Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full-length Article

Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) represents a novel pneumonia leading to severe acute respiratory syndrome (SARS). Recent studies documented that SARS-Coronavirus2 (SARS-CoV2), responsible for COVID-19, can affect the nervous system. The aim of the present observational study was to prospectively assess subjective neurological symptoms (sNS) in patients with SARS-CoV2 infection.

Methods: We included patients hospitalized at the University Hospital of Rome "Tor Vergata", medical center dedicated to the treatment of patients with COVID-19 diagnosis, who underwent an anamnestic interview about sNS consisting of 13 items, each related to a specific symptom, requiring a dichotomized answer.

Results: We included 103 patients with SARS-CoV2 infection. Ninety-four patients (91.3%) reported at least one sNS. Sleep impairment was the most frequent symptom, followed by dysgeusia, headache, hyposmia, and depression. Women more frequently complained hyposmia, dysgeusia, dizziness, numbeness/paresthesias, daytime sleepiness, and muscle ache. Moreover, muscle ache and daytime sleepiness were more frequent in the first 2 days after admission. Conversely, sleep impairment was more frequent in patients with more than 7 days of hospitalization. In these patients we also documented higher white blood cells and lower C-reactive protein levels. These laboratory findings correlated with the occurrence of hyposmia, dysgeusia, headache, daytime sleepiness, and depression.

Conclusions: Patients with SARS-CoV2 infection frequently present with sNS. These symptoms are present from the early phases of the disease. The possibly intrinsic neurotropic properties of SARS-CoV2 may justify the very high frequency of sNS. Further studies targeted at investigating the consequences of SARS-CoV2 infection on the CNS should be planned.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel pathology due to severe acute respiratory syndrome (SARS) – coronavirus-2 (CoV2) infection, currently representing a great global public health concern causing a SARS with a mortality higher than other acute pneumonia (Khalili et al., 2020). However, the majority of patients with infection develop mild to moderate respiratory illness, whose clinical manifestations are fever and cough (Bi et al., 2020). A part the respiratory illness, an increasing number of reports pointed out that SARS-CoV2 can also affect the nervous system, since neurological manifestations may occur quite frequently in hospitalized patients (National Health Commission of the People's Republic of China, 2020; Mao et al., 2020). COVID-19 has been associated with various neurological complications, such as acute cerebrovascular disease and seizures, as well as with several neurological symptoms, including

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myalgia, headache, confusion, and dizziness (Chen T et al., 2020; Chen N et al., 2020; Lechien et al., 2020). Moreover, hyposmia and dysgeusia have been reported as early manifestations of SARS-CoV2 infection (Lechien et al., 2020). A large retrospective analysis carried out in China on 214 patients affected by SARS-CoV2 infection confirmed that hospitalized patients complained of subjective neurological symptoms (sNS) in a 36.4% of cases, including headache, disturbed consciousness, and paresthesia as the most frequent (Mao et al., 2020). However, it is not well-defined whether neurological manifestations are consequences of hypoxia and prolonged hospitalization or rather they are related to the neurotropic properties of SARS-CoV2. Therefore, it has been proposed that the virus may infiltrate the central nervous system (CNS) by possibly passing the blood–brain barrier (BBB) or gathering the olfactory bulb and vagus nerve (Wu et al., 2020).

In order to carefully explore the presence of sNS during COVID-19, we conducted an observational study aimed at identifying and quantifying the occurrence of sNS by an anamnestic interview in hospitalized patients with SARS-CoV2 infection.

2. Methods

2.1. Patients and study design

The study was designed as an observational data collection carried out in patients affected by COVID-19. All patients were hospitalized at the University Hospital of Rome “Tor Vergata”, representing a medical center dedicated to the treatment of patients with a confirmed diagnosis of COVID-19.

Eligible patients had to meet the following inclusion criteria: be over 18-year-old, conscious, cognitively and mentally conserved, and linguistically competent to respond to the anamnestic interview; diagnosis of COVID-19 based on clinical suspicion and confirmed by viral RNA detection at oropharyngeal and nasopharyngeal swabs; be affected by non-severe respiratory form of COVID-19, as defined using the American Thoracic Society guidelines for community-acquired pneumonia (Metlay et al., 2019). Additionally, the access to patients’ demographic and clinical data, including their corporeal temperature (CT) and their ongoing pharmacological treatments, was mandatory for inclusion. Exclusion Criteria were: previous diagnosis of neurologic and psychiatric disorders; CT > 38 °C at the time of the anamnestic interview.

At the time of admission or during hospitalization, patients with COVID-19 fulfilling the entry criteria for the study underwent an anamnestic interview to investigate the presence of sNS. The interview consisted of 13 items, each related to a specific symptom, requiring a dichotomized answer (YES/NO): 1) hyposmia, 2) dysgeusia, 3) auditory dysfunction, 4) headache, 5) confusion, 6) dizziness, 7) numbness/paresthesia, 8) fatigue, 9) daytime sleepiness, 10) sleep impairment, 11) muscle ache, 12) depression, 13) anxiety.

All anamnestic interviews were collected by clinicians from the care units where patients were hospitalized, and reviewed and confirmed by two trained neurologists (CL and MP).

For the purpose of this observational study, we collected the following patients’ data: age, sex, CT, laboratory test, duration of hospitalization and sNS recorded at the time of anamnestic interview.

Laboratory testing was performed at the time of anamnestic interview and the following serum markers were included in the analysis: white blood cell (WBC) count, neutrophil total cell count and percentage of WBC, lymphocyte total cell count and percentage of WBC, C-reactive protein (CRP). Quantitative measurements of WBC and serum CRP were analyzed by an immunonephelometric method, performed on a Dimension System Vista (Siemens Healthcare Diagnostics).

2.2. Standard protocol approvals, registrations, and patient consents

All participants gave written informed consent after receiving an extensive disclosure of study purposes. The local ethics committee at University Hospital of Rome Tor Vergata approved the procedures (protocol no. 48.20, version 2020).

2.3. Statistical analysis

Statistical Package for the Social Sciences for Windows (SPSS version 22,0; IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses.

Categorical data were expressed as absolute frequencies and percentages where appropriate. The parametric data are presented using descriptive statistics (mean ± standard deviation). Proportions for categorical variables were compared using the χ^2test or ANOVA with post-hoc analysis, when appropriate. The significance threshold was set at a 2-sided *P* value less than 0.05.

3. Results

3.1. Demographic data

103 patients with a confirmed SARS-CoV2 infection were included in the analysis following the inclusion and exclusion criteria for the study within the time interval between 30th March and 24th April 2020. Fifty-nine patients were men and 44 patients were women. Thirty-three patients underwent the anamnestic interview to assess the sNS on the 1st and 2nd day after admission, 31 patients responded to the interview between the 3rd and 7th day of hospitalization, and the remaining 39 patients after the 7th day of hospitalization. Demographic and clinical characteristics are shown in Table 1 and Table 2.

3.2. sNS analysis

Within the whole sample of patients included in the study, 94/103 patients (91.3%) reported at least one sNS and only 9/103 patients (8.7%) did not report them at the anamnestic interview. In particular, 54/59 men (91.5%) and 40/44 women (90.9%) reported at least one sNS.

Among sNS complained by the whole group of patients (n = 103), sleep impairment resulted as the most frequent symptom (51/103; 49.51%); it was followed in order of prevalence by dysgeusia (48/103; 46.60%), headache (40/103; 38.83%), hyposmia (40/103; 38.83%), and depression (39/103; 37.86%). Moreover, we performed a sex-based analysis comparing the occurrence of sNS between men and women and documented that hyposmia, dysgeusia, headache, dizziness, numbness/paresthesia, daytime sleepiness, and muscle ache were more frequent in women than men (Table 1).

Distributing patients by the occurrence of sNS, 26/103 patients (25.24%) reported 1 or 2 sNS, and 68/103 patients (66.02%) complained 3 or more sNS (Table 3). In patients reporting 1 or 2 sNS (n = 26) sleep impairment was the most frequent complaint (11/26; 42.31%), followed by daytime sleepiness (7/26, 26.92%). In patients with 3 or more sNS (n = 68), dysgeusia was the main disturbance (46/68, 67.65%), followed by sleep impairment (40/68, 58.82%), hyposmia (38/68, 55.88%), headache (37/68, 54.41%), and depression (35/68, 51.47%) (Table 3).

When comparing the data achieved by the anamnestic interview during the period of hospitalization, we documented that sNS were more frequent in the first 2 days after admission and after the 7th day of hospitalization than in the period in between (Table 2). Muscle ache and daytime sleepiness were more frequent in patients evaluated on the first 2 days and in the period between the 3rd and 7th day after admission compared to patients with a hospitalization longer than 7 days; moreover, sleep impairment was more frequent after the 7th day of hospitalization than the other analyzed periods (Table 2).

Table 1
Demographic and clinical data of the whole group, also distributed for sex.

Demographic and Clinical Data	Total (n = 103)	Man (n = 59)	Woman (n = 44)	p Value
Age (Mean ± SD)	55 ± 14.65	56 ± 13.86	52.35 ± 15.64	*ns*
Temperature (Mean ± SD)	36 ± 0.45	36 ± 0.42	36.36 ± 0.49	*ns*
Inflammatory serum markers				
WBC (x10^9/L) (Mean ± SD)	8.55 ± 6.23	9.65 ± 7.44	6.61 ± 2.15	*0.0082*
Neutrophil, count (Mean ± SD)	5.9 ± 5.23	6.69 ± 6.18	4.5 ± 2.44	*0.0136*
Lymphocyte, count (Mean ± SD)	2.09 ± 4.35	2.41 ± 5.43	1.54 ± 0.65	*ns*
Neutrophil, %WB (Mean ± SD)	65.9 ± 18.7	0.67 ± 0.2	0.64 ± 0.15	*ns*
Lymphocyte, %WB (Mean ± SD)	24.22 ± 15.84	0.23 ± 0.17	0.25 ± 0.13	*ns*
CRP (Mean ± SD)	19.97 ± 34.56	21.49 ± 34.25	17.31 ± 34.92	*0.0024*
sNS				
0n (%)	9 (8.74)	5 (8.47)	4 (9.09)	*ns*
1–2n (%)	26 (25.24)	19 (32.2)	7 (15.91)	*ns*
≥ 3n (%)	68 (66.02)	35 (59.32)	33 (75)	*ns*
sNS distribution				
Any n (%)	94 (91.3)	54 (91.52)	40 (90.9)	*ns*
Hyposmia n (%)	40 (38.83)	16 (27.12)	24 (55.54)	*0.0047*
Dysgeusia n (%)	48 (46.60)	20 (33.9)	28 (63.63)	*0.0028*
Auditory Dysfunction n (%)	2 (1.94)	0 (0)	2 (5.26)	*ns*
Headache n (%)	40 (38.83)	16 (27.12)	24 (54.54)	*0.0047*
Confusion n (%)	23 (22.33)	12 (20.34)	11 (25)	*ns*
Dizziness n (%)	27 (26.21)	11 (18.64)	16 (36.36)	*0.0431*
Numbness/Paresthesia n (%)	6 (5.8)	0 (0)	6 (13.63)	*0.0035*
Fatigue n (%)	33 (32.04)	22 (37.29)	11 (25)	*ns*
Daytime Sleepiness n (%)	34 (33.01)	13 (22.03)	21 (47.72)	*0.0061*
Sleep Impairment n (%)	51 (49.51)	33 (55.93)	18 (40.9)	*ns*
Muscle Ache n (%)	25 (24.27)	8 (13.56)	17 (38.63)	*0.0033*
Depression n (%)	39 (37.86)	19 (32.20)	20 (45.45)	*ns*
Anxiety n (%)	34 (33.01)	18 (30.51)	16 (36.36)	*ns*

List of abbreviations: n, Number of patients; SD, Standard Deviation; WBC, white blood cells; CRP, C-reactive protein; sNS, Subjective Neurological Symptoms; ns, Not Significant.

3.3. Laboratory findings

Considering the sex-based distribution of patients, we documented higher WBC and CRP in man than women (Table 1). In patients evaluated after the 7th day of hospitalization, we documented higher WBC and lower CRP levels than the other two groups of patients (Table 2). Considering the subgroups of patients distributed based on the sNS, we did not find differences among the three groups (Table 3). Taking the sNS into account, we documented lower WBC in patients with hyposmia (6.13 ± 2.6 vs 10.03 ± 7.3, p = 0.027), dysgeusia (6.37 ± 2.55 vs10.9 ± 7.92, p = 0.008), headache (6.17 ± 2.19 vs 10.19 ± 7.44, p = 0.023), and daytime sleepiness (6.19 ± 1.61 vs 9.96 ± 7.37, p = 0.033). Moreover, in patients with depression we documented higher CRP (34.37 ± 49.41 vs 11.43 ± 16.55, p = 0.023).

4. Discussion

This observational study, carried out in 103 patients affected by SARS-CoV2 infection, documents the high prevalence of sNS during the course of the disease, even immediately after admission to the Hospital.

Although the involvement of nervous system during SARS-CoV2 infection has been extensively proposed (Pérez, 2020; Nath, 2020; Pleasure et al., 2020), few studies focused the investigation on neurological symptoms in patients with COVID-19 (Mao et al., 2020; Lechien et al., 2020). The largest study examining the neurological manifestations of hospitalized patients with COVID-19 was a retrospective analysis achieved by reviewing patients' clinical charts (Mao et al., 2020). The authors documented a neurological manifestation in 36.4% of cases, reporting that patients with severe COVID-19 showed more nervous system symptoms than patients with the non-severe form of infection (Mao et al., 2020). Moreover, other reports, not centered on the neurological manifestations of COVID-19, reported the presence of few neurological symptoms in patients with SARS-CoV2 infection (Chen T et al., 2020; Chen N et al., 2020; Xu et al., 2020; Huang et al., 2020). However, since all these studies have a retrospective design and data were achieved by the extraction from electronic medical records, detection of slight neurological manifestations, such as sleep and wake impairment, headache, dysgeusia, hyposmia, and dizziness, could be limited (Sun et al., 2020).

In the present study, we performed a prospective observation in patients with non-severe respiratory form of SARS-CoV2 infection by using an anamnestic interview designed to better determinate the occurrence and type of sNS over the course of the disease. Based on the prospective design of this examination, we documented a very high number of patients complaining sNS. Consistently, only 9 out of 103 patients (less than 10%) did not report sNS and more than 65% of the whole sample described three or more sNS at the interview. Namely, in the total group of patients, sleep impairment, dysgeusia, headache and hyposmia were the most frequent complained sNS. Notably, the frequency of sNS was elevated from the early phases of the disease, immediately after the admission to the hospital, remaining high also after a prolonged hospitalization. Considering the different timing of administration of the anamnestic interview in the patients included, muscle ache and daytime sleepiness were more frequent in the first two days after admission, whereas sleep impairment appeared more frequently after the 7th day of hospitalization.

Taking all the findings of this study into account, it appears evident that patients with SARS-CoV2 infection frequently experienced sNS. Accordingly, during the infection, sNS seem to be present from the very early stages of the disease and in some cases prior to the hospitalization, as previously reported (Lechien et al., 2020; Beltrán-Corbellini et al., 2020). We also document that patients reported more than one sNS during the prolonged hospitalization and sleep impairment was the main complain in those interviewed after the 7th day from admission. It

Table 2
Demographic and clinical data of the patients distributed according to the time of the anamnestic interview.

Demographic and Clinical Data	Group 1 1st-2th Day (n = 33)	Group 2 3th-7th Day (n = 31)	Group 3 >7th Day (n = 39)	*p Value*
Age (Mean ± SD)	53 ± 15.65	55 ± 12.44	58 ± 16.64	*ns*
Sex (M, F)	15, 18	15, 16	29, 10	*0.01* *1vs3 0.01* *2vs3 0.02*
Temperature (Mean ± SD)	36 ± 0.42	36 ± 0.41	36 ± 0.4	*ns*
Inflammatory serum markers				
WBC (x10^9/L) (Mean ± SD)	7.21 ± 4.59	6.1 ± 2.34	10.47 ± 7.65	*0.0057* *1 vs 3 0.028* *2 vs 3 0.0062*
Neutrophil, count (Mean ± SD)	5.35 ± 4.59	4.28 ± 2.64	7.03 ± 6.33	*ns*
Lymphocyte, count (Mean ± SD)	1.25 ± 0.84	1.29 ± 0.62	2.88 ± 6.01	*ns*
Neutrophil, %WB (Mean ± SD)	0.7 ± 0.26	0.66 ± 0.14	0.64 ± 0.22	*ns*
Lymphocyte, %WB (Mean ± SD)	0.2 ± 0.14	0.24 ± 0.12	0.26 ± 0.18	*ns*
CRP (Mean ± SD)	26.69 ± 43.83	36.93 ± 45.14	6.47 ± 12.13	*0.0008* *1 vs 3 0.009* *2 vs 3 0.0011*
sNS				
0n (%)	2 (6.06)	3 (9.68)	4 (10.26)	*ns*
1–2n (%)	7 (21.21)	9 (29.03)	10 (25.64)	*ns*
≥ 3n (%)	24 (72.72)	19 (61.29)	25 (64.10)	*ns*
sNS Distribution				
Any n (%)	30 (90.9)	24 (77.42)	37 (94.87)	*0.04* *1vs2 0.04* *2vs3 0.04*
Hyposmia n (%)	15 (45.45)	11 (35.48)	15 (38.46)	*ns*
Dysgeusia n (%)	16 (48.48)	12 (38.7)	20 (51.28)	*ns*
Auditory Dysfunction n (%)	0 (0)	1 (3.22)	1 (2.56)	*ns*
Headache n (%)	16 (48.48)	14 (45.16)	11 (28.2)	*ns*
Confusion n (%)	12 (36.36)	5 (16.12)	8 (20.51)	*ns*
Dizziness n (%)	9 (27.27)	7 (22.58)	11 (28.2)	*ns*
Numbness/Pareshesia n (%)	4 (12.12)	2 (6.45)	0 (0)	*ns*
Fatigue n (%)	15 (45.45)	7 (22.58)	12 (30.77)	*ns*
Daytime Sleepiness n (%)	15 (45.45)	14 (45.16)	7 (17.95)	*0.01* *1vs3; 0.037* *2vs3; 0.044*
Sleep Impairment n (%)	12 (36.36)	12 (38.7)	27 (69.23)	*0.03* *1vs3 0.042* *2vs3 0.044*
Muscle Ache n (%)	13 (39.39)	11 (35.48)	2 (5.13)	*0.004* *1vs3 0.02* *2vs3 0.008*
Depression n (%)	15 (45.45)	7 (22.58)	17 (43.59)	*ns*
Anxiety n (%)	13 (39.39)	7 (22.58)	14 (35.9)	*ns*

List of abbreviations: n, Number of patients; M, Male patients; F, Female patients; SD, Standard Deviation; sNS, Subjective Neurological Symptoms; WBC, white blood cells; CRP, C-reactive protein; ns, Not Significant.

has been already explained that hospitalization may significantly disrupt sleep, thus clinically producing insomnia symptoms (Young et al., 2008).

The mechanisms at the basis of the high frequency of neurologic complaints in patients with SARS-CoV2 infection are not completely understood and thus they are still hypothetical (Wu et al., 2020; Baig et al., 2020; Li et al., 2020). The autoptic studies performed in patients with COVID-19 documented hyperemia, oedema, and neuronal degeneration reflecting nervous system damage (National Health Commission of the People's Republic of China, 2020). Therefore, the intrinsic properties of this novel coronavirus may represent possible mechanisms for affecting the nervous system. SARS-CoV2 may enter the nervous system through hematogenous or non-hematogenous routes. No study demonstrated the ability of the novel coronavirus to pass the BBB, but only singular case reports documented encephalitis due to SARS-CoV2 possibly passing the BBB by increasing its permeability through the production of cytokines or by the action of concomitant bacteria destroying it. Therefore, the non-hematogenous route of infection has been mostly hypothesized (Wu et al., 2020; Moriguchi et al., 2020; Poyiadji et al., 2020; Ye et al., 2020). Considering this latter route of infection, neuronal pathway represents the most suitable mechanism of infection, since it is considered an important vehicle for neurotropic viruses to enter the CNS. In the hypothetical model of CNS invasion, virus can migrate by infecting nerve endings and achieving retrograde or anterograde neuronal transport through the motor proteins, dynein and kinesins (Swanson and McGavern, 2015). The main gate of CNS infection by neurotropic viruses is the olfactory pathway (Koyuncu et al., 2013). As a consequence, SARS-CoV2, similarly to other coronaviruses affecting the nasal mucosa, can enter the brain through the olfactory tract from the early stages of infection (Wu et al., 2020; Desforges et al., 2019; Mori, 2015). Moreover, coronaviruses can migrate from the olfactory bulb to cortex, basal ganglia, and midbrain, which are affected during their spreading (Netland et al., 2008). This hypothesis has been confirmed in animal models by the removal of the olfactory bulb, which resulted in a restricted invasion of coronaviruses into CNS (Bohmwald et al., 2018). Taken together, the potential

Table 3
Demographic and clinical data of the patient's subgroups, distributed based on the concurrency of subjective neurological symptoms.

Demographic and Clinical Data	0 sNS (n = 9)	1–2 sNS (n = 26)	≥3 sNS (n = 68)	p Value
Sex (M, F)	5, 4	19, 7	35, 33	*ns*
Age (Mean ± SD)	55.56 ± 12.48	55.61 ± 13.84	54.41 ± 15.35	*ns*
Temperature (Mean ± SD)	36.3 ± 0.41	36.26 ± 0.45	36.31 ± 0.46	*ns*
Inflammatory serum markers				
WBC (x10^9/L) (Mean ± SD)	6.79 ± 4.12	9.98 ± 7.57	8.32 ± 6.65	*ns*
Neutrophil, count (Mean ± SD)	4.88 ± 4.5	7.75 ± 7.69	5.44 ± 4.33	*ns*
Lymphocyte, count (Mean ± SD)	1.37 ± 0.71	1.55 ± 0.87	2.36 ± 5.21	*ns*
Neutrophil, %WB (Mean ± SD)	0.64 ± 0.16	0.68 ± 0.18	0.65 ± 0.2	*ns*
Lymphocyte, %WB (Mean ± SD)	0.26 ± 0.14	0.22 ± 0.15	0.24 ± 0.17	*ns*
CRP (Mean ± SD)	14.34 ± 15.73	12.13 ± 21.38	23.19 ± 39.32	*ns*
sNS	n (%)	n (%)	n (%)	
in order of frequency	NA	Sleep Impairment 11 (42.31) Daytime Sleepiness 7 (26.92) Headache 4 (15.38) Depression 4 (15.38) Anxiety 4 (15.38) Fatigue 4 (15.38) Muscle Ache 3 (11.54) Dizziness 2 (7.69) Hyposmia 2 (7.69) Dysgeusia 1 (3.85) Confusion 1 (3.85) Numbness/Paresthesia 0 (0) Auditory Dysfunction 0 (0)	Dysgeusia 46 (67.65) Sleep Impairment 40 (58.82) Hyposmia 38 (55.88) Headache 37 (54.41) Depression 35 (51.47) Anxiety 30 (44.11) Fatigue 29 (42.65) Daytime Sleepiness 27 (39.70) Dizziness 24 (35.29) Muscle Ache 23 (33.82) Confusion 22 (32.35) Numbness/Paresthesia 6 (8.82) Auditory Dysfunction 2 (2.94)	NA

List of abbreviations: n, Number; SD, Standard Deviation; M, Male patients; F, Female patients; sNS, Subjective Neurological Symptoms; WBC, white blood cells; CRP, C-reactive protein; ns, Not Significant; NA, not admitted.

neuroinvasive propensity of SARS-CoV2 may justify the sNS complained by patients. Further possible mechanism explaining the involvement of nervous system during COVID-19 is related to ACE2 that represents the functional receptor of SARS-CoV2 and is widely expressed in multiple tissues, including the nervous system (Zhao et al., 2020; Hamming et al., 2004). Finally, the nervous system can by indirectly affected by SARS-CoV2 due to the mediated effects generated by the immune system (Klein et al., 2017). Accordingly, this neurotropic virus can trigger the development of a systemic inflammatory response syndrome (SIRS). SIRS can be localized also in the nervous system and is mediated by activated glial cells inducing a pro-inflammatory state during the SARS-CoV2 infection (Li et al., 2004). As a consequence, activated glial cells release several inflammatory factors, such as interleukin (IL)-6, which is an important member of the cytokine storm (Bohmwald et al., 2018; Wan et al., 2020). This inflammatory response may be responsible for sNS in patients with COVID-19. Consistently, IL-6, IL-1, and tumor necrosis factor (TNF)-α have been reported to induce symptoms such as impaired mood, anxiety, cognitive disturbances, fatigue, hyperalgesia (Hart, 1988; Kent et al., 1992; Engler et al., 2016). We also included in the analysis the main laboratory findings used for quantifying the immune and inflammatory response, such as WBC and CRP, in order to investigate the relationship between these immune parameters and the occurrence of sNS. Significantly, the increment of CRP is evident in the first days after admission, while WBC count is higher in patients evaluated after a prolonged hospitalization. This finding may reflect the initial inflammatory response and possibly subsequent bacterial co-infection in patients with SARS-CoV2 infection (Qin et al., 2020). In patients with more than 3 sNS the CRP tends to be higher, but the distribution of patients in the three groups cannot allow achieving the statistical significance. This point needs to be further analyzed in studies focused on the relationship between the inflammatory response and the occurrence of sNS in patients with SARS-CoV2 infection (Sun et al., 2020).

The sex-based distribution of patients shows that female patients report more frequently sNS than men. In particular, hyposmia, dysgeusia, headache, dizziness, numbness/paresthesia, daytime sleepiness, and muscle ache are more frequent in women than men. This sex-based difference can be attributed to the humoral and innate immune responses to viral infections more marked in women than men (Young et al., 2008; Schröder et al., 1998; Whitacre, 2001; Spinato et al., 2020). However, we document higher CRP, WBC, and neutrophil cell count in men than women, which can reflect an higher immune response in men possibly driven by the occurrence of a concomitant bacterial infection leading to a more severe infection (Qin et al., 2020; Qin et al., 2020; Yang et al., 2020)

In this study we document the high frequency of neurological symptoms in patients with SARS-CoV2 infection. In particular, sNS are present in patients not admitted to intensive care units and without severe pneumonia. Hence, it is conceivable that the infection *per se,* more than the severity of pneumonia, prolonged hospitalization, or adverse effects of the anti-COVID treatments, may affect the CNS and thus cause the neurological symptoms in patients with COVID-19 (Liu et al., 2020). To check this hypothesis, we document the relationship between the occurrence of sNS and the alteration of the main laboratory findings reflecting the immune and inflammatory responses (CRP and WBC) (Yang et al., 2020); however, this very preliminary impression needs to be further investigated in larger studies evaluating different infection-related biomarkers, inflammatory cytokines, and WBC subsets.

5. Limitations

We are aware that this study presents some limitations. We included patients admitted to a single hospital recognized by the Government for treating patients with SARS-CoV2 infection; more information about patients confined to home isolation can be useful to mitigate the possibly negative effects of hospitalization. We performed an observational, but cross-sectional analysis, in patients at different time points

during their hospitalization and a longitudinal evaluation of patients during the course of the disease can give more information about the progression of the sNS. However, the strength of this study is the homogeneous sample of patients prospectively evaluated by using an anamnestic interview centered on sNS, which were categorized for better analyzing their prevalence.

6. Conclusions

This study shows that neurological symptoms may be frequently complained in patients with COVID-19. Moreover, they may contribute to hospitalization, and increase the distress due to SARS-CoV2 infection also in patients without severe forms of the disease. As a consequence, it is particularly required to make clinicians aware of the impact of SARS-CoV2 infection on the nervous system, also in patients without severe respiratory infection.

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