

Functional neurological disorders after COVID-19 and SARS-CoV-2 vaccines: a national multicentre observational study

INTRODUCTION

Functional neurological disorders (FNDs) are a common cause of neurology consultations.¹ Dissociative seizures, motor and cognitive disorders are the main phenotypes. Diagnosis is made on positive terms: signs of inconsistency, incongruence and variability of physical signs with attention on clinical examination.¹ Abnormal emotional processing and expectations are involved in the genesis and perpetuation of FND.¹

From the onset of SARS-CoV-2 pandemic, world population has been affected by high levels of stress, uncertainty and misleading information, with a potential impact on mental health. Different studies have ascertained an increase of FND consultations (threefold in an emergency department).² On the development of SARS-CoV-2 vaccines, several cases of FND following vaccination were published, as well as an official warning from the Functional Neurological Society.³ Post-COVID-19 symptoms (known as Long-COVID-19) have also become a frequent reason for neurology consultation.⁴ Somatic symptom disorder may be common in these patients, and socioeconomic implications are vast.⁵

Our experience is that a proportion of patients with FND describe an association with COVID-19 infection/vaccination. Here, we report a cohort of patients with FND for whom COVID-19 or SARS-CoV-2 vaccines were the main precipitant factors.

METHODS

We performed an observational retrospective analysis in eight tertiary university hospitals with special interest in FND. Electronic clinical records (March 2020–November 2022) were reviewed and FND which developed after COVID-19 disease (Co-FND) or SARS-CoV2 vaccines (Va-FND) were recorded. Diagnosis of FND was performed by an expert, based on clinical history and positive motor or sensory signs on examination. Hence, isolated phenotypes such as dissociative seizures, cognitive disorders or PPPD were excluded. Disability was defined as a situation of work-leave due to symptoms for

active subjects and disability to perform daily-living activities for students or retired subjects.

Clinical differences between Co-FND and Va-FND were analysed with Fisher's exact test for qualitative variables, and Kruskal-Wallis test for quantitative variables, using G-Stat V2.0 statistical program. Statistical significance was set at $p < 0.05$.

RESULTS

Forty-six patients, 36 (78%) women, mean age of 43 ± 13 years, were included. Thirty-three (72%) in the Co-FND and 13 (28%) in the Va-FND groups. Phenotype was purely motor in 30 (65%), mixed sensorimotor in 15 (32%) and 1 isolated sensory syndrome. Positive FND signs are described in online supplemental table 1. Most patients displayed a mixed motor phenotype, being tremor/jerks (23) and gait abnormalities the most frequent (22). Fatigue (72%), pain (57%) and cognitive difficulties (30%) were common.

In the Co-FND group, 19 (58%) patients had previously received a Long-COVID diagnosis. FND symptoms started within the convalescence period in 87%. In the Va-FND group, FND symptoms started within 1 week after vaccination in most cases.

Twenty-two (48%) patients required treatment with psychiatry/psychology specialists, 15 (33%) physical therapy and 1 case speech therapy. After a mean follow-up of 14 ± 8 months from onset, 46% had improved, 39% remained stable and 9% patients had worsened (follow-up unavailable after diagnosis in 3). Disability was present in 63% at the end of follow-up.

When comparing Co-FND and Va-FND groups, a significantly older age (46 ± 12 vs 35 ± 10 , $p = 0.0229$) and higher disability (76% vs 31%, $p = 0.0071$) were found in Co-FND. A trend towards more frequent male gender (24% vs 15%), previous psychological difficulties (50% vs 23%) and less frequent abrupt onset (38% vs 62%) was also noted in that group.

DISCUSSION

We describe clinical phenotypes, diagnosis and outcomes of 46 patients who developed FND after COVID-19 infection or SARS-CoV-2 vaccines. This is the first multicentre study and the largest cohort published to date. Previous literature, mainly single case reports and a few case series, depicted mild-to-moderate FND in association with SARS-CoV-2 vaccines,

while more disabling and COVID-19 related FND were anecdotal (online supplemental table 2).

Our results are of interest for several reasons. First, they suggest there might be a different clinical profile for patients who develop FND after COVID-19 infection and after SARS-CoV-2 vaccines. The features of the latter group closely resemble the classic FND, with younger patients, an acute onset and tremor as the most common phenotype.¹ Consequently, FND diagnosis in this group may be more straight-forward, which could explain why most published reports of FND have been related to SARS-CoV-2 vaccines. In contrast, patients with FND after COVID-19 infection tended to be older, with a more insidious onset and higher disability. This, along with the uncertainty surrounding many post-COVID-19 symptoms, might render FND diagnosis more difficult in the absence of appropriate clinical expertise.





Second, our results highlight the challenges of the Long-COVID diagnosis. This umbrella term includes more than 200 heterogeneous symptoms such as fatigue, cognitive complaints or pain, which are also common in FND, and especially frequent in our sample. Long-COVID lacks consensus definition, diagnostic criteria, biomarkers and a clear underlying pathology. In this context of uncertainty, a guiding principle should be that not all patients with post-COVID-19 symptoms necessarily have a Long-COVID, and a broad differential diagnosis should be considered. Our results suggest that FND should be part of this differential as nearly 60% of our patients had received the diagnosis of Long-COVID. Viral infections and vaccines have long been recognised as potential triggers for FND.¹

Lastly, FNDs are a source of treatable disability. Since there is no specific therapy for Long-COVID, recognising patients with FND is essential to plan early treatment and improve prognosis. A multidisciplinary approach based on an empathetic communication of the diagnosis, specific physical and psychological therapies might be of help in a proportion of patients.¹

Our study has limitations, mainly the small sample size and its retrospective nature. A selection bias is likely, since only patients with motor or sensory positive signs on exam were included. They were recruited mainly from FND clinics, a highly specialised resource. This likely leads to an underestimation of FND after COVID-19 infection and SARS-CoV-2 vaccines.

CONCLUSIONS

COVID-19 pandemic has introduced a complex worldwide stressor and an increased incidence of FND has been noted. Specific occurrence of FND after COVID-19 infection and vaccines are increasingly recognised, but likely under-reported or misdiagnosed as Long-COVID. FNDs are source of treatable disability, and its early recognition is essential to plan therapies and improve prognosis.

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