	normal brain and cervical spinal cord	ND	normal brachial plexus and cervical spinal cord	ND	ND	normal brain and total spinal cord	ND
EMG-NCV	ND	ND	ND	Brachial plexopathy lower trunk	ND	normal	mild peripheral neuropathy	ND
Other tests	ND	ND	tilt table test fulfilled clinical criteria for POTS	ND	ND	tilt table test fulfilled clinical criteria for POTS, skin biopsy showed small fiber neuropathy	ND	ND
Corticosteroid treatment	ND	Prednisone 20 mg two times a day for 5 days	Prednisone 30 mg/day with weekly taper	Prednisone 60 mg/day for 3 days, tapered every 3 days	ND	Prednisone 40 mg/day, tapered every 3 days	ND	ND
Course of Disease	no improvement after 3-4 weeks	improvement started 1-2 weeks after corticosteroid treatment. Complete improvement after 10-12 weeks.	improvement started 1-2 weeks after corticosteroid treatment. Complete improvement after 8 weeks.	improvement started at1-2 weeks after corticosteroid treatment. Complete recovery after 6-8 weeks.	partial improvement after 6 weeks	Improvement started 1-2 weeks after corticosteroid treatment. complete improvement after 8-10 weeks,	partial improvement after 8-10 weeks	complete improvement after 2 weeks

Symptom characteristics	17	18	19	20	21	22	23	24
Time from vaccination to any symptoms	4 minutes	20 minutes	5 hours	10 minutes	2 hours	1 day	3 hours	15 minutes
Symptom at onset	sensation of tremor from head to toe	dizziness, presyncope	severe tingling in all limbs	numbness in both arms	transient right side face numbness	fatigue, headache, loss of appetite	intermittent cognitive changes, headache, dizziness	transient burning and tingling in mouth
Onset of neurological symptoms	2.5 hours	2 days	5 hours	10 min	2 days	6 days	5 days	7 days
Neurological symptoms	distal paresthesia and numbness in all limbs	formication in V1 distribution of trigeminal nerve progressed to severe paresthesia and burning sensation with tearing and burning in eyes	tingling and burning sensation followed by fasciculations in both thighs and forearms	Internal tremor, paresthesia and numbness in all limbs. Variable tachycardia.	Intermittent face, hands and feet paresthesia, burning and numbness. Mild right-hand weakness and paresthesia in right ulnar distribution	both legs weakness; fasciculations in all limbs; internal tremor, facial paresthesia; band like tightness in ribcage	photophobia, paresthesia and burning sensation in V1 distribution of trigeminal nerves	paresthesia and burning sensation in upper and lower limbs; fasciculations in limbs
Neurological examination	normal	normal	normal	ND	normal	normal	normal	normal
MRI	ND	normal brain	ND	ND	normal brain, cervical and thoracic spinal cord	ND	ND	normal brain
EMG-NCV	ND	ND	ND	ND	right lower trunk brachial plexopathy with no active denervation	ND	ND	normal
Other tests	ND	ND	ND	ND	ND	ND	ND	ND
Corticosteroid treatment	ND	Prednisone 40 mg/day, tapered every 3 days	ND	ND	ND	ND	Prednisone 50 mg/day, tapered every 2 days	ND
Course of Disease	no improvement after 4 weeks	Improvement started 1-2 weeks after corticosteroid treatment. Partial improvement after 4 weeks	partial improvement after 8 weeks	partial improvement after one week	partial improvement after 10-12 weeks	no improvement after 4 weeks	Improvement started 1-2 weeks after corticosteroid treatment. Partial improvement after 8-10 weeks	no improvement after 7 weeks

*Clinical Criteria for Positional Orthostatic Tachycardia Syndrome (POTS): Increase in heart rate more than 30 beats per minutes with tilt table test

AchR = Acetylcholine receptor; ND = not done; MRI = magnetic resonance imaging; EMG-NCV = electromyography and nerve conduction velocities

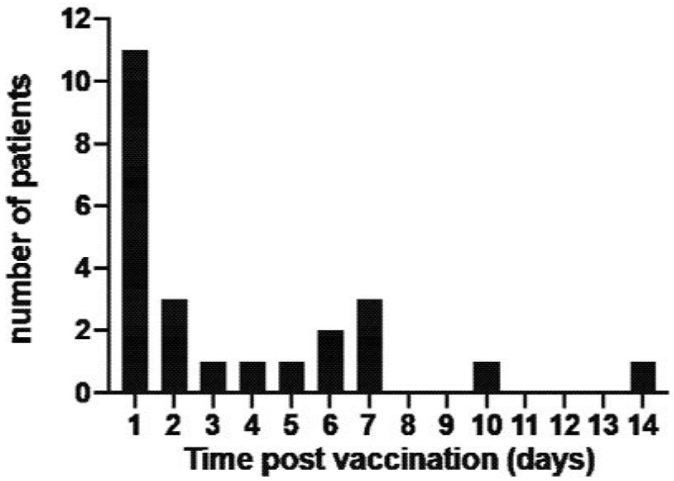

Figure S1: Onset of neurological symptoms from time of receiving the vaccine. Except for two patients, all patients developed symptoms within the first week following vaccination

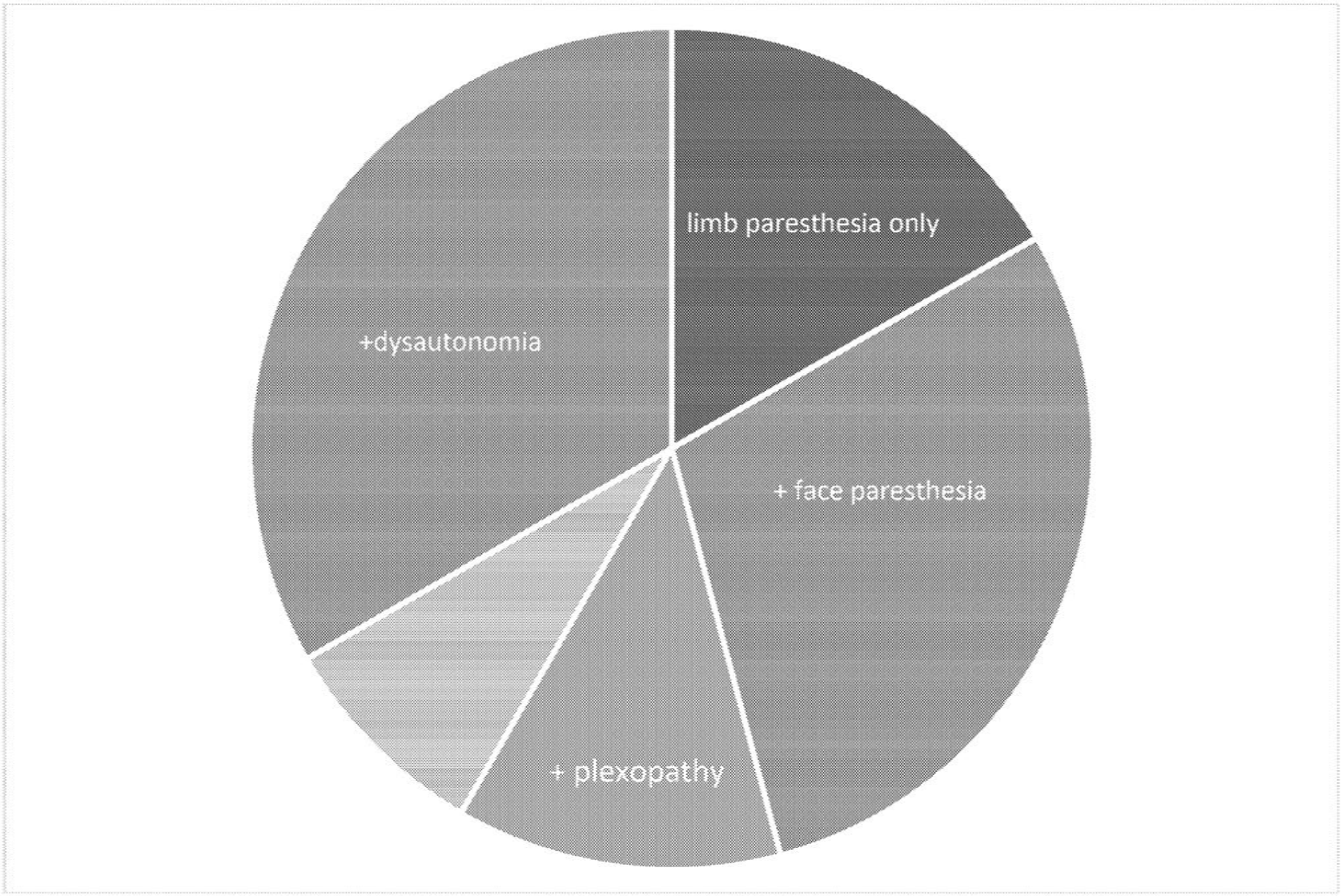

Figure S2: Neuropathic symptoms post-SARS-CoV-2 vaccination: All patients had parasthesia. Some patients had additional symptoms of parasthesia in face, brachial plexopathy, trigeminal neuralgia or dysautonomia.

POST COVID-19 VACCINE SMALL FIBER NEUROPATHY

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We confirm that we have read the Journals' position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflicts of interest to disclose.

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POST COVID-19 VACCINE SMALL FIBER NEUROPATHY

We describe the case of a 57-year old female who presented one week after receiving the second dose of the Pfizer ® COVID-19 vaccine with subacute 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; a COVID-19 reverse-transcriptase-polymerase-chain-reaction test 9 months before this presentation was negative. She was not on any medications and denied the use of alcohol. Besides the distal loss of pinprick and cold sensations in the feet, her examination was unremarkable.

An electrodiagnostic study performed on the day of presentation (including left median, peroneal, and tibial motor nerves with F-waves; left median, sural, and superficial peroneal sensory nerves; and needle examination of the left tibialis anterior, gastrocnemius, vastus medialis, iliopsoas, and lower lumbar paraspinal muscles), was normal. Skin biopsies showed multifocal involvement[1] (Figure). Hematoxylin and eosin and CD3 staining showed no histologic abnormalities.

The following laboratory tests were normal or negative: complete blood count, comprehensive metabolic profile, thyroid-stimulating hormone, methylmalonic acid, folic acid, thiamine, pyridoxine, hemoglobin A1c, serum and urine electrophoresis with immunofixation, serum-free light chains, HIV antibody, Lyme antibody, sedimentation rate, anti-double-stranded DNA antibody, rheumatoid factor, anti-Smith antibody, antineutrophil cytoplasmic antibodies, anti-SSA/SSB antibodies, complement levels,

and a serum paraneoplastic antibody profile. The SARS-CoV-2 antibody profile was consistent with a post-vaccination state and ruled out previous asymptomatic COVID-19 exposure.

Treatment with gabapentin provided symptomatic improvement. At 2 week follow-up, she reported complete resolution of neuropathic pain and successfully discontinued gabapentin therapy, although stocking-type small fiber modality loss persisted on examination.

We have identified a case of biopsy-proven small fiber neuropathy as a post-vaccination complication. The SARS-CoV-2 antibody profile was consistent with a post-vaccination state but ruled out previous asymptomatic COVID-19 exposure, which could have resulted in a robust immune response. The development of our patient's presentation soon after the vaccination, and exclusion of other known etiologies, support a possible causal association. A proposed pathophysiologic mechanism for vaccine-associated polyneuropathy is an immune-mediated hypersensitivity to the solvent/adjuvant (polyethylene glycol).[2]

Concerns regarding neurologic complications of vaccination are not new and include the development of Guillain-Barré syndrome (GBS); however, the associated risk is minute – on the scale of 1-2 additional GBS cases per million doses of influenza vaccine administered, favoring a recommendation for flu vaccination.[3] Although rare, a small number of case reports of small fiber neuropathy have been described in the literature following various vaccinations.[3]

With regard to SARS-CoV-2, a recent study from the UK found no association between COVID-19 and GBS.[4] Further, the lack of significant homology between any SARS-CoV-2 genetic or linear protein structure and human linear protein structures in this study make molecular mimicry as a cause less likely, thus minimizing the concerns for COVID-19 vaccination-associated GBS.[4]

Rare cases of Bell's palsy were noted in phase III trials with both COVID -19 vaccines (Moderna: 3 in the vaccine and 1 in the placebo group; Pfizer: 4 in the vaccine and 0 in the placebo group); however, the observed frequency rates did not exceed the background rate found in the general population.[5]

A temporary pause after rare reports of transverse myelitis in other COVID -19 vaccination trials, by AstraZeneca and Sinopharm, was removed after documentation of safety and lack of causal relationship.[6]

Adverse neuromuscular events following immunization against SARS-CoV-2 were not seen in the pivotal vaccine trials; however, vaccine safety monitoring is an ongoing process. As of February 19, 2021, 28 cases of GBS and no case of Bell's palsy have been reported to the Vaccine Adverse Event Reporting System (VAERS) following the COVID-19 vaccination.[7] In addition to our biopsy-proven report of small fiber neuropathy, VAERS has received additional reports: 2 of acute motor-sensory axonal neuropathy, 27 of peripheral neuropathy, 1 of mononeuropathy, 1 of peripheral sensorimotor neuropathy, and 3 of polyneuropathy. New-onset neuropathies following inoculation against SARS-CoV-2 remain rare, with incidence rates between 0.01% and 0.13%.[7]

In summary, rare occurrences of COVID-19 vaccine-related neuromuscular complications are indeed possible. Although infrequent, any serious adverse reaction to vaccines must be sought, reported and rigorously investigated to facilitate ongoing safety evaluation and to minimize vaccine hesitancy among the general population. Further studies are warranted to better understand the spectrum of neurological complications after COVID-19 vaccination and to determine whether a causal relationship exists between these vaccines and neurological sequelae, including small fiber neuropathy.

Abbreviations

COVID-19	Coronavirus disease 2019
GBS	Guillain-Barré syndrome
IENFD	Intra-epidermal nerve fiber density
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S1	Subunit 1
VAERS	Vaccine Adverse Event Reporting System

REFERENCES:

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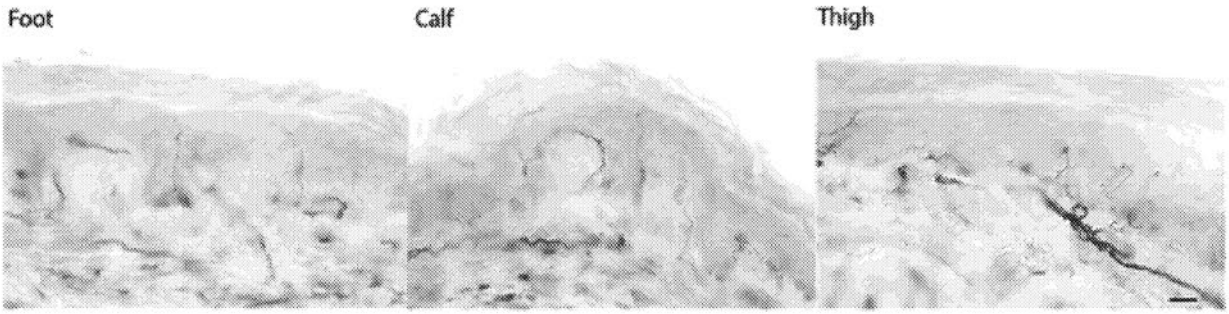
FIGURE LEGEND:

Three mm punch biopsies of skin undertaken confirmed multifocal small fiber neuropathy, suggested by loss of protein gene product 9.5 immunolabeled nerve fibers in the dorsum of left foot, over the extensor digitorum brevis muscle (2.1 fibers/mm of skin; normal >3.0) and left upper thigh at the level of ischial tuberosity (3.8 fibers/mm of skin; normal >6.0), and low normal intra-epidermal nerve fiber density (IENFD) in the calf segment,10 cm above the lateral malleolus (4.7 fibers/mm of skin; normal >4.3). Scale bar represents 20 μm.

Interpretation of IENFD was done by Corinthian Reference Laboratory, Benbrook, TX.

Figure 1



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