Received: 22 August 2023 | Accepted: 12 December 2023

DOI: 10.1111/ene.16191

european journal of neurology
the official journal of the european academy of neurology

SHORT COMMUNICATION

Increased risk of functional neurological disorders following SARS-CoV-2 vaccination

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Abstract

Background and purpose: The purpose of this study was to evaluate the possible correlation between SARS-CoV-2 vaccines and the onset of neurological syndromes. The aim was to challenge the association between SARS-CoV-2 vaccinations and the onset of acute functional neurological disorders (FNDs) compared to other neurological syndromes in hospitalized patients.

Methods: In this prospective cohort study, all adult inpatients consecutively admitted to a tertiary neurological centre were included. The prevalence and characteristics of neurological syndromes were compared between unvaccinated and vaccinated cases stratified according to the onset from vaccination. The study involved 843 subjects, namely 411 unvaccinated (UVC) and 432 vaccinated cases; these groups were comparable for demographics and clinical diagnosis distribution.

Results: Compared to UVC, subjects hospitalized within the first 30 days from vaccine exhibited higher prevalence of FNDs (12.3% vs. 3.6%; odds ratio 4.2, 95% confidence interval 1.6–11.1) and headache (10.8% vs. 5%; odds ratio 4.1, 95% confidence interval 1.9–8.8) but no other neurological syndromes. The FND cases following vaccinations showed similar premorbid conditions and severity but a higher percentage of sensory symptoms and pain compared to UVC FND cases.

Conclusions: SARS-CoV-2 vaccination is associated with a significant short-term increased risk of FND and headache requiring hospitalization in an acute neurological setting.

KEYWORDS
acute neurology, medical unexplained symptoms, functional neurological disorders, SARS-CoV-2 vaccination

INTRODUCTION

During the last year, SARS-CoV-2 vaccination distribution has rapidly increased across the globe, such that between 60% and 65% of the world population and 75% of Europeans were fully vaccinated in 2023 (https://vaccinetracker.ecdc.europa.eu). Transient influenza-like symptoms such as headache, myalgia and fatigue have been reported in up to 5% of SARS-CoV-2 vaccine cases, whereas psychiatric and neurological (such as cerebral venous sinus thrombosis) complications appeared to be rare, as confirmed by clinical trials and active surveillance [1–4]. The media and medical attention have focused on potential neurological side effects eliciting a

somatic hypervigilance for specific symptoms in some individuals, probably contributing to an increased risk of functional neurological disorders (FNDs) instead of organic neurological syndromes [3–6]. Indeed, FNDs have been reported in response to previous vaccination campaigns, and a few case reports precipitated by SARS-CoV-2 have also been reported [7, 8].

In this large prospective study, neurological patients admitted to a tertiary hub were consecutively investigated and unvaccinated and vaccinated subjects were contrasted to evaluate the specific risk of neurological syndromes and FNDs associated with vaccination.

METHODS

The study included all neurological adult inpatients admitted at the Neurology Unit of the ASST Spedali Civili Hospital, Brescia, from January 2021 to January 2022. All subjects were assessed with an extensive medical and neurological evaluation. Each patient underwent a routine standard medical and neurological evaluation and a routine blood analysis. Acute SARS-CoV-2 infection was excluded by reverse transcription polymerase chain reaction in nasopharyngeal/oropharyngeal swabs or bronchoalveolar lavage.

All data were imputed by physicians of the Neurology Department and checked by four independent raters (AP, MC, NZ, AP) [9]. This study received approval from the ethical standards committee on human experimentation (local ethics committee of the ASST Spedali Civili Hospital, Brescia, NP 4067, approved in its last version on 10 December 2020). Epidemiological, demographical, clinical and outcome data were extracted from both printed and electronic medical records using standardized anonymized data collection forms. Premorbid conditions were recorded at admission using the Cumulative Illness Rating Scale, the premorbid modified Rankin Scale and the Clinical Frailty Scale, whereas the neurological severity was addressed through the modified version of the Neurological Impairment Scale (NIMS). FND was diagnosed in the presence of (i) one or more patterns of deficits consistent predominantly with dysfunction of the nervous system and (ii) variability in performance within and between tasks [6], whereas medical unexplained symptoms (MUS) were diagnosed according to current criteria [9]. Demographics, clinical characteristics and diagnosis distribution were contrasted between vaccinated and non-vaccinated cases and a subgroup of patients according to the onset of neurological manifestations in the first 30 days ($V<30$ days), 30–60 days (V 30–60 days) and more than 60 days ($V>60$ days) following SARS-CoV-2 vaccination.

Statistical analysis

Demographics and clinical characteristics were compared between vaccinated and non-vaccinated cases (and subgroups) using chi squared and ANOVA for dichotomous and continuous variables, respectively. Post hoc analyses were performed using Bonferroni correction. Differences in distribution for final diagnosis between subgroups were evaluated using a logistic regression model adjusted for age, sex and comorbidity status. Analyses were conducted using SPSS IBM statistics version 25.

RESULTS

A total number of 909 patients consecutively hospitalized for neurological disorders were screened; of them, 66 were excluded for data collection refusal ($n=28$) or missing clinical data ($n=38$). Thus, 843 cases including 432 vaccinated and 411 unvaccinated patients were included in the final analyses. The rate of vaccinated patients increased from 2% to 90% within the observation time (Figure S1). Vaccinated and not vaccinated subjects were comparable for age, sex distribution, premorbid comorbidity disability and diagnosis distribution (Table 1).

Compared to unvaccinated cases, $V<30$ days showed a similar sex distribution but were significantly younger (53.7 ± 20.2 vs. 58.3 ± 20.1 years, $p<0.001$) and presented slightly fewer comorbidities (Table 1). In the $V<30$ days subgroup, 31 patients followed the first, 49 the second and 27 the third dose of vaccine, with a different distribution compared to the general group ($p=0.001$, Table 1). Most patients underwent an mRNA vaccination (BNT162b2 67.9%, mRNA-1273 12.2%), whereas 11% followed ChAdOx1-S and 9% Ad26.COV2 subtype. The distribution between vaccine subtypes was similar in the $V<30$ days subgroup ($p=0.25$, Table 1).

Out of 432 vaccinated subjects, 106 cases manifested neurological syndromes within 30 days from SARS-CoV-2 vaccination ($V<30$ days), 71 between 30 and 60 days (V 30–60 days) and 255 after 60 days from vaccination ($V>60$ days). Compared to unvaccinated subjects, $V<30$ days cases exhibited an increased risk of FNDs (odds ratio [OR] 4.2, 95% confidence interval [CI] 1.6–11.1, $p=0.004$) and primary headache (OR 4.1, 95% CI 1.9–8.8, $p=0.001$), whereas V 30–60 days subjects exhibited an increased prevalence of MUS (OR 2.6, 95% CI 1.2–5.6, $p=0.012$) and similar FND distribution compared to unvaccinated cases. Subjects hospitalized more than 60 days from vaccination exhibited a similar diagnosis distribution compared to unvaccinated cases (Tables 2 and S1).

Functional neurological disorders following SARS-CoV-2 vaccination

Cases of FNDs following vaccination included transient sensory disturbances ($n=6$), painful dysaesthesia or sensory deficits associated with headache ($n=4$), combined sensory–motor deficits ($n=1$), diplopia ($n=1$) and gait alterations with postural instability ($n=1$). The majority (10/13) of cases developed in the time frame from April to July 2021 and all have a favourable outcome (Table S2 for details). Compared to unvaccinated FND subjects, cases associated with vaccination exhibited a higher prevalence of females (11/13 vs. 7/16, $p=0.029$) but did not differ for age

TABLE 1 Demographic variables according to vaccination profile.

	UVC	*V* < 30 days	*V* 30–60 days	*V* > 60 days	*p* value
N	411	106	71	255	
Age, years	58.3 ± 20.1	53.7 ± 20.2	58.6 ± 19.7	61.3 ± 19.4	**0.015**[a]
Female, *n* (%)	198 (50%)	63 (62.4%)	33 (47.8%)	119 (47.6%)	0.08
Day of hospitalization	8.2 ± 6.2	7.4 ± 5.3	9.2 ± 6.9	8.5 ± 6.6	0.92
CIRS comorbidity	2.1 ± 1.8	1.6 ± 1.9	2.1 ± 2.1	2.1 ± 1.7	0.89
Clinical Frailty Scale	3.4 ± 1.9	3.5 ± 1.8	2.7 ± 1.9	2.9 ± 1.5	0.07
Premorbid mRS	1.9 ± 1.3	1.5 ± 2.0	1.7 ± 1.8	1.70 ± 1.2	0.08
NIMS	5.8 ± 5.9	3.8 ± 3.4	4.9 ± 4.3	4.9 ± 4.4	0.07
Symptoms following					
First dose, *n* (%)		31 (29. %)	5 (7%)	2 (0.7%)	**0.001**
Second dose, *n* (%)		49 (46%)	46 (65%)	235 (92%)	
Third dose, *n* (%)		27 (25%)	20 (28%)	18 (7.3%)	
Vaccines subtypes					
mRNA vaccines		85 (80%)	56 (79%)	193 (75.6%)	0.25
Viral-vectored vaccines		21 (20%)	15 (21%)	62 (24.4%)	

Note: Significance level set at $p = 0.05$, highlighted by bold values in the table.

Abbreviations: CIRS, Comorbidity Index Rating Scale; mRS, modified Rankin Scale; NIMS, Neurological Impairment Modified Scale; UVC, unvaccinated subjects; *V* < 30 days, subjects with onset of neurological symptoms between 0 and 30 days after the last dose of SARS-COV-2 vaccine; *V* > 60 days, subjects with onset of neurological symptoms at least 60 days after the last dose of SARS-COV-2 vaccine; *V* 30–60 days, subjects with onset of neurological symptoms between 30 and 60 days after the last dose of SARS-COV-2 vaccine.Post hoc Bonferroni comparison: [a]*V* < 30 days vs. UVC.

(35.3 ± 14.1 years vs. 36.7 ± 11.9 years), comorbidities and severity at admission (NIMS 4.5 ± 3.7 vs. 5.1 ± 4.1, $p = 0.67$). None of the patients (vaccinated or not vaccinated) had been diagnosed with FND or neurological disease prior to admission. Compared with unvaccinated FND subjects, cases associated with vaccination showed a higher prevalence of sensory disturbances (11/13 vs. 9/16) and symptoms associated with pain (4/13 vs. 0/16) and headache (5/13 vs. 1/16). The two FND groups had similar duration of hospitalization and neurological severity at discharge (NIMS 1.3 ± 2.4 vs. 1.7 ± 2.4, $p = 0.37$).

DISCUSSION

The study indicated a notable correlation between SARS-CoV-2 vaccination and a higher risk of FND and hospitalization for headaches in an acute care environment. Additionally, our extensive consecutive cohort did not yield any particular association with acute neurological syndromes.

These data add important insights for understanding the real impact of vaccination on acute neurological manifestations, a still open issue [3, 6, 10, 11]. Findings showed that FNDs, headache and MUS represent more than a third of patients hospitalized in the 30 days following SARS-CoV-2 vaccination. FNDs following vaccination were similar in terms of demographics compared to unvaccinated cases and showed a prompt amelioration of symptoms in a few days of hospitalization. Furthermore, an interesting higher prevalence of sensory disturbances and pain was observed in these specific groups compared to unvaccinated FNDs. This might suggest that vaccination can trigger the development of FNDs possibly through physiological reactions (i.e., influenza-like symptoms or unilateral pain) in subjects with increased attention towards body signal [3–6]. The increased number of hospitalized subjects with negative findings following vaccination might be related to the patients' and clinicians' concerns raised by rare known complications of vaccines, thus leading to a risk of over-diagnosis and hospitalization especially for patients with headache [3, 11, 12]. On one hand, the numbers provided for headache and pain are in line with the recent meta-analyses indicating a higher risk of this symptom following COVID-19 vaccination [13]. On the other, the great emphasis in scientific literature and mass media of these cases might lead to a higher number of subjects presenting with acute onset neurological manifestations supposed to be associated with vaccination. Most FND cases following vaccination were indeed recorded in the earlier phase of the vaccine campaign, when the awareness of side effects was at maximum levels, as reported in previous vaccination campaigns [14].

The present findings are highly significant for both clinicians and health authorities, as the global health system is implored to strike a balance between thorough investigation and reassurance in patients in whom a functional reaction is identified. The information (and misinformation) pressure on single subjects and clinicians and the concerns for a clinically relevant diagnosis such

TABLE 2 Diagnosis distribution according to the time of vaccines.

	UVC	*V* < 30 days	*V* 30–60 days	*V* > 60 days
N	411	106	71	255
Cerebrovascular diseases	167 (41.9%)	32 (30.7%)[a]	27 (38%)	96 (37.9%)
Epilepsy	62 (15.3%)	8 (7.8%)[a]	4 (5.6%)[a]	34 (13.6%)
Headache	20 (5%)	11 (10.8%)[a]	9 (12.7%)	14 (5.6%)
Brain tumour	18 (4.5%)	4 (3.8%)	0 (0%)	12 (4.8%)
Encephalitis	7 (1.7%)	1 (0.9%)	2 (2.8%)	4 (1.6%)
Encephalopathies	9 (2.2%)	5 (4.8%)	3 (4.2%)	7 (2.8%)
Neurodegenerative diseases	20 (5.0%)	2 (1.9%)	3 (4.2%)	14 (5.6%)
Neuromuscular disorders	12 (3.0%)	3 (2.8%)	2 (2.8%)	8 (3.2%)
CNS inflammatory disorders	26 (6.4)	6 (5.7%)	6 (8.4%)	27 (10.8%)
Myelitis	5 (1.2%)	1 (0.9%)	0 (0%)	2 (0.8%)
ADEM	0 (0%)	1 (0.9%)	0 (0%)	1 (0.8%)
Vertigo and cranial nerve deficit	9 (2.3%)	5 (4.8)	2 (2.8%)	7 (2.7%)
Traumatic brain injury	14 (3.5%)	1 (0.9%)	0 (0%)	10 (4.0%)
FND	15 (3.6%)	13 (12.3%)[b]	3 (4.2%)	6 (2.3%)
MUS	27 (6.5%)	13 (12.3%)	10 (14%)[b]	13 (5.1%)

Abbreviations: ADEM, acute demyelinating encephalomyelitis; CNS, central nervous system; FND, functional neurological disorder; MUS, medical unexplained symptoms; UVC, unvaccinated subjects; *V* > 60 days, subjects with onset of neurological symptoms at least 60 days after the last dose of SARS-COV-2 vaccine; *V* 30–60 days, subjects with onset of neurological symptoms between 30 and 60 days after the last dose of SARS-COV-2 vaccine; *V* < 30 days, subjects with onset of neurological symptoms between 0 and 30 days after the last dose of SARS-COV-2 vaccine.

Significance versus UVC groups in linear regression analyses adjusted for age, sex and premorbid conditions: [a]$p < 0.05$; [b]$p < 0.005$ significance level in post hoc analyses.

as cerebrovascular or inflammatory diseases might largely explain these findings, which need to be verified in larger multi-centre surveys, also including rare conditions with potential inflammatory/vascular mechanisms [15]. Being focused on hospitalized patients in a single tertiary neurological centre, the design of the study did not allow the evaluation of incidence and prevalence of rare conditions or less severe manifestations (including FNDs) not requiring hospitalization [3, 13]. Additionally, the research did not adequately tackle the psychological and physical challenges faced by FND patients, which are recognized to be incapacitating and often require specialized care [6]. Furthermore, the sample size unfortunately limited the analyses of a possible association between type of vaccination and FND and specific studies are needed to evaluate the role of psychological stressors, abnormal expectations but also somatic symptoms in explaining this association. The findings did not find any association with inflammatory or cerebrovascular diseases, confirming the general safety profile of vaccination in people with different premorbid conditions and age classes [3, 12, 13]. Nevertheless, a prompt recognition of FNDs is pivotal for reassuring patients and social media to reduce the risk of vaccine hesitation for the general population.

AUTHOR CONTRIBUTIONS

Andrea Pilotto: Conceptualization; formal analysis; supervision; writing – review and editing; methodology. **Marcello Catania:** Writing – original draft; conceptualization; methodology; investigation; formal analysis. **Irene Mattioli:** Validation; methodology; formal analysis; visualization. **Nicola Zoppi:** Software; formal analysis. **Giulia Ceccardi:** Methodology; investigation; validation; visualization. **Renata Rao:** Project administration; visualization. **Stefano Gipponi:** Supervision; data curation. **Mauro Magoni:** Supervision. **Massimo Gamba:** Supervision. **Alessandro Padovani:** Supervision; writing – review and editing; conceptualization; methodology; project administration; resources; funding acquisition; visualization.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

No targeted funding reported.

CONFLICT OF INTEREST STATEMENT

Andrea Pilotto, Marcello Catania, Irene Mattioli, Giulia Ceccardi, Renata Rao, Stefano Gipponi Mauro Magoni, Massimo Gamba and Alessandro Padovani report no disclosures relevant to the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pilotto A, Catania M, Mattioli I, et al. Increased risk of functional neurological disorders following SARS-CoV-2 vaccination. *Eur J Neurol*. 2023;00:e16191. doi:10.1111/ene.16191