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Review Article

Features of Neurologic Manifestations in Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Impact on COVID-19 Patients Outcome: A Cohort-Study

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Abstract

Background and purpose: Spectrum of clinical manifestations of coronavirus disease 2019 (COVID-19) includes central and peripheral neurologic symptoms. We aimed to characterize neurologic manifestations in hospitalized patients, notably in terms of time line and impact on outcome.

Methods: Retrospective cohort including during a 4 weeks-period consecutive COVID-19 patients admitted in general ward (mild forms) or in intermediate or intensive care unit (severe forms). Clinical and paraclinical examinations were reviewed blindly to outcomes evaluated at hospital discharge or day 28 after admission (with a six-point Acute Respiratory Disease Syndrome outcome scale and with the modified Rankin Scale). Poor respiratory outcome was hospitalization with supplemental oxygen, with or without mechanical ventilation, or death. Poor functional outcome was moderate to severe disability or death.

Results: 101 patients were included: 58 (57%) with mild and 43 (43%) with severe forms. 75 (74%) patients displayed neurologic symptoms: 58 (57%) with central and 40 (40%) with peripheral neurologic symptoms. Neurologic features did not differ between mild and severe forms. Extra neurologic symptoms, occurring at median day -4 [(-21) - 0] before hospitalization, preceded neurologic symptoms, with median for first occurrence on day 0 [(-30) - (+23)] ($p < 0.001$). Neurologic symptoms had no impact on respiratory nor functional outcomes. Only central neurologic symptoms were associated with poorer functional outcome ($p = 0.04$).

Conclusion: Neurologic manifestations seem to be a common feature in COVID-19 hospitalized patients. Most frequently, neurologic symptoms come after extra neurologic symptoms and have no impact on respiratory outcome. However, central neurologic symptoms may be associated with poorer functional outcome.

Keywords

COVID-19, Nervous system, Clinical manifestations, Prognosis

Introduction

In December 2019, a pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China [1]. In January 2020, the first case in Europe was confirmed in France, and later on, Europe became in March 2020, the epicenter of the Coronavirus Disease 2019 (COVID-19) pandemic. Attention was initially paid to respiratory symptoms of this new disease [2-5], but thereafter, neurologic manifestations were pointed out in few reports, especially because coronaviruses (CoVs) are known to have neurotropic and neuroinvasive properties [6]. However, these investigations were restricted to subpopulations of COVID-19 patients, such patients with mild form of the disease [7] or, on the contrary, with severe form [8]. Moreover the temporal sequence of apparition of neurologic symptoms was partially known with few data on timing of onset in relation to extra-neurologic symptoms, questioning the possibility that COVID-19 patients may display neurologic features at the forefront [9], isolated or preceding and partially explaining respiratory symptoms through coronaviruses neurotropism. Lastly, impacts of neurologic symptoms on COVID-19 patients' outcome were unknown [10].

Herein, is described a cohort, designed in a French University Hospital, including all the hospitalized patients with a polymerase chain reaction (PCR) analysis-confirmed diagnosis of COVID-19 during a 4 weeks-period after the first case hospitalized.

Our objectives were first to present an overview of neurologic symptomatology in a representative cohort of hospitalized forms of COVID-19 (i.e. mild as severe forms), and notably, to evaluate in which extent COVID-19 patients display neurologic symptoms. Secondly, we wanted to establish the timeline of symptoms, including central and peripheral neurologic symptoms, as extra-neurologic symptoms. Thirdly, we wanted to evaluate the impact of neurologic symptoms on COVID-19 patients' respiratory and functional outcome.

Patients and Methods

According to the French law [11], ethical approval for this study was obtained from the French Ethics Committee for Research in Anesthesia and Critical Care (IRB number: 00010254-2020067). The report of this cohort-study is in accordance with the STROBE statements.

Patients, COVID diagnosis, and severity condition

A retrospective cohort-study was designed including all consecutive adults (≥ 18-year-old) hospitalized in the University Hospital of Caen, Normandy, France, with a PCR analysis-confirmed diagnosis of COVID-19, during a 4 weeks-period after the first COVID-19 patient hospitalized in the institution. In March and April 2020, patients already hospitalized, or referred to the University Hospital of Caen, whatever the reason for referral, with fever, throat pain, shortness of breath, breathing difficulties or cough, were screened in order to diagnose COVID-19. Patients with a positive SARS-CoV-2 nucleic detection were considered as COVID-19 patients. Then, they were managed in different settings [12] mainly according to their respiratory supportive care requirements as following: Need for supplemental oxygen less than 5 L/min: General hospital ward; need for supplemental oxygen upper to 5 L/min or rapid increase of oxygen requirement: Intermediate care unit (IMCU); intubation with mechanical ventilation: Intensive Care Unit (ICU). Severity of patients' condition was stratified in two levels according to the maximal intensity of care required during their hospitalization: Mild form: No IMCU nor ICU admission during the hospitalization; severe form: At least once stay in IMCU or ICU during the hospitalization.

Neurologic and extra-neurologic manifestations

Neurologic as extra-neurologic manifestations mentioned in medical records were reviewed with a standardized form and confirmed independently of any outcome information by two investigators. Disagreement between the two reviewers was resolved by consultation with a third reviewer. Neurologic manifestations were categorized into three categories [10]: Central nervous system (CNS) manifestations (headache, dizziness, delirium, ataxia, seizure, impaired consciousness, and acute cerebrovascular disease), peripheral nervous system (PNS) manifestations (smell, taste or vision impairment, neuropathic pain), and skeletal muscular symptoms. Extra-neurologic manifestations were categorized as following: Fever (temperature ≥ 38°), throat pain, cough, dyspnea, and abdominal pain. Time to onset for symptoms was determined relatively to the day of hospital admission (day of hospital admission was considered as day 0).

Neuroimaging

Neuroimaging - computed tomography or magnetic resonance imaging (MRI, 1.5T) - was performed according to institutional guidelines, in case of neurologic manifestations. MRI when performed included systematically fluid attenuated inversion recovery, diffusion weighted and T2* weighted sequences. All radiologic examinations were retrospectively reviewed by two trained neuro-radiologists independently of any outcome information.

Electrophysiological assessment

The electroencephalograms (EEGs) were recorded with 8 or 19 electrodes placed according the international 10-20 system and were retrospectively reviewed by a neurophysiologist expert, blinded to patient's outcome.

Laboratory findings

Laboratory analyses (biochemistry, hematology, microbiology, virology) were performed according clinical care needs and were retrospectively screened in order to highlight significant differences between patients with or without neurologic manifestations.

Patient outcomes

Respiratory outcome was evaluated at hospital discharge or day 28 after admission with a six-point ordinal scale assessing Acute Respiratory Disease Syndrome (ARDS) outcome [13]: 1) Not hospitalized; 2) Hospitalized, not requiring supplemental oxygen; 3) Hospitalized, requiring supplemental oxygen; 4) Hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5) Hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 6) Death. Poor respiratory outcome was considered for respiratory scale score > 2. Functional outcome was evaluated at hospital discharge or day 28 after admission with the modified Rankin Scale (mRS): 0) No symptoms; 1) No significant disability; 2) Slight disability; 3) Moderate disability; 4) Moderately severe disability; 5) Severe disability; 6) Death. Poor functional outcome was considered for mRS score > 2.

Statistics

Categorical variables were reported as count and proportions, and continuous variables as median with minima and maxima. Statistical tests were performed for categorical (Fisher exact test or Chi [2]) and continuous variables (Mann-Whitney or Student's t-test) when appropriate. Time to event for apparition of symptoms was reported with Kaplan-Meier curves along with log-rank test. All P values were 2-tailed, and a P value of < 0.05 was required to reject the null hypothesis. Statistical analysis was performed using R: A Language and Environment for Statistical Computing (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and specific packages.

Results

Participants

In the four following weeks after the first COVID-19 patient admission in the University Hospital of Caen in March 2020, 101 patients were hospitalized with a polymerase chain reaction (PCR) analysis-confirmed diagnosis of COVID-19 and were included in the present cohort with full follow-up and analyzed data. Slightly

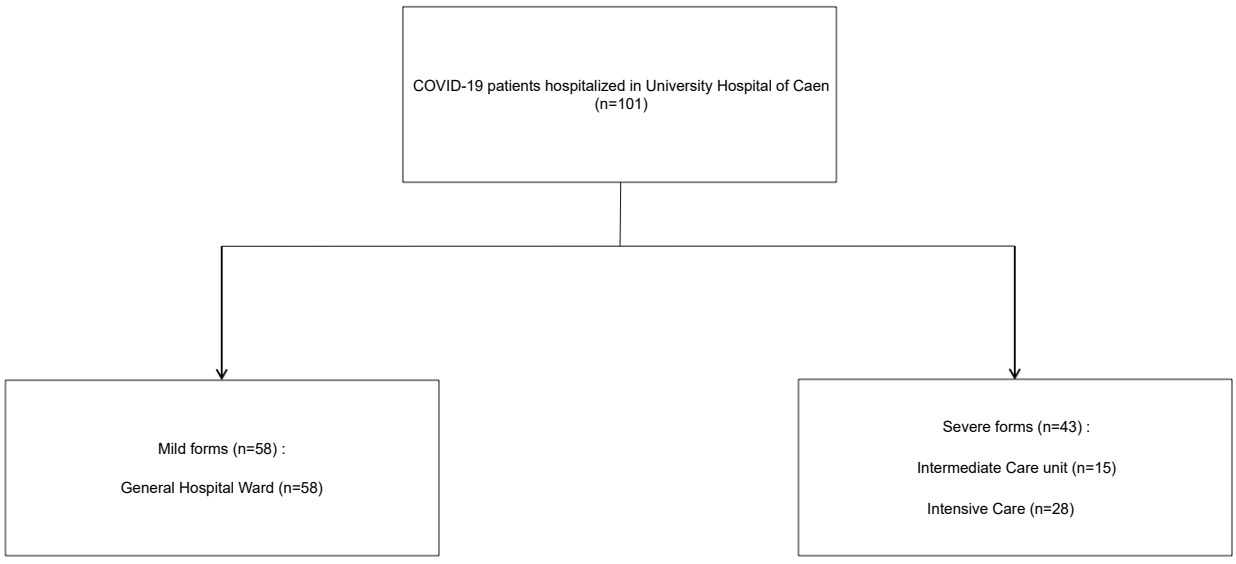

Figure 1: Flow diagram. In the first four following weeks after the first COVID-19 patient admission, 101 patients were admitted in the University Hospital of Caen for more than 48 hours. Fifty-height patients remained in general hospital ward while 15 required at least one admission in Intermediate Care Unit and 28 in Intensive Care Unit.

more than half of the cohort (57%) remained in general hospital ward while around one fourth (27%) required admission in ICU (Figure 1).

Demographic and clinical characteristics

Most of the patients were male with a median age of 67-years-old (Table 1). At the time of admission, the most reported pre-existing medical condition was hypertension (45%) and the most current treatment was anti-platelets (23%). Extra-neurological symptoms were present in 98 patients (97% of the cohort) with mainly in descending order: Dyspnea (81%), cough (80%), and fever (69%). Neurological symptoms were reported in 75 patients (74% of the cohort). CNS symptoms in 58 patients were mainly delirium (29 patients), impaired consciousness (24 patients), and headache (17 patients). PNS symptoms reported in 40 patients were skeletal muscular symptoms (29 patients), taste (23 patients), and smell (14 patients) impairment. Univariate comparison of characteristics between severe and mild form showed than the proportion of male was significantly higher in the former than in the latter: 31 (72%) versus 30 (52%), p = 0.04.

Onset of symptoms to hospital admission

Extra-neurologic symptoms, with median first occurrence on day -4 [(-21) - 0] before hospitalization, preceded peripheral and central neurologic symptoms,

Table 1: Demographic and clinical characteristics of COVID-19 patients with mild and severe form of the disease.

Characteristics		Total (N = 101)	Mild forms (N = 58)	Severe forms (N = 43)	p-value
Demographics	Age (y.o.), median [min-max]	67 [24-92]	66 [24-92]	64 [28-89]	0.32
	Male, n (%)	61 (60%)	30 (52%)	31 (72%)	0.04
	Body Mass Index, median [min-max]	27 [16-50]	26 [16-43]	27 (21-50)	0.32
Comorbidities	Hypertension, n (%)	45 (45%)	28 (48%)	17 (40%)	0.38
	Diabetes, n (%)	18 (18%)	11 (19%)	7 (16%)	0.73
	Tobacco use, n (%)	4 (4%)	2 (3%)	2 (5%)	0.76
	Stroke, n (%)	9 (9%)	7 (12%)	2 (5%)	0.19
	Dementia, n (%)	5 (5%)	4 (7%)	1 (2%)	0.29
	Reduced autonomy, n (%)	9 (9%)	9 (16%)	0 (0%)	0.01
Treatments	Antiplatelets, n (%)	23 (23%)	17 (29%)	6 (14%)	0.11
	Anticoagulant, n (%)	14 (14%)	8 (14%)	6 (14%)	1
	Nonsteroidal Anti-inflammatory Drug, n (%)	1 (1%)	1 (2%)	0 (0%)	0.39
Extra-neurological symptoms	Any extra-neurological symptoms, n (%)	98 (97%)	55 (95%)	42 (98%)	0.39
	Fever, n (%)	70 (69%)	39 (67%)	31 (72%)	0.82
	Throat pain, n (%)	2 (2%)	2 (3%)	0 (0%)	0.22
	Cough, n (%)	81 (80%)	45 (78%)	36 (84%)	0.8
	Dyspnea, n (%)	82 (81%)	44 (76%)	38 (88%)	0.11
	Abdominal pain, n (%)	13 (13%)	10 (17%)	3 (7%)	0.13
Neurological symptoms	Any neurological symptoms, n (%)	75 (74%)	44 (76%)	31 (72%)	0.67
	Central neurologic symptoms, n (%)	58 (57%)	35 (60%)	23 (53%)	0.49
	Headache, n (%)	17 (17%)	12 (21%)	5 (12%)	0.23
	Dizziness, n (%)	3 (3%)	3 (5%)	0 (0%)	0.13
	Delirium, n (%)	29 (29%)	15 (26%)	14 (33%)	0.46
	Ataxia, n (%)	1 (1%)	1 (2%)	0 (0%)	0.39
	Seizure, n (%)	3 (3%)	3 (5%)	0 (0%)	0.13
	Impaired consciousness, n (%)	24 (24%)	17 (29%)	7 (16%)	0.13
	Peripheral neurologic symptoms, n (%)	40 (40%)	20 (34%)	20 (47%)	0.22
	Smell impairment, n (%)	14 (14%)	6 (10%)	8 (19%)	0.23
	Taste impairment, n (%)	23 (23%)	10 (17%)	13 (30%)	0.12
	Skeletal muscular symptoms, n (%)	29 (29%)	16 (28%)	13 (30%)	0.77

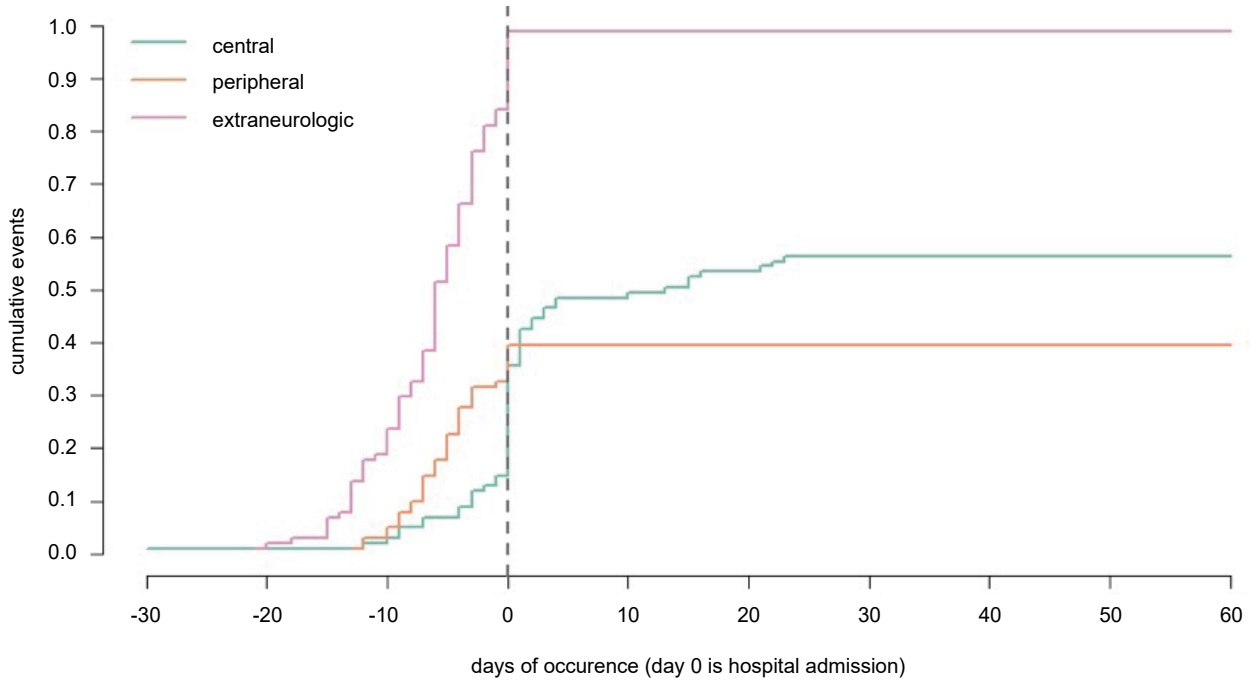

Figure 2: Time to onset for extra neurologic, central and peripheral neurologic symptoms (with day of hospital admission as day 0). Extra-neurologic symptoms, with median first occurrence on day -4 [(-21) - 0] before hospitalization, preceded peripheral and central neurologic symptoms, with median for first occurrence on day 0 [(-30) - (+23)] (log-rank test: p < 0.001).

with median for first occurrence on day 0 [(-30) - (+23)] (log-rank test: p < 0.001) (Figure 2). Median day of taste and/or smell impairment reporting was day -4 [(-13) - (+1)]. Considering the 75 patients with neurologic symptoms, 8 (11%) displayed neurologic symptoms before extra-neurologic symptoms, 32 (43%) concurrently and 35 (47%) neurologic symptoms after extra-neurologic symptoms.

Paraclinical examinations: Neuroimaging, electrophysiological assessment and laboratory findings

MRI was performed in 7 patients and did not reveal any acute finding. Three patients had electrophysiological studies: EEGs in each case. Two patients had reactive diffuse non specific non-epileptiform background slowing and one had frontal intermittent rhythmic delta activity pattern consistent with encephalopathy. Comparison of laboratory findings between patients with and without neurologic manifestations did not show any significant differences. Lumbar punctures were performed in two patients: SARS-CoV-2 ribonucleic acid could not be detected in cerebrospinal fluid samples.

Patients outcome

Outcomes until hospital discharge or day 28 after admission were available for all the patients. In hospital mortality was 10% (8% for mild versus 19% for severe forms, p = 0.01). Median ARDS outcome scale at day 28 or discharge was 1 [1-6] (1 [0-6] for mild versus 2 [1-6] for severe forms, p = 0.005). Poor respiratory outcome (supplemental oxygen, nasal high-flow oxygen therapy, noninvasive or invasive mechanical ventilation or death) was observed for19% of the cohort (11% for mild versus 30% for severe forms, p = 0.01). Median mRS at day 28 or discharge was 2 [0-6] (2 [0-6] for mild versus 4 [0-6] for severe forms, p = 0.005). Poor functional outcome (moderate to severe disability or death) was described for 48% of the cohort (35% for mild versus 65% for severe forms, p = 0.002).

Neurologic manifestations and outcomes

Mortality did not differ significantly between patients with or without neurologic manifestations (respectively 7% versus 19%, p = 0.19) (Figure 3). Neurologic manifestations had no impact on median ARDS outcome scale at day 28 or discharge (1 [1-6] in case of neurologic manifestations versus 1 [0-6] in absence of neurologic manifestations, p = 0.41), nor on the proportion of patients with poor respiratory outcome (19% in case of neurologic manifestations versus 27% in absence of neurologic manifestations, p = 0.40). Median mRS at day 28 or discharge did not differ in case of neurologic manifestations or without (respectively 49% versus 50%, p = 1.00).

Central neurologic manifestations had no impact on mortality (respectively 9% versus y: 2 [0-6] versus 3 [0-6], p = 0.60) nor the proportion of patients with poor functional outcome (respectively: 12% for patients without CNS, p = 0.74), on median ARDS outcome

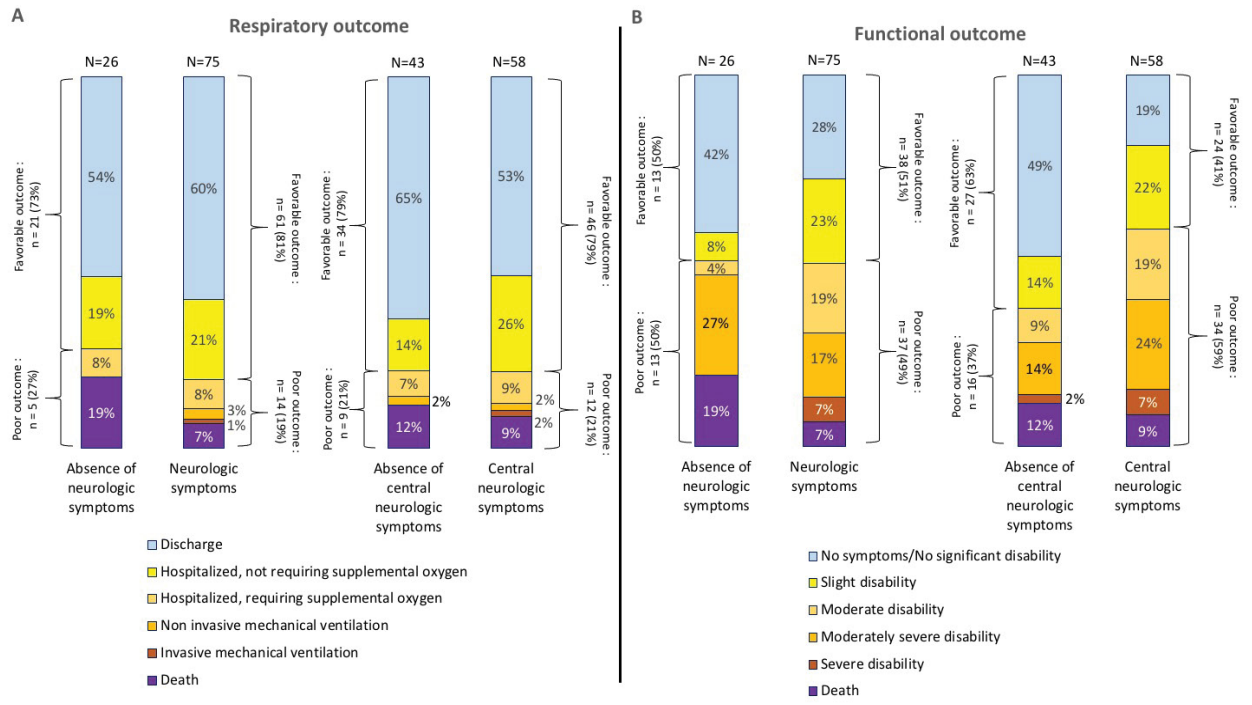

Figure 3:

(A): Respiratory outcome at day 28 or discharge, assessed with the Acute Respiratory Disease Syndrome (ARDS) outcome scale (which range from 1 = discharge, to 6 = death), with poor respiratory outcome defined by respiratory scale score > 2. The numbers above the bars are the total numbers of patients in each subgroup, and the numbers in the bars are percentages of patients with each score of the scale.

Distribution of scores on ARDS outcome scale did not differ significantly in case of presence or absence of neurologic symptoms (p = 0.84) and proportion of poor respiratory outcomes did not differ between patients with and without neurologic symptoms (respectively 19% versus 27%, p = 0.40).

Distribution of scores on ARDS outcome scale did not differ significantly in case of presence or absence of central neurologic symptoms (p = 0.65) and proportion of poor respiratory outcomes did not differ between patients with and without neurologic symptoms (respectively 21% versus 21%, p = 1.00).

(B) Functional outcome at day 28 or discharge, assessed with the modified Rankin Scale (mRS) which range from 0-1 = no symptoms/no significant disability to 6 = death. Poor functional outcome was defined by mRS > 2. The numbers above the bars are the total numbers of patients in each subgroup, and the numbers in the bars are percentages of patients with each score of the scale.

Distribution of scores on mRS outcome scale differed significantly in case of presence or absence of neurologic symptoms (p = 0.03), but proportion of poor functional outcomes did not differ between patients with and without neurologic symptoms (respectively 49% versus 50%, p = 1.00).

Distribution of scores on mRS outcome scale differed significantly in case of presence or absence of central neurologic symptoms (p = 0.04) and proportion of poor functional outcome was significantly higher in patients with central neurologic symptoms versus patients without central neurologic symptoms (respectively 59% versus 37%, p = 0.04).

scale at day 28 or discharge (1 [1-6] versus 1 [0-6], p = 0.41) for patient without CNS), nor on the proportion of patients with poor respiratory outcome (21% versus 21% for patient without CNS, p = 1.00). Median mRSat day 28 or discharge did not differ significantly with or without CNS (respectively 3 [0-6] versus 2 [0-6], p = 0.07). In contrast, CNS was associated with poorer functional outcome: 59% for patients with CNS versus 37% for patients without CNS (p = 0.04).

Taste and/or smell impairment (compared with absence of reporting of these symptoms) had no significant impact on any outcomes: Nor in hospital mortality (respectively 0% versus 13%, p = 0.11), median ARDS outcome scale at day 28 or discharge (respectively 1 [1-4] versus 1 [1-6], p = 0.12), proportion of patients with poor respiratory outcome (respectively 13% versus 23%, p = 0.39), median mRSat day 28 or discharge (respectively: 2 [0-5] versus 3 [0-6], p = 0.83), or the proportion of patients with poor functional outcome (respectively: 46% versus 51%, p = 0.82).

Discussion

In a representative cohort of the spectrum of COVID-19 hospitalized forms (i.e. mild as severe forms), a majority of patients (74%) displayed neurologic symptoms including central (57%) and peripheral (40%). The order of apparition of symptoms is more frequently: First extra-neurologic and then neurologic

symptoms. Neurologic symptoms, including taste and/or smell impairment, have no impact on mortality nor respiratory or functional outcome. The only association with patient's outcome observed was with central neurologic symptoms associated with poorer functional outcome.

Our observational study has several limitations. First the size of our population is limited and data are issued from a monocentric registry. But our registry is exhaustive including all the COVID-19 patients hospitalized over a given period of time. Larger and multi centric retrospective cohorts have been described [14] but, in contrast with our study, do not systematically report data relative to COVID-19 patients free of neurologic symptoms and, if based on a voluntary basis for patients recruitment, could be affected by a recruitment bias. Secondly, some symptoms reported here, like throat pain or headache for example, are subjective symptoms felt and expressed by patients in contrast with physical signs like dyspnea or impairment of consciousness that can be objectively reported by physicians. Thirdly, due to our retrospective design, our investigations were restricted only to data available on medical records and we were not able to use more accurate methods to define some symptoms. For example, anosmia or dysgeusia were not screened using a standardized questionnaire [15] and creatine kinase was not systematically dosed for hospitalized COVID-19 patients in order to detect skeletal muscle injury. At last, the follow-up of the patients was restricted to a maximum of 28 days after hospital admission. This end-point is not relevant for evaluation of potential long-term consequences of COVID-19. Indeed for example, the question has been raised whether SARS-CoV-2 infection could favor installation of psychological manifestations [16] and/or neurodegenerative diseases [17].

Never the less, some information can be drawn from our cohort. Our report indicates a high frequency of neurologic manifestations (74%). This elevated incidence contrasts with the lower frequency (36.4%) reported in the first available cohort studying neurologic features of COVID-19 [10]. This discrepancy could be related to the difference between population characteristics of these two studies. A more recent report identified age > 60 y.o. and previous neurological conditions as risk factors for critical neurologic events in COVID-19 patients [18]. Comparison of our cohort with Mao and collaborators' one, shows that our patients were older (mean+/-SD: 65.6+/-16.2 y.o. versus 52.7+/-15.5 y.o.), with more male (59% versus 40%) and with probably more neurologic disease in their medical history (9% in our cohort presented stroke before disease onset versus 7% patients in cohort of Mao, et al. who had previously cerebrovascular or cardiac disease). More consistently with our observations, in a cohort of mean age of 66.4 ± 15 y.o. with 56.2% of males and 6.3% of patients with prior stroke, Romero-Sánchez, et al. reported 57.4% of the patients with neurologic symptoms [19]. A further difference with previously reported observations [10] is that neurologic symptoms did not differ significantly in our cohort between mild and severe forms of the disease.

Describing neurologic manifestations of COVID-19 is of interest since a possible entry of SARS-CoV-2 in central nervous system, notably via cribri form plate, was hypothesized, possibly explaining loss of involuntary control of breathing and then acute respiratory insufficiency in COVID-19 patients [20,21]. Our observations could not support this hypothesis since occurrence of neurologic symptoms does not seem to have any impact on respiratory outcome of COVID-19 patients. Moreover, respiratory symptoms most frequently precede neurologic symptoms (central as peripheral). This is consistent with other observations reporting neurologic manifestation as first symptom in only 20% of cases [14]. However, we have to be cautious on this point since clinical manifestations of SARS-CoV-2 infection could not be correlated to dissemination of the virus in organism.

Of note, our absence of findings of SARS-CoV-2 ribonucleic acid in cerebrospinal fluid samples is coherent with the scarcity of such observations [22,23]. As a matter of fact, presence of the virus in the central nervous system may not be the only way that could explain neurologic manifestations associated with SARS-CoV-2 infection. The virus could also cause neurologic insult indirectly through SARS-CoV-2 infection-induced hypoxia [24], cerebrovascular changes [9], exposure to inflammatory mediators [25], or even peripheral organ dysfunction. So far the exact mechanisms remain to be determined. Some singularities were reported in the neurologic manifestations of COVID-19 when compared with other virus diseases [26,27] but the scarcity and the heterogeneity of the paraclinical findings (imaging, electrophysiology, laboratory), herein and in other cohorts [8], does not argue in favor of a single and specific mechanism. More recently, a neuropathology post-mortem case series reported non-specific neuro inflammatory lesions such astrogliosis in an ubiquitous pattern and activated microglia with infiltration by cytotoxic T lymphocytes more pronounced in the brainstem and in the cerebellum [28]. In this series of fatal cases, the detection of SARS-CoV-2 in CNS was frequent (in 21 out of 40 brain investigated with PCR or immune histochemical analyses) but interestingly, the presence of SARS-CoV-2 in the CNS was not associated with the severity of the neuropathological changes. This

observation might also support an indirect mechanism responsible for CNS lesions associated with SARS-CoV-2 infection.

Although the spectrum of neurologic symptoms is increasingly reported in the literature [27], the impact of such manifestations on COVID-19 patients' outcome, in a cohort including both severe as non-severe forms, remains unknown. Regarding previous data analyzing neurologic manifestations, it could be hypothesized that neurologic symptoms would be associated with worse outcome since such clinical signs seemed to be more frequent in COVID-19 severe forms [10]. However, our results do not support this hypothesis since nor respiratory or functional outcomes were impacted by occurrence of neurologic manifestations. Only central neurologic symptoms appeared to be associated with worse functional outcome. This is consistent with clinical cases reporting poor outcome with central neurologic manifestations in COVID-19 patients [22].

Conclusion

Neurologic manifestations seem to be a common feature in COVID-19 hospitalized patients. Neurologic symptoms most frequently come after extra neurologic symptoms and are not associated with worse respiratory outcome. Only central neurologic manifestations could be taken into account in the estimation of the functional outcome of COVID-19 patients.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request.

Declaration of Interest

None.

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