Acta Scientific Neurology (ISSN: 2582-1121)

Volume 5 Issue 5 May 2022

Case Report

Small Fiber Neuropathy and Intrathecal Presence of IgG Oligoclonal Bands Post- Vaccination with Oxford-AstraZeneca Covid-19 Vaccine

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Received: March 22, 2022

Published: April 22, 2022

Abstract

Since the COVID-19 pandemic outbreak, the development of vaccines for passive immunization against SARS-CoV-2 has been a great scientific achievement. However, all these vaccines have been rarely related to neurological adverse events. We present an extremely rare case of a 39-year-old healthy male adult who developed an immune-mediated adverse event of a small fiber neuropathy and radiculopathy post-anti-COVID vaccination with Oxford-Astra Zeneca Covid-19 vaccine. Despite this rare adverse event, we underline that both at an individual and a population level, the benefits of COVID-19 vaccination far outweigh the risks of a neurological complication.

Keywords: Small Fiber; Neuropathy; Covid-19; Intrathecal

Introduction

Case Report

A 39-year-old male patient presented in the emergency department of a private clinic, six days after he received the first dose of Oxford-Astra Zeneca Covid-19 vaccine, because of subacute dysesthesia in gloves-stocking distribution and fatigue. The patient had no medical history and received no medication previously. His laboratory tests were normal. There was no known prior Covid-19 exposure. A Covid-19 RT-PCR test at the time of presentation was negative. He got vaccinated at 30/4/2021 and the first symptoms began on 3/5/2021, affecting both lower legs, mainly in the plantar area. Gradually, the tingling sensation spread upward, to the knee area, as well as also in the upper limbs from fingernails till elbow height. On 5/5/2021 he was hospitalized for further investigation.

His neurological examination revealed decreased tendon reflexes in upper and lower limbs, and a decreased vibration in lower limbs. The lumbar puncture showed normal CSF pressure: of 130mm H_2O (normal values = 70-180mm H_2O); 11 cells (normal values = 0-5) and CSF protein: 57.8 mg/dl (normal values = 15-45mg/dl). Despite the marginal abnormal cell count and high

protein values, there was no albuminocytological dissociation. The neurophysiological test performed in upper and lower limbs, in the tenth day was normal.

Three skin punch biopsies were performed. Two from lesional skin of the right and left calf and one from the non-affected skin of the right arm. The latter specimen was used as control for intra-epidermal nerve fiber density (IENFD). Hematoxylin and eosin staining from every specimen showed very mild perivascular dermal lymphocytic infiltrate without any other histologic abnormalities.

Immunohistochemistry was performed on 4μm formalin fixed paraffin embedded sections from all the tissue blocks. Specifically, two, at different level, unstained sections form each tissue block, were stained using protein gene product 9.5 (PGP 9.5) on an automated immunostainer. The IENFD was measured in all stained sections and defined as the mean number of intra-epidermal nerve fibers per mm in each case. The IENFD in skin from the right and left knees was 1.1 fibers/mm and 1.45 fibers/mm respectively, whereas on normal skin (right arm), 5 fibers/mm (Figure 1), suggesting a small fiber neuropathy.

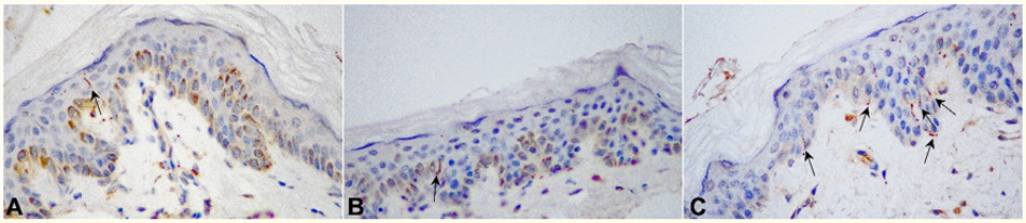

Figure 1: Immunohistochemical findings of skin biopsies using the anti-protein gene product 9.5 (PGP 9.5) antibody. A and B: The skin biopsies from right and left calf respectively suggested a significant loss of PGP 9.5 immunolabeled epidermal nerve fibers (black arrows). C: Punch biopsy specimen from normal skin (right arm) demonstrated normal intra-epidermal nerve fiber density (black arrows). A, B, C: DAB & Mayer hematoxylin as counterstain x 400.

The patient was treated with pregabalin with gradual titration and mild improvement of the symptoms.

Two months later an exacerbation of symptoms occurred with painful tingling in low extremities and excessive fatigue. The patient performed an MRI in lumbar-sacral area and I1 root enhancement was found (see Figure 2). His neurological examination revealed diminished tendon reflexes (A5-A6) in upper limbs and decreased in lower limbs. There was also a decreased sensation of pain distally in all four limbs and a decreased vibration in lower limbs. A new lumbar puncture revealed normal CSF pressure, 0-1 cells (0-5) and CSF protein 51 mg/dl (15-45mg/dl). There was also intrathecal IgG production (oligoclonal band (OCB) type 2, number of OCB:2) determined by isoelectric focusing coupled to immunofixation. A further imaging and laboratory investigation was performed: chest and abdominal CT, brain and cervical spine MRI, antibodies for: systemic autoimmune syndromes; gangliosides; paraneoplastic antibodies; lysosomal enzyme activity for Fabry's disease and heavy metal exposure. The only abnormal finding was a marginal positivity of ANA antibodies (1/160). (See Table 1) The patient was treated with IV methylprednisolone 1gr for five days with a moderate symptoms' remission, limited to the distal low extremities.

Discussion

To the best of our knowledge, this is the first case of post Covid-19 vaccination small fiber neuropathy combined with intrathecal IgG presence without an underlying CNS demyelinating disease using the Vaxzevria / COVID-19 Vaccine, AstraZeneca. There is a previously reported case of Small Fiber Neuropathy post Pfizer BioNTech COVID-19 Vaccine [1], also defined by skin biopsy and immunohistochemistry.

Neurologic complications after vaccination have been previously reported. Dysesthesias may be the most common complain persisting days after vaccination [2], usually starting few days after

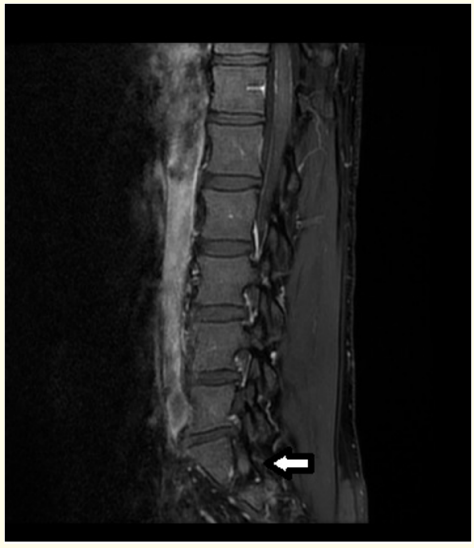

Figure 2: T1W with IV contrast (Sagittal T1 FS FSE) showing mild right I1 root enhancement (white arrow).

Test Normal values	May 2021	August 2021	Test	May 2021	August 2021
WBC 3,8 - 10,5 K/µL	5,73	6,34	Glucose 74-106 mg/dl	63	83
RBC 4,20 - 6,30 M/µL	5,53	5,28	Urea 16,6-48,5 mg/dl	22	40
HGB 14,0 - 18,0 g/dL	15,50	14,3	Creatinine 0,7-1,2 mg/dl	1.0	1.09
HCT 40,0 - 52,0 %	45,50	42,3	K^+ 3,5 - 5,1 mmol/l	5.00	4.3
MCV 80,0 - 99,0 fL	82,30	80,1	Na^+ 136 - 145 mmol/l	142	142
MCH 27,0 - 32,0 pg	28,00	27,1	Ca^{2+} 8,6-10,2 mg/dl	9.40	9.83
MCHC 32,0 - 35,0 g/dl	34,00	33,8	CPK 0 - 190 U/l		42
PLT 150 - 450 K/µL	228	288	Mg 1,6-2,6 mg/dl	2.30	2.24
ESR 0 - 20 mm	4	5	Bilirubin -total < = 1,4 mg/dl		0.56
PT%		11,70	Bilirubin-direct 0,00 - 0,30 mg/dl		0.21
INR 0,85-1,15 INR		1,00	SGOT < 40 U/l	13	12
APTT 25-35 sec		25,20	SGPT 0 - 41 U/l	25	10
Fibrinogen 200-450 mg/dl		260	γ-GT 8 - 61 U/l		12
D-dimers < 0.4 mcg/mL		284	ALP 30-120 units /L	54	
Cholesterol < 200 mg/dl		170	LDH 135-225 U/l		139
LDL < 130 mg/dl		107	Total Protein 6,4-8,3 gr/dl		6.53
HDL > 65 mg/dl		42	Albumin 3,5 - 5,2 gr/dl		4.51
ACE 13.3-63.9 U/L		44.0	Fe 33 - 193 µg/dl	124	
RPR		negative	HIV Ag-Ab		negative
HBsAg		negative	HCV		negative
Procalcitonin		0.0.3	Ferritin 30 - 400 ng/mL		59.7

CRP < 0,5 mg/dl	0,01	0.123	TSH 0,27 - 4,20 μIU/ml	1,51	1.52
ACE 13,3 - 63,9 U/L			FT4 12,0 - 22,0 pmol/l	1,27	1.33
C3 79 - 152 mg/dl	95.0	86.6	IGG 751-1560 mg/dl	1005	986
C4 16 - 38 mg/dl	20.1	18.2	IGA 82-453 mg/dl		260
RA test 0 - 20 IU/ml		< 20	IGM 46-304 mg/dl	60	40
B12 145-569 pmol/l	305		IGE 22 - 165 IU/ml		< 5.0
Folic acid 8,83-60,8 nmol/l	3.51		C.E.A. < 3,8 ng/ml		0.71
Anti-ENA screen < 20 RU/mL	Negative	2.530 negative	CA 15.3 < 25 U/ml		6.78
Anti-Cardiolipin IGG		2.640 negative	CA 19.9 < 27 U/ml		3.14
Anti-Cardiolipin IGM	< 2 negatives	< 2 negative	CA 125 < 35 U/ml		8.18
ANA < 1:160	Negative	1/160	PSA < 2ng/ml		0.58
Anti-ds DNA < 1:10	Negative	negative	Uric acid 3,4 - 7,0 mg/dl		
ANCA-c	< 2 negatives	< 2 negatives	25(OH) vit D3 > 20 ng/dl	12.5	28
ANCA-p	< 2 negative	< 2 negative	Homocysteine μmol/L	9.7	
β2GPI (IgG) < 20 RU/ml	< 2 negative	< 2 negative	Seruloplasmin 22-58mg/dl		27.1
β2 GPI (IgM) < 20 RU/ml	< 2 negative	2,680 negative	HbA1C 4-6%		5.20
k light chains 629-1350 mg/dl		769	Serum-Free kappa 0.33-1.94		1.4
λ light chains 313-723mg/dl		448	Serum Free lambda 0.571-2.63		1.4
electrophoresis of serum proteins- Immunofixation		No monoclonal band	Free k /free λ Serum ratio 0.26-1.65		1
Urine examination					
Color	yellow		Microscopic examination		
Appearance	clear		RBC	0-1	
Specific Gravity	1005		WBC	0-1	
PH	6		Glucose	negative	
HGB			Urobilinogen	0.1	
Protein	negative		Nitrogen	negative	
Bence-Jones protein Urine 24h		negative			
CSF					
Glucose 40-70mg-dl	48	59	IgG CSF 0.48-5.86 mg/dl	3.35	
Protein (15-45mg/dl)	57.8	51	IgG serum 751-1560 mg/dl	973	
Cells (0-5)	11	0-1	Albumin CSF 13.9-24.6 mg/dl	29	
Pressure 70-180mm H_2O	130		Albumin Serum 3660-5100 mg/dl	4660	

Oligoclonal Band (OLB)		Intrathecal IgG, type 2			
IgG -INDEX > 0,65		0.55			
Serum Antibodies		IgG-IgM			IgG
Sulfatide		Negative	Ampiphysin		Negative
GM1		Negative	CV2/CRMP5		Negative
GM2		Negative	Ma2/Ta		Negative
GM3		Negative	Ri/ANNA2		Negative
GM4		Negative	Yo/PCA1		Negative
GD1a		Negative	Hu/ANNA1		Negative
GD1b		Negative	Recoverin		Negative
GD2		Negative	Sox1		Negative
GD3		Negative	Zic4		Negative
GT1a		Negative			
GT1b		Negative	Dry Blood Spot		
GQ1b		Negative	a-Galactosidase > 2.8 µmol/L/h	3.2	
HSV I-II IgG < 0.9 AU/mL		> 200	VZV IgG ELIZA < 0.9 AU/mL		1.16
HSV I-II IgM < 0.9 AU/mL		Negative	VZV IgM ELIZA < 0.9 AU/mL		0.09
CMV IgG < 6 AU/mL		181.00	EBV IgG < 0.75 S/CO		78.36
CMV IgM < 0.85 AU/mL		0.08	EBV IgM < ,0.5 S/CO		0.02

Table 1: Patients Laboratory Test results at the begging of symptoms and after the exacerbation.

vaccination. It is also commonly regarded as a functional disturbance [3]. However, in our case, the abnormal values in the CSF might indicate that these symptoms may have an immunological origin and may be vaccine related.

Small Fiber Neuropathy (SFN) is a relatively rare neuropathy and can be caused by various factors [4-6]. There are previous reports correlating its incidence with vaccination [7]. Unfortunately, the response of immunologic origin SFN to immunotherapy (Corticosteroid, Intravenous immune globulin (IVIG)- is limited and there is currently a lack of optimal treatment [6,8]. We used high dose corticosteroids with moderate outcome. Our patient is still symptomatic and under surveillance.

Adverse events (AEs) following immunization may be a chance phenomenon or may be causally related to the vaccine [7,9]. To answer this question, a temporal relationship with vaccination and AEs is necessary and a pathophysiological mechanism explaining the association should be proposed. In our case, the temporal association of the symptoms' onset and the exclusion of any other underlying disease, led us to the conclusion that the patient's status was probably related with the vaccination. A vaccine occasionally can act as a trigger of an adverse immune response, affecting the peripheral nervous system [10,11]. The Bell's paralysis and the most well-known syndrome of inflammatory polyneuropathy, Guillain-Barré syndrome, have been added in the summary of product characteristics, as a rare/very rare possible adverse events of the Vaxveria Vaccine [12]. It is probable that our case shares a common pathophysiological mechanism with the above inflammatory peripheral neuropathies. Post-marketing surveillance is destined to detect rare or unexpected patterns of AEs. Reporting of AEs in large databases is very important [13].

Conclusion

Rare occurrences of COVID-19 vaccine-related neurological complications are indeed possible [2,14,15]. Although infrequent,

any serious adverse reaction to vaccines must be reported, and investigated to facilitate ongoing safety evaluation.

The benefit of COVID-19 vaccination outweighs the potential side effect risk. Nonetheless, we should not ignore and underestimate as functional-psychological, our patients complains.-

Consent for Publication

Written informed consent was obtained from the patient for this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interests

The authors report no actual or potential conflict of interest.

Funding

This Case Report article did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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