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Review Article

Vaccine-Induced Functional Neurological Disorders in the Covid-19 Era

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ABSTRACT: The large amount of information available to the public regarding vaccines against Covid-19 coupled with pandemic stress and increased somatic attention could potentially precipitate development of functional neurological disorders (FNDs) following vaccination. A growing number of reports indicate that functional symptoms may follow Covid-19 vaccination, similar to those observed with other vaccines previously. We review previously reported cases of FND following vaccination against Covid-19 and present three additional cases. While two patients presented to the Emergency Department with functional movement disorders, one patient presented with protracted limb weakness and sensory dysfunction. The superficial resemblance to Guillain–Barré syndrome, a known but uncommon complication of vaccination prompted an extensive workup. Clinicians need to convey the diagnosis of FND in clear and unequivocal terms to facilitate institution of appropriate therapy and rehabilitation, but importantly also to dispel any doubts in the minds of the public regarding the safety of the available vaccines. Given the presence of significant vaccine hesitancy in many countries, this is critical to the success of the global immunisation effort.

RÉSUMÉ : Des troubles neurologiques fonctionnels induits par les vaccins à l'ère de la pandémie de COVID-19. La grande quantité de renseignements disponibles au public concernant les vaccins contre l'infection à la COVID-19, le tout associé au stress induit par la pandémie et à une attention somatique accrue, pourrait potentiellement précipiter le développement de troubles neurologiques fonctionnels après la vaccination. En effet, un nombre croissant de rapports indique que des symptômes fonctionnels, à l'instar de ceux observés précédemment avec d'autres vaccins, peuvent apparaître à la suite de la vaccination contre l'infection à la COVID-19. Nous entendons ici passer en revue les cas précédemment signalés de troubles neurologiques fonctionnels consécutifs à la vaccination contre l'infection à la COVID-19 et présenter trois cas supplémentaires. Alors que deux patients se sont présentés à un service d'urgence avec des troubles fonctionnels du mouvement, un autre patient a donné à voir une faiblesse prolongée des membres et un dysfonctionnement sensoriel. La ressemblance superficielle avec le syndrome de Guillain-Barré (SGB), une complication connue mais peu fréquente liée à la vaccination, a motivé l'établissement d'un bilan approfondi. Chose certaine, les cliniciens doivent transmettre un diagnostic de trouble neurologique fonctionnel en termes clairs et sans équivoque pour faciliter l'amorce d'un traitement et d'une rééducation appropriées, mais aussi, et c'est important de le souligner, pour dissiper tout doute dans l'esprit du public quant à la sécurité des vaccins disponibles. Compte tenu d'une hésitation importante à l'égard des vaccins dans de nombreux pays, il s'agit là d'un aspect crucial du succès de l'effort mondial de vaccination.

Keywords: Covid-19; AstraZeneca vaccine; Functional neurological disorder; Guillain–Barré syndrome

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Introduction

The introduction of vaccines against SARS-CoV-2 coronavirus disease 2019 (Covid-19) has attracted unprecedented attention from the lay public as well as medical professionals. The large amount of information available online and in the media about each vaccine, its reported efficacy and potential adverse effects has served not merely to educate but also to heighten concerns regarding vaccination in the minds of a proportion of the public. Indeed, vaccine hesitancy – the lack of confidence in vaccination – is now recognised as a serious impediment to the goal of control of the Covid-19 pandemic by achieving near-universal immunisation. This is exacerbated by worries about side effects attributed to vaccines and can adversely affect the success of vaccination programmes that rely on high rates of public acceptance and population coverage.[1]

Functional neurological disorders (FND) are conditions related to altered functioning of brain networks rather than structural disease of the nervous system resulting in a variety of neurological symptoms including seizures, paralysis and movement disorders.[1–4] The diagnosis of FND rests on the demonstration of

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clinical findings incongruent with a known clinical pattern, that may be variable or inconsistent over time and which may include certain positive signs consistent with FND.[2,4] Among many other factors, these conditions may be triggered by vaccination and are classified by the World Health Organisation (WHO) as neurological immunisation stress-related responses (ISRR).[5] The global drive to deliver Covid-19 vaccines to as many people as possible, pandemic stress, feelings of uncertainty about Covid-19 vaccinations and the normal transient physical symptoms and discomfort after vaccination have led to several reports of FND following vaccination.[1–3,6,7] We review cases of FND following Covid-19 vaccination reported in the English medical literature to date and present three additional patients who presented to the emergency department at our centre, two with functional movement disorders after receiving the Pfizer-BioNTech BNT162b2 vaccine and the Moderna mRNA-1273 vaccine and one with functional limb weakness and sensory dysfunction following the ChAdOx1 nCoV-19 (AstraZeneca, AZ) vaccine. Management was complicated by a self-diagnosis of post-vaccinal Guillain-Barré syndrome (GBS), an uncommon side effect that has been reported both from our centre[8] and from elsewhere.[9,10]

Methods

We report three patients seen at our centre and diagnosed with FND, with onset after receiving vaccination against Covid-19. We reviewed available reports of FND diagnosed following Covid-19 vaccination. We searched PubMed, EMBASE, Google and Google Scholar databases using the keywords 'functional neurological disorder' and 'COVID-19' (or 'SARS-CoV-2') and 'vaccination' (or 'vaccine') to identify all published reports in English on patients diagnosed with FND by a neurologist or neuropsychiatrist with a temporal relationship of onset to vaccination against Covid-19. The last search was performed on March 18, 2022.

Illustrative Case Reports

Patient 1

A 22-year-old woman with previous glandular fever and chronic fatigue presented to the ED with involuntary movements of the neck and back beginning as a brief 'twitch' a day after the first dose of the Pfizer BNT162b2 vaccine, increasing in frequency and intensity over the next fortnight. After the second dose 3 weeks later, she noticed pain in the right arm and the left radial forearm and hand with increased involuntary movements, which present irregularly but persistent throughout the day. Less prominent on lying down or on moving around, these movements increased in amplitude and frequency on sitting but remitted when asleep. They were not voluntarily suppressible. No prescription or recreational drug use was identified. Examination revealed tonic head deviation to the right with taut sternocleidomastoids bilaterally and irregular tremulous movements of the head, neck and right shoulder. These tremors varied in frequency and amplitude were entrainable and diminished with distraction. Amplitude of the tremor increased with weighting.

Imaging of the brain and cervical spine and blood workup was normal. We explained the diagnosis of FND and its management in detail. She opted for low-dose diazepam therapy in view of domestic stressors, which produced nearly compete resolution of symptoms after a week.

Patient 2

A 21-year-old woman, with previous migraine with aura, asthma and eczema, presented to the ED with light-headedness, tremulousness of the left upper limb and 'internal shivers' for 2 weeks progressing to a bilateral upper limb tremor which she attributed to the mRNA-1273 Moderna vaccine that she had received 8 weeks previously. MRI of the brain was normal. An upper limb and head tremor was noted to be irregular, jerky, variable in frequency and direction, distractable and entrainable spreading to other parts of the body (head, legs) on attempted voluntary suppression. Handwriting and fine motor movements were unaffected by an otherwise prominent tremor. MRI of the brain and blood workup for infection or metabolic disease were normal. The patient was explained the diagnosis of a functional movement disorder and a plan for rehabilitation was made.

Patient 3

A 69-year-old woman, with premorbid history of migraine, hypertension, fibrocystic breast disease and gastro-oesophageal reflux presented to the ED with 7 weeks of numbness and weakness of all limbs, beginning 1 week after receiving the first dose of the AZ vaccine. She reported falls due to her legs 'giving way', and subsequently experienced worsening lower limb weakness with difficulty walking and expressed concern regarding possible GBS due to the AZ vaccine. She was unable to stand on her toes or heels and reported reduced touch perception distally from the knees. Workup for systemic immunological or endocrine disease and paraproteinaemia was negative, and imaging and CSF examination were unremarkable. Over the next 5 weeks, her limb weakness improved subjectively, with persistent limb paraesthesia.

She received the second dose of the AZ vaccine as scheduled, experienced worsening paraesthesia up to the forehead, and presented a week later with lower limb weakness and shortness of breath worsening over the next 4 days. Pain shooting up from the ankles to the thighs produced jerky involuntary movements of both lower limbs. Upon examination, all four limbs were globally weak and flaccid. Catatonic posturing was noted in both upper limbs, and despite apparent weakness she exhibited associated movements when asked to move around in bed and was able to deflect her arm away from her face. Reflexes were normal with flexor plantar responses, and perception of pinprick was reduced over the limbs but preserved over the trunk and face. MRI of the neuraxis, nerve conduction studies and EMG were normal. A diagnosis of FND was made and was explained in detail to the patient, emphasising the very real nature of the illness and the potential for recovery. She was discharged back to her local hospital for rehabilitation, with rapid improvement in her weakness, resuming ambulation with minimal support in a week.

Previous Reports of FND Associated with COVID-19 Vaccination

Table provides a comprehensive list of reports of FND following Covid-19 vaccination published in the medical literature to date. In addition, numerous online reports exist, presented as 'vaccine side effects' or 'medical mysteries' despite public affirmation from expert neuropsychiatrists that these symptoms were likely due to FND.[6,11,12] Expert review of online videos purporting to depict movement disorders can reliably diagnose FND.[13] We are aware of only one report in the Australian media of a patient who developed FND after the AZ vaccine. A 23-year-old woman developed

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tremors in the upper and then lower limbs within 4 hours of the injection. A diagnosis of FND was made by her physicians. We reviewed an online video recording demonstrating irregular and variable tremors of the hands and head, flapping of the hands, abduction of both arms and axial jerks, consistent with a functional movement disorder.[14] FND have been reported after the first or second doses of four different Covid-19 vaccines, at variable latencies ranging from a few minutes to 3 weeks. In line with the symptoms of FND in general, patients manifested variable and inconsistent combinations of weakness, sensory or speech dysfunction, non-epileptic seizures or involuntary movements.

Discussion

The broad range of neurological symptoms in FND includes functional movement disorders presenting with various phenotypes such as tremor, weakness and gait disorder. In a recent meta-analysis of 4905 patients with functional movement disorders mixed movement disorders were most encountered, followed by isolated tremor or weakness. Women were more often affected, and symptoms peaked in mid-life.[15] In an Italian database, mono-symptomatic functional movement disorders presented commonly with tremor, weakness and dystonia.[16] Dissociative or psychogenic non-epileptic seizures are paroxysmal episodes of altered awareness, resembling epileptic seizures or syncope, which are not explained by these or other medical disorders and usually have distinctive clinical features.[17] Differing phenotypes have been proposed to indicate diverse pathophysiological mechanisms, but these are now thought more likely to represent varying manifestations of a unitary disorder, a concept also supported by the frequent overlap of different functional symptoms in the same patient.[15,16]

These symptoms may be precipitated by biological, environmental or psychosocial factors.[3,12] Sensory perceptions – for example the pain of the injection needle or myalgia that follows immunisation as well as increased somatic attention from checking for signs of Covid-19 – in combination with abnormal expectations or beliefs may trigger or exacerbate cognitive and neurobiological processes that result in FND development and persistence.[3,6,12,18,19] As an example, it is possible that vaccine-related FND may arise in the context of prior beliefs about illness and expectations regarding the (putative) harmful effects of vaccines.[12]

The ongoing Covid-19 pandemic and the attendant disruption of usual social and economic activity from lockdowns have resulted in increased levels of stress and anxiety. Italian patients with functional movement disorders reported significantly higher levels of anxiety and perceived stress than healthy controls during the first 2 months of the Covid-19 pandemic.[20] Intense, pervasive or ubiquitous stressors such as stressful life events, physical trauma including infections and adverse drug reactions and comorbid medical illnesses have been linked to the development of FND or to worsening of pre-existing symptoms.[1,2,20–22] Indeed, the proportion of patients diagnosed with FND among those presenting to emergency neurology services in Mexico increased during the pandemic, with an odds ratio of 2.91.[23] A mass sociogenic illness with limb movements, coprolalia and self-injurious behaviour resembling functional tics has been reported to be prevalent on the social media platform TikTok, the format of which might facilitate spontaneous spread of behaviours and emotions among users.[24] However, established FND in a cohort of Australian patients deteriorated only in a minority, related to increased anxiety and to imposed restrictions on activity.[19]

While FND has previously been reported following administration of other vaccines,[1,25–28] the intense scrutiny of vaccines against Covid-19, particularly by vaccine sceptics aiming to discredit the vaccination drive, has led to an unfortunate magnification of side effects – whether actual, potential or merely theoretical. The easy availability of online videos claiming the dramatic development of involuntary movements following the administration of vaccines has led to fear and distrust of the vaccines. Misinformation is widely prevalent in social media, including conspiracy theories promoted by anti-vaccine fringe groups, and has a critical role in amplifying otherwise valid concerns about vaccine safety, leading to hesitancy and a decline in public trust.[1,3] Prompt diagnosis of FND is essential to avoid misleading conclusions about vaccine safety and disruption to vaccination programmes. Moreover, diagnostic delay has been shown to be a strong predictor of poor prognosis in people with FND.[16] An incorrect diagnosis leads to prolongation of the clinical course with considerable negative effects on the patient and denial of multidisciplinary treatment for FND, wherever necessary.[2–4,6,29]

Our patients had protracted symptoms for 1–3 months before a diagnosis was reached, necessitating multiple trips to the ED with variable and inconsistent involuntary movements, limb weakness and paraesthesia. In each case, formal neurological examination demonstrated positive signs consistent with the diagnosis of FND, including tremor entrainment, distractibility, catatonic posturing and preservation of reflex and associated limb movements in the face of claimed severe paralysis. Extensive laboratory, imaging and electrophysiological workup were undertaken to exclude alternative conditions. Given the relatively recent development of vaccines against Covid-19 and ongoing research into their effects, a detailed evaluation of patients who present with what appears to be FND is essential to avoid missing other concomitant or underlying neurological disorders. This is particularly important in view of the frequent coexistence of FND with other neurological conditions.[29] The well-documented occurrence of neuropsychiatric and neuro-inflammatory side effects after vaccination against Covid-19 including headache, fatigue and central and peripheral nervous system demyelination should be considered when evaluating possible FND.[3,8,30,31]

We anticipate that more such cases will occur as the vaccination drive expands. As patients are likely to turn to other, less evidence-based explanations in the absence of appropriate information from their doctors, it is imperative that the medical community provides unambiguous and clear explanations to the public regarding the nature of FND symptoms and the safety of vaccines currently in use to mitigate the negative impact that such reports of FND might have on vaccination campaigns.[1–3,6,12,29] Further epidemiologic studies of neuropsychiatric symptoms and signs post-vaccination are required to ascertain the incidence of FND and other neuropsychiatric effects.[29]

Conclusions

Our report adds to the growing literature on the development of FND following vaccination against Covid-19. This is no doubt a consequence of the attention given to, and the widespread availability of information on, the disease and its vaccines in the media, often of doubtful provenance. Our patients' symptoms are similar to those described in previous reports of vaccine-related FND (Table 1) and in one patient superficially resembled a recognised,

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Table 1: Cases of functional neurological disorder following vaccination against Covid 19 reported in the English medical literature to date

Serial No	Ref	Age (years) /sex	Vaccine, dose	Latency to onset	Clinical features	Outcome
1.	Present report	22/F	P 1,2	One day	Tremors of neck, back and shoulder; tonic neck deviation	Significant improvement over 1 month
2.	Present report	21/F	Mo, 2	Six weeks	Tremors of upper limbs, light-headedness, "internal shivers"	Symptoms persist
3.	Present report	69/F	AZ, 1,2	One week	Fluctuating limb weakness, paraesthesia, pain, leg jerks	Ambulant after 1 week of rehabilitation
4.	14*	23/F	AZ 1	Four hours	Irregular variable hand and head tremors, hand flapping, arm abduction, axial jerks	Not known
5.	1	?	P, 2	20 min	Generalised non-epileptic seizures; episodic limb paralysis	?
6.	1	?	AZ, 2	Two weeks	Dizziness, loss of sensation over right side	?
7.	1†	M	S	Few minutes	Loss of consciousness, unilateral facial palsy	?
8.	1†	F	Mo	?	"uncontrollable shaking and tongue spasms", axial jerks	?
9.	2	41/M	? 1,2	Few minutes	Bifacial weakness for 40 min after first dose. "Swollen tongue" and dyspnoea after second dose, followed by weakness of right upper limb and then left facial hypoaesthesia.	Normal neurological examination at 2 weeks
10.	3	38/F	P, 1	20 min	Left-sided sensory disturbances, then left facial and limb weakness, word-finding difficulties, stammering.	Variable improvement in weakness over 2 months
11.	3	36/F	Mo, 2	Few minutes	Weakness of right hand, limping with right leg for 2 hours. Fluctuating weakness of right or left side, fatigue, neck tightness, tremor.	?
12.	7	42/F	AZ, 1	?	Episodic loss of consciousness, inability to open eyes	Improved in 1 day
13.	7	28/F	?, 2	Immediate	Bilateral foot drop, paraparesis	Improved in 2 days

F: female; M: male; AZ: AstraZeneca vaccine; P: Pfizer-BioNTech BNT162b2 vaccine; Mo: Moderna mRNA-1273 vaccine; S: Sinovac vaccine; ?: not specified.
*Online videos reviewed by us.
†Online videos reviewed by authors of the cited paper.

albeit uncommon, complication of the AZ vaccine. Careful clinical examination and appropriate testing were essential in excluding other conditions and in proving the functional nature of the symptoms, thereby enabling commencement of appropriate treatment, and preventing the unnecessary and futile use of expensive and potentially harmful therapies.

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