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Long-term outcomes after NeuroCOVID: a 6-month follow-up study on 60 patients

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*Contributors to the French NeuroCOVID registry are listed to Supplementary Table S1.

Declaration of interests

H. Chaumont: received travel grants from PEPS development, Roche and Pfizer. E. Roze: served on scientific advisory boards for Orkyn, Aguetant, Merz-Pharma; received honoraria for speeches from Orkyn, Aguetant, Merz-Pharma, Medday-Pharma, Everpharma, International Parkinson and Movement disorders Society; received research support from Merz-Pharma, Orkyn, Aguetant, Elivie, Ipsen, Everpharma, Fondation Desmarest, AMADYS, Fonds de Dotation Brou de Laurière, Agence Nationale de la Recherche; received travel grant from Vitalair, PEPS development, Aguetant, Merz-Pharma, Ipsen, Merck, Orkyn, Elivie, Adelia Medical, Dystonia Medical Research Foundation, International Parkinson and Movement disorders Society, European Academy of Neurology, International Association of Parkinsonism and Related Disorders. A. Lannuzel: received research support from France Parkinson, PSP France, Agence Nationale de la Recherche, Fonds européen de développement regional, French Ministry of Health, University Hospital of Guadeloupe; received honoraria from Association des Neurologues du Québec and travel grants from Vitalair, PEPS development, Merz-Pharma, International Parkinson and Movement disorders Society. E. Meppiel, B. Tressières, and T. de Broucker have nothing to declare.

Abstract

Background and purpose: Long-term outcomes after neurological manifestations due to COVID-19 are poorly known. The aim of our study was to evaluate the functional outcome and identify the risk factors of neurologic sequelae after COVID-19 associated with neurological manifestations (NeuroCOVID).

Methods: We conducted a multi-center observational study six months after the acute neurological symptoms in patients from the French NeuroCOVID hospital-based registry.

Results: We obtained data on 60 patients. NeuroCOVID had a negative impact on the quality of life (QoL) of 49% of patients. Age was a predictor of residual QoL impairment (OR: 1.06, 95% CI: 1.01 – 1.13, $p = 0.026$). At six months, a significant residual disability was found in 51.7% of patients, and impaired cognition in 68.9% of cases. The main persistent neuropsychiatric manifestations were a persistent smell/taste disorder in 45% of patients, memory complaints in 34% of patients, anxiety or depression in 32% of patients.

Conclusions: NeuroCOVID likely carries a high risk of long-term neuropsychiatric disability. Long-term care and special attention should be given to COVID-19 patients, especially if they had neurological manifestations during acute infection.

Keywords: COVID-19, Neurological manifestation, NeuroCOVID, Post-COVID Syndrome, Long-term outcomes.

1. Introduction

SARS-CoV-2 infection is characterized by many persistent symptoms or sequelae known beyond two months after the acute phase of mild to severe COVID-19 [1,2]. Six months after acute infection, 76% of hospital-discharged patients reported persistent symptoms [3]. The most common symptoms are fatigue, muscle weakness, sleep difficulties [3], post-exertional malaise [4], and cognitive dysfunction [4,5]. Patients have an increased risk of mood and anxiety disorders within three months after COVID-19 infection [6]. The 6-month prevalence of self-reported olfactory dysfunction was evaluated at 60% in mild symptomatic COVID-19 patients [7].

During the acute phase of COVID-19, up to 36% of patients develop neurological manifestations [8]. Typically they consist of mild or nonspecific neurological symptoms such as confusion, dizziness, headache, and myalgia [8]. Less common severe diseases such as encephalopathy, encephalitis, stroke, Guillain-Barre syndrome, cranial nerves palsy, acute cerebellar ataxia, myoclonus, and mixed neurological disorders may also occur [9–15]. The long-term outcome of patients with neurological manifestations related to SARS-CoV-2 (NeuroCOVID) is poorly known.

To evaluate functional outcomes and identify risk factors of sequelae after COVID-19 associated with neurological manifestations, we conducted a multicenter observational study six months after the acute neurological episode in patients from the French NeuroCOVID multicenter registry [16].

2. Methods

2.1. Patients and Study Design

We included patients from the multicenter registry of 222 adult patients admitted for neurological manifestations associated with COVID-19. In this hospital-based study established during the first French epidemic wave in March and April 2020 [16], patients were considered to have NeuroCOVID in the presence of *de novo* neurological manifestations occurring five days before to 35 days after the first symptoms of COVID-19. The diagnosis of COVID-19 required either a positive SARS-CoV-2 real-time reverse transcriptase PCR assay result on a nasopharyngeal sample or typical clinical history and chest computed tomographic scan. The illness was classified as mild, moderate, severe, and critical according to the United States National Institutes of Health criteria [17]. Mild Illness for any infectious signs and symptoms of COVID-19 but no shortness of breath, dyspnea, or abnormal chest imaging; Moderate Illness for respiratory clinical or radiological involvement with saturation of oxygen (SpO₂) ≥ 94% on room air; Severe Illness for SpO₂ < 94% on room

air, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%; Critical Illness for respiratory failure, septic shock, and/or multiple organ dysfunction. Neurologic manifestations were classified as either involving the central nervous system (CNS) or peripheral nervous system (PNS): encephalopathy (38.3%), stroke (28.4%), encephalitis and meningitis (10.9%), other CNS (7.7%), Guillain-Barre syndrome (6.8%), other PNS (9%) and mixed CNS and PNS (5.9%). Anosmia (3.2%) and ageusia (1.8%) were certainly underestimated as they may have been considered minor manifestations and, as such, not consistently recognized as neurological manifestations. All centers involved in this registry were contacted to participate in the follow-up study. Patients who died during the acute phase of COVID-19 and those followed in centers that declined their participation were not included. Six months after the onset of neurological signs, clinical assessment was scheduled during a telephone interview or by routine medical advice. The study was approved by the French Ile de France VIII ethic committee (2020-A01882-37).

2.2. Data collection and neurological investigations

We collected the following data: age, sex, clinical characteristics of COVID-19 defined in the multicenter registry (illness severity, neurological comorbidities, type, and chronology of neurologic manifestations). The severity of disability was graded using the modified Rankin Scale (mRS) [18]. Long-term residual disability was defined as mRS ≥ 2 (level 2 corresponding to a slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities). The 3-level version of the EuroQol five-dimension scale (EQ-5D-3L) was used to measure the quality of life [19]. EQ-5D-3L consists of five questions and a health-related visual analogue scale (VAS). In these questions, the respondents are asked to rate their current health state on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) into one of three levels (no problems (1), some problems (2) or a lot of problems (3)). The answers are transformed into a utility value, describing the respondent's health, where utility=0 equals death and utility=1 equals perfect health. For example, the answer pattern 11111 would result in an ideal health state (utility=1), whereas 33333 would result in the worst possible health state. Our study considers a significant alteration of the quality of life if more than one question is at least two points (example: 12211, 21112). The EQ-VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labeled "Best imaginable health state" and "Worst imaginable health state." The VAS is a quantitative measure of health outcome that reflects the patient's judgment. Evaluation of cognition and mood included Montreal Cognitive Assessment Blind [20] (MoCA-Blind), 35-item version of Cognitive Difficulties Scale (CDS) [21], and Hospital Anxiety and Depression Scale (HADS) [22].

The MoCA-Blind is a version of the MoCA test without the visual elements (first four items). This score evaluates memory, attention, language, abstraction, delayed recall, and orientation. Scoring ranges from 0 to 22, with higher scores indicating better performance. A persistent cognitive dysfunction is defined by a MoCA-Blind score < 19 . The 35-item version of CDS is used to assess memory complaints et was considered abnormal if ≥ 15 . HADS is a 14-item inventory: seven to evaluate depression and seven to assess anxiety. Each item scores 0-3. After summing up scores, a total score of 0-7 was taken as “no depression/anxiety”, 8-10 was taken as “moderate depression/anxiety”, and 11-21 was taken as “severe depression/anxiety”. Taste and Smell Survey (TSS) [23] was used to detect persistent olfactory or gustatory dysfunction. Persistent olfactory or gustatory dysfunction was present if the olfactory score or gustatory score were ≥ 1 .

2.3. Statistical analysis

Quantitative variables were summarized as median with interquartile range (IQR) and compared across groups using the Wilcoxon test. Categorical data were expressed as a percentage and compared between groups using the Chi-square test or Fisher exact test, depending on the sample size. Logistic regression models were used to identify factors associated with long-term residual disability, significant alteration of the quality of life, memory complaints, persistent cognitive dysfunction, moderate or severe depression/anxiety, and persistent olfactory or gustatory dysfunction. Factors investigated were the demographic characteristics, neurologic comorbidities, types of neurological manifestations, occurrence of neurologic manifestations relative to COVID-19 symptoms, neurological symptoms, and severity of COVID-19. All statistical analyses were performed using R 4.0.2, and significance was considered at the level 5%.

2.4. Data availability

Some data will be made available from the corresponding author, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of our patients.

3. Results

Sixty patients among the 194 who survived a confirmed diagnosis of COVID-19 were included in this study performed within a median of 6 months (IQR 6-7) after the acute phase of NeuroCOVID (Fig 1). Fifty patients (83.3%) had central nervous system (CNS) involvement, five (8.3%) had peripheral nervous system (PNS) disorder. For five of them (8.3%), the mechanism was undetermined (Table 1). Twenty-six patients (43.3%) had a severe or critical NeuroCOVID and ten (16.7%) had a history of neurological comorbidities :

stroke (n = 3), neurodegenerative disorder (n = 3), epilepsy (n = 2), sequels of Guillain-Barre syndrome (n = 1), axonal sensitive neuropathy (n = 1). No difference was observed in patients' demographic and neurological characteristics included in the follow-up study than those from the initial registry (Supplementary Table S2). The follow-up was done by phone interview (n = 49) or during a medical visit (n = 11). Results are shown in Table 2.

Of the 60 patients, 31 (51.7%) had a residual disability (mRS \geq 2). Slight disability (mRS = 2) was found in ten patients (16.7%) who were able to look after their affairs without assistance but unable to carry out all previous activities. Disability was moderate in 11 patients (18.3%) (mRS = 3). These patients required some help but able to walk without assistance. Ten (16.6%) had a severe residual disability, two of them (3%, mRS = 4) were unable to walk without assistance and unable to attend to their own bodily needs without assistance, and eight (13.3%, mRS = 5) were bedridden and required constant nursing care and attention. Severely disabled patients could not perform tests or questionnaires concerning the quality of life, memory complaints, cognitive and sensory deficit. NeuroCOVID had a negative impact on the quality of life in 49% of cases (25/51 patients). The most altered sub-scores were mobility, with 35% of patients reporting having problems walking, and pain with 43% having moderate pain and 15% severe pain. Thirty-four percent (17/50 patients) had residual memory complaints. The MoCA-Blind score was abnormal ($<$ 19/30) in 68.9% of cases (31/45 patients). Fourteen patients (28%, 14/50 patients) had anxiety symptoms, and eight patients (16%, 8/50 patients) reported symptoms of depression. Overall, 32% (16/50 patients) presented at least one symptom of anxiety or depression. Smell or taste persistent disorder was found in twenty-three patients (45%, 23/51 patients) six months after NeuroCOVID.

In multivariate analysis, age was found as a risk factor of impaired quality of life (OR 1.06 per year, 95% CI 1.01, 1.13, $P = 0.026$). Neither age, sex, neurological comorbidities, the severity of COVID-19, type of neurological manifestation was associated with residual disability, cognitive impairment, depression or anxiety, or the presence of a sensory deficit.

4. Discussion

Our study describes the long-term course of NeuroCOVID. Half of our patients had residual disability and impaired quality of life six months after the acute phase. Cognitive difficulties, anxious and depressive symptoms, and smell/taste disorders were the most frequent neuropsychiatric sequelae. Interestingly, we found that age predicts the long-term alteration of QoL after NeuroCOVID. This emphasizes the need for special attention and long-term care over months in patients with NeuroCOVID, particularly in the oldest patients.

Our study has limitations. First, the retrospective nature of the study puts at risk the possibility of recall bias. Second, many patients from the registry refuse to answer the phone

interview, introducing a bias of selection. The study group was comparable to the registered population (Supplementary Table), which partially limits this bias. The relatively small number of patients could also have led to a lack of statistical power. Additionally, in the absence of a control group of COVID patients with no neurological manifestation, we cannot definitively distinguish the impact of neurological involvement from the consequences of COVID in other organs and functions. Lastly, the lack of comprehensive information on the premorbid functional status of our patients could represent another difficulty for results interpretation.

Half of our patients (49%) reported an alteration of their QoL six months after discharge. It is consistent with the findings of a previous 6-month follow-up studies in older COVID-19 patients with or without neurological involvement (median 74 years versus 66 years in our study) discharged from hospital [24]. Age is reported as a predictor of residual impaired quality of life in a previous 3-month follow-up study of COVID-19 patients [25]. In some COVID-19 series, patients are primarily classified according to the severity of the disease without detailed information about specific involvement of various organs, including nervous system [24–26]. The long-term consequences of neurological impairment on the QoL could be drowned in those of severe overall impairment. In our younger population, a significant recovery of the worsening of the neurological symptoms within six months after the acute phase, a lack of control group, or a lack of statistical power could have prevented us to detect a potential impact of neurological damage on the alteration in the quality of life.

In our study, preexisting neurological comorbidities, reported in 17% of patients, were not statistically related to a poor neuropsychiatric outcome at six months. In retrospective COVID-19 hospital-based cohort studies, preexisting neurological diseases were found as an independent risk factor for poor outcomes during the acute phase [27,28] and at discharge [29–31]. Furthermore, worsening of preexisting neurological conditions was frequently observed immediately after a COVID-19 [30–32]. A significant recovery of the worsening of the neurological comorbidity six months after the acute phase or a lack of statistical power could explain this discordant result in our study.

Anxiety and depression were present six months after discharge in 10-31% in cohort studies of COVID-19 patients [3,5,33], and in 25-46% in a recent prospective study among hospitalized COVID-19 patients with neurological complications [34]. These symptoms were detected in the same proportion in our study (32%), and no risk factors were identified. The severity of COVID-19 disease was previously identified as a risk factor for developing anxiety disorders [3]. It was not found in our study (43% with severe or critical disease), possibly due to the lack of statistical power.

Persistent cognitive impairment ranged from 36% and 65% of COVID-19 patients three/four months after discharge [5,33,35], and in 50% of patients with neurological complications of COVID-19 during the index hospitalization [34]. The higher proportion in our

study (68.9%) could be explained by the use of various cognitive tests. Critically ill patients are known to have a risk of developing cognitive impairment 12 months after discharge due to a longer duration of delirium (mainly sedative-associated-delirium), sepsis, hypoxemia, and doses of sedatives [36]. This condition explains a part of persistence of cognitive impairment in 43% of our patients but is probably not the only cause of this condition since around 60% of patients had persistent cognitive disorders after seven months, even in mild COVID-19 [4]. Prolonged systemic inflammation might predispose to persistent depression and associated neurocognitive dysfunction [37]. Whether prolonged cognitive impairment might be related to pathological changes associated with critical illness-related encephalopathy or specific to SARS-CoV-2 infection remains unclarified. Retrograde neuroinvasion from the olfactory sensory neurons to their downstream brain structures is likely to be involved in selective neurological damage related to SARS-CoV-2 infection [38]. Other possible gateways to the CNS comprise the blood-brain barrier epithelium and brain infiltration by peripheral immune cells [38].

Loss of smell or taste is a frequent symptom of acute COVID-19 [39,40]. Various non-exclusive pathogenic mechanisms can account for these manifestations, namely obstruction of the olfactory cleft [41], perturbation of supporting cells of the olfactory epithelium [42], alteration of olfactory sensory neurons neurogenesis [43], and secondary neurological damage related to edema in the olfactory bulb [44,45]. A recent study indicates that olfactory neuroepithelium is an important site of SARS-CoV-2 infection and that SARS-CoV-2 persistence and related inflammation likely account for the prolonged loss of smell in patients [38]. When detected by a specific questionnaire, olfactory dysfunction was found in 51.3% of mild symptomatic COVID-19 patients one month after the acute phase [46] and 60% after six months [7], which is closed to our result (45%) after six months. The balance of patients with smell or taste sequelae is lower (between 10 and 20%) when patients are simply asked about the presence of smell or taste symptoms [47,48].

NeuroCOVID likely carries a risk of long-term neuropsychiatric disability. Further NeuroCOVID cohort studies using control groups are needed to assess specific long-term outcomes of neurological manifestations associated with COVID-19 infection and clarify their pathogenesis.

Disclosure of interest

H. Chaumont: received travel grants from PEPS development, Roche and Pfizer. E. Roze: served on scientific advisory boards for Orkyn, Aguetant, Merz-Pharma; received honoraria for speeches from Orkyn, Aguetant, Merz-Pharma, Medday-Pharma, Everpharma, International Parkinson and Movement disorders Society; received research support from

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Table 1 Demographic and neurological characteristics

At acute phase	n (%)
N	60
Age , median (IQR)	66 (55-73)
Male	36 (60.0%)
Neurological comorbidities	
No	50 (83.3%)
Yes ^{&}	10 (16.7%)
Severity of COVID-19	
Mild/Moderate	34 (56.7%)
Severe/Critical	26 (43.3%)
Neurological manifestations in the acute phase	
Stroke	18 (30.0%)
Encephalopathy	18 (30.0%)
Encephalitis-Meningitis	8 (13.3%)
Other CNS [‡]	6 (10.0%)
PNS [§]	5 (8.3%)
Undetermined mechanism	5 (8.3%)
Anosmia	4 (6.7%)
Ageusia	3 (5.0%)
Type of stroke	
Ischemic stroke	14 (23.3%)
Transient ischemic attack	3 (5.0%)
Intracerebral hemorrhage	1 (1.7%)
Cerebral venous thrombosis	0 (0%)

Abbreviations: IQR: Inter Quartile Range; CNS: central nervous system; PNS: peripheral nervous system.

[&]Stroke (n = 3), neurodegenerative disorder (n = 3), epilepsy (n = 2), others (n = 2).

[‡]Transient alteration of consciousness (n=3), isolated seizure (n=2), and generalized myoclonus with cerebellar ataxia (n=1).

[§]Peripheral complications of intensive care unit (n=2), Guillain-Barre syndrome (n=3).

TABLE 2 Characteristics of NeuroCOVID patients at the follow-up evaluation

	n/N	%	95% CI
Disability (mRS^a)			
Score - median (IQR)	2 (1-3)		
0-1	29/60	48.3	35.2 - 61.6
2-5	31/60	51.7	38.4 - 64.8
Quality of live (EQ-5D-3L^b)			
Not altered	26/51	51.0	36.6 - 65.2
Altered	25/51	49.0	34.8 - 63.4
Memory complain (CDS)			
Score - median (IQR)	11 (5-18)		
Normal (<15)	33/50	66.0	51.2 - 78.8
Abnormal (≥15)	17/50	34.0	21.2 - 48.8
Cognitive assessment (MoCA-Blind)			
Score - median (IQR)	17 (14-19)		
Normal (≥19)	14/45	31.1	18.2 - 46.6
Abnormal (<19)	31/45	68.9	53.4 - 81.8
Anxiety - Depression (HADS^c)			
Anxiety score - median (IQR)	5 (1-9)		
Depression score - median (IQR)	2 (1-6)		
Not altered	34/50	68.0	53.8 - 80.5
Altered	16/50	32.0	19.5 - 46.7
Taste and Smell Survey (TSS^d)			
Taste score - median (IQR)	0 (0-4)		
Smell score - median (IQR)	0 (0-3)		
Not altered	28/51	54.9	40.3 - 68.9
Altered	23/51	45.1	31.1 - 59.7

Abbreviations: 95% CI: 95% Confidence Interval; IQR: Inter Quartile Range; mRS: modified Rankin Scale; EQ-5D-3L: 3-level version of the EuroQol five-dimension scale; CDS: 35-item version of Cognitive Difficulties Scale; MoCA-Blind: Montreal Cognitive Assessment Blind; HADS : Hospital Anxiety and Depression Scale; TSS: Taste and Smell Survey.

^a 0: no symptoms at all; 1: no significant disability despite symptoms; able to carry out all usual duties and activities; 2: slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3: moderate disability; requiring some help, but able to walk without assistance; 4: moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5: severe disability; bedridden, incontinent and requiring constant nursing care and attention.

^b Significant alteration when more than one question is at least two points (example: 12211, 21112...).

^c Altered when at least one score, depression or anxiety was > 7 .

^d Altered when at least one score, taste or smell was ≥ 1 .

Figures Legends

Fig 1 Enrollment and outcome in the French NeuroCOVID multicenter registry

