

Assessment of neurological manifestations in hospitalized patients with COVID-19

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Background and purpose: The objective of this study was to assess the neurological manifestations in a series of consecutive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive patients, comparing their frequency with a population hospitalized in the same period for flu/respiratory symptoms, finally not related to SARS-CoV-2.

Methods: Patients with flu/respiratory symptoms admitted to Fondazione Policlinico Gemelli hospital from 14 March 2020 to 20 April 2020 were retrospectively enrolled. The frequency of neurological manifestations of patients with SARS-CoV-2 infection was compared with a control group.

Results: In all, 213 patients were found to be positive for SARS-CoV-2, after reverse transcriptase polymerase chain reaction on nasal or throat swabs, whilst 218 patients were found to be negative and were used as a control group. Regarding central nervous system manifestations, in SARS-CoV-2-positive patients a higher frequency of headache, hyposmia and encephalopathy always related to systemic conditions (fever or hypoxia) was observed. Furthermore, muscular involvement was more frequent in SARS-CoV-2 infection.

Conclusions: Patients with COVID-19 commonly have neurological manifestations but only hyposmia and muscle involvement seem more frequent compared with other flu diseases.

Introduction

In December 2019, the current outbreak of the novel coronavirus 19 (CoV) started in Wuhan, China, and then rapidly spread over the world. Italy was the first country involved in Europe from February 2020 [1].

Patients with the novel CoV were reported to have symptoms resembling those of severe acute respiratory syndrome CoV (SARS-CoV) in 2002–2004, both viruses sharing the same receptor, angiotensin-converting enzyme 2 [2,3]. Therefore, the new virus was named SARS-CoV-2, and in February 2020 the World

Health Organization named the disease COVID-19 [4,5]. Infection in humans often leads to severe clinical symptoms and high mortality [4,5]. Several studies have described the typical clinical manifestations including fever, cough, diarrhoea and fatigue and also characteristic laboratory findings [increase of interleukin-6 (IL-6) and D-dimer values] and lung computed tomography (CT) abnormalities (bilateral lung involvement with sub-pleural ground-glass opacities) [4–7].

Neurological manifestations of COVID-19 are not infrequent, being reported in about one-third of patients: symptoms and signs may involve the nervous system at all levels from brain to muscles [5].

Here, the neurological manifestations were assessed in a series of consecutive patients with COVID-19 admitted to a referral centre in Rome, Italy,

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comparing their frequency with a population hospitalized in the same period for flu/respiratory symptoms, finally not related to COVID-19.

Patients and methods

Standard protocol approvals, registrations and patient consents

This is a retrospective, observational study done at Fondazione Policlinico Gemelli hospital, a centre designated to treat patients with COVID-19. The study was approved by the Ethical Committee of the Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore. All participants provided informed consent.

Study subjects

Consecutive patients hospitalized in non-intensive COVID-19 units from 14 March 2020 to 20 April 2020 were retrospectively enrolled. A confirmed case of COVID-19 was defined as a positive result of reverse transcriptase polymerase chain reaction (RT-PCR) on nasal or throat swabs. As control group the population hospitalized in the same period for flu/respiratory symptoms, tested negative for SARS-CoV-2, was used. To consider a patient negative for SARS-CoV-2 nasal or throat swabs had to be repeated and found to be negative twice. Patients with severe flu/respiratory symptoms compatible with COVID-19 were not included in the study, even if multiple nasal or throat swabs tested negative.

Electronic medical and nursing records, laboratory findings and radiological tests of all patients with laboratory-confirmed SARS-CoV-2 infection and of controls were reviewed. Data on age, sex, comorbidities (hypertension, diabetes, cardiac disease, malignancy and chronic kidney disease), typical respiratory symptoms from onset to hospital admission (dyspnoea, fever, cough), neurological symptoms and laboratory findings were collected. The clinical severity of respiratory symptoms was assessed with the P/F ratio (arterial pO_2 divided by the FiO_2): patients with $P/F < 200$ were considered to have moderate/severe respiratory failure.

Subjective symptoms were collected by clinicians from conscious, cognitively and mentally preserved patients, at admission or during hospitalization. Incomplete electronic records were not included.

Neurological manifestations were categorized into two categories: central nervous system (CNS) manifestations (headache, dizziness, balance impairment, encephalopathy related to fever or hypoxia,

encephalopathy not related to fever or hypoxia, taste or smell impairment, seizures, stroke, encephalitis, myelitis) and muscular manifestations (generalized weakness, myalgia, skeletal muscle injury).

Encephalopathy, i.e. any disorder or disease of the brain leading to an overall brain dysfunction, characterized by altered mental state or delirium [8], was considered a consequence of fever for temperatures $>39.5^\circ\text{C}$ or a consequence of hypoxia if O_2 saturation was $<85\%$, if it was reversible once respiratory or metabolic dysfunctions were resolved. Acute cerebrovascular disease included ischaemic stroke and cerebral haemorrhage diagnosed by clinical symptoms and head CT. Seizure was based on the clinical symptoms at the time of presentation. Skeletal muscle injury was defined as when a patient had myalgia and an elevated serum creatine kinase level greater than 200 U/l [5].

Statistical analysis

The two-tailed Fisher's exact test was performed to compare categorical variables and the Mann-Whitney test was used to compare continuous variables. A P value <0.05 was considered significant.

Results

A total of 452 patients were hospitalized for flu/respiratory symptoms in the period examined. 213 patients were positive for SARS-CoV-2, after RT-PCR on nasal or throat swabs; 21 patients were excluded because, although multiple nasal or throat swabs were negative for SARS-CoV-2, a therapy with antiretroviral, anti-IL-6 or hydroxychloroquine was started, considering radiological findings and clinical manifestations suspicious for COVID-19; 23 patients were excluded for incomplete electronic records; 218 patients were negative for SARS-CoV-2 after RT-PCR on nasal or throat swabs and were used as the control group. In the control group, a microbiological agent was found in 63/214 patients (28%).

Patients' demographic, laboratory and clinical characteristics regarding flu/respiratory symptoms and administered therapies are summarized in Table 1. Neurological manifestations are summarized in Table 2.

Patients positive for SARS-CoV-2 were younger compared with controls and showed a slight prevalence of male gender. Cardiovascular risk factors were not different between the two groups, whilst cancer and chronic renal failure were more frequently observed in SARS-CoV-2-negative patients. Rate of death was not significantly different between the two

Table 1 Patients' demographic, laboratory and clinical characteristics regarding flu/respiratory symptoms

| | SARS-CoV-2-positive | SARS-CoV-2-negative | <i>P</i> value | Excluded patients |
|--|------------------------------|-------------------------------|----------------|------------------------------|
| Total patients | 213 | 218 | | 21 |
| Mean age at onset, years | 70.2 ± 13.9 (range 21–97) | 75.9 ± 12.6 (range 18–101) | <0.0001 | 61.5 ± 16.5 (range 34–90) |
| Median age at onset, years | 72 | 79 | 0.0145 | 59 |
| M/F | 1.8 (137/76) | 1.1 (114/104) | | 1.1 (11/10) |
| Fever | 97.1% (207/213) | 67.5% (169/218) | <0.0001 | 95.2% (20/21) |
| Dyspnoea | 74.6% (159/213) | 60.5% (132/218) | 0.002 | 80.9% (17/21) |
| Cough | 57.2% (122/213) | 26.1% (57/218) | <0.0001 | 57.1% (12/21) |
| <i>P/F</i> <200 | 43.1% (92/213) | 22.4% (49/218) | <0.0001 | 28.6% (6/21) |
| Ischaemic cardiomyopathy | 31.2% (68/213) | 35.8% (78/218) | NS | 9.5% (2/21) |
| Diabetes | 23.5% (50/213) | 24.8% (54/218) | NS | 4.7% (1/21) |
| Hypertension | 58.2% (124/213) | 58.7% (128/218) | NS | 23.8 (5/21) |
| Chronic renal failure | 21.1% (45/213) | 34.5% (73/218) | 0.004 | 14.3% (3/21) |
| Cancer | 14.6% (31/213) | 26.6% (58/218) | 0.002 | 19.0% (4/21) |
| Deep venous thrombosis | 4.2% (9/213) | 6.4% (14/218) | NS | 4.7% (1/21) |
| Death | 18.7% (40/213) | 11.9% (26/218) | NS | 14.3% (3/21) |
| Antiretroviral (ritonavir/darunavir/lopinavir) | 83.0% (177/213) | – | – | 95.2% (20/21) |
| Hydroxychloroquine | 86.8% (185/213) | – | – | 90.5% (19/21) |
| Tocilizumab | 28.6% (61/213) | – | – | 14.3% (3/21) |
| Antibiotic | 2.8% (6/213) | 40.8% (89/218) | <0.0001 | 100% (21/21) |
| CRP | 135.3 ± 103.5 | 98.9 ± 90.9 | 0.0004 | 126.9 ± 90.1 |
| D-dimer | 5925.2 ± 26931.4 | 4124.1 ± 7282.4 | NS | 3459.0 ± 6356.0 |
| IL-6 | 490.0 ± 1303.9 | 408.5 ± 1288.9 | NS | 42.2 ± 31.5 |

IL-6, interleukin-6; CRP, c-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

groups ($P = 0.0606$), although it showed a tendency to be higher in SARS-CoV-2-positive patients.

On the other hand, each single respiratory symptom (fever, dyspnoea, cough) was more frequent in SARS-CoV-2-positive patients. SARS-CoV-2-positive patients also showed more frequently a moderate/severe respiratory syndrome with a *P/F* ratio <200.

Considering inflammatory markers, only C-reactive protein (CRP) values (available for all cases) were significantly different between the two groups. D-dimer was available for 178/213 SARS-CoV-2-positive patients and for 113/218 SARS-CoV-2-negative patients (and for 12 excluded patients), and IL-6 was available for 58/213 SARS-CoV-2-positive and for 38/218 SARS-CoV-2-negative patients (and only for two excluded patients). Both laboratory values were found to be comparable between patients and controls.

The great majority of SARS-CoV-2-positive patients (189/213, 88.7%) received at least one treatment indicated for COVID-19; conversely, antibiotics were more frequently used in the control population.

Regarding neurological signs/symptoms, CNS manifestations were similarly reported between the two groups. A higher frequency of headache and encephalopathy was observed in COVID-19 patients but only related to fever or hypoxia. Olfactory dysfunction was a common clinical finding in SARS-CoV-2-positive patients, more frequently compared with controls.

Moreover, muscular involvement was more frequent in SARS-CoV-2 infection.

Interestingly, one patient presented symptoms suggestive of encephalitis: cerebrospinal fluid (CSF) analysis revealed no pleocytosis and increased protein (115 mg/dl), but RT-PCR for SARS-CoV-2 was found to be negative. Brain CT scan was normal. The patient improved after treatment with hydroxychloroquine and tocilizumab and was discharged. No patients presented myelitis.

Discussion

Neurological manifestations have been reported within the clinical spectrum of COVID-19 [5]. However, the full-blown syndrome of this virus is still not clear. To assess the frequency of neurological manifestations of hospitalized patients with COVID-19, the neurological disturbances of SARS-CoV-2-positive patients were compared with those experienced by a group of patients hospitalized in the same period for similar symptoms but who were found to be negative after RT-PCR on nasal or throat swabs.

Our study has several limitations: (i) it is a retrospective study with a non-systematic neurological phenotype assessment; (ii) the control group is heterogeneous and includes patients with respiratory syndrome with undefined aetiology; (iii) false-negative COVID-19 patients in the control group or in the

Table 2 Patients' neurological manifestations

| | SARS-CoV-2-positive | SARS-CoV-2-negative | P value |
|--|---------------------|---------------------|---------|
| Total patients | 213 | 218 | |
| Headache | 4.6% (10/213) | 0.4% (1/218) | 0.0044 |
| Dizziness | 1.4% (3/213) | 0.9% (2/218) | NS |
| Balance impairment | 1.4% (3/213) | 2.3% (5/218) | NS |
| Encephalopathy related to fever or hypoxia | 35.2% (75/213) | 21.1% (46/218) | 0.0013 |
| Encephalopathy not related to fever or hypoxia | 5.1% (11/213) | 3.6% (8/218) | NS |
| Ageusia/dysgeusia | 2.8% (6/213) | 0.9% (2/218) | NS |
| Anosmia/hyposmia | 6.1% (13/213) | 0.9% (2/218) | 0.0033 |
| Seizure | 2.8% (6/213) | 1.8% (4/218) | NS |
| Ischaemic stroke | 0.9% (2/213) | 7.3% (16/218) | 0.0012 |
| Haemorrhagic stroke | 0.9% (2/213) | 1.3% (3/218) | NS |
| Encephalitis | 0.5% (1/213) | 0% (0/218) | NS |
| Myelitis | 0% (0/213) | 0% (0/218) | NS |
| Weakness | 32.3% (69/213) | 7.3% (16/218) | <0.0001 |
| Myalgia | 9.3 (20/213) | 0.9% (2/218) | <0.0001 |
| Skeletal muscle injury | 4.7% (10/213) | 0% (0/218) | 0.0008 |
| CK elevation | 58.2% (124/213) | 24.7% (54/218) | <0.0001 |
| Mean CK values | 223.9 ± 501.3 | 98.9 ± 90.9 | 0.0072 |

CK, creatine kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

excluded patients may represent a bias; (iv) in some patients compliance might have been decreased by concurrent encephalopathy.

Neurological manifestations were observed in 64/213 patients (30%), confirming previous data in the Chinese population [5].

Generally, CNS manifestations showed a lower frequency compared with previously published data [5] and were not different with respect to the control population.

Encephalopathy was the most frequent CNS manifestation reported, but only due to a possible secondary effect related to respiratory symptoms. Indeed, its frequency in patients without predisposing systemic/respiratory conditions was analysed and no difference was found between the two groups.

Furthermore, a direct invasion of virus on the CNS seems extremely rare, being reported in only a few

cases [9–11]. In our cohort, just one patient was diagnosed as affected by encephalitis. In this case, CSF examination confirmed signs of inflammation but the virus was not detected. Although the definitive diagnosis of viral encephalitis largely depends on virus isolation, this is difficult to obtain for COVID-19 because SARS-CoV-2 dissemination is transient and its CSF titre may be extremely low [9].

The other CNS manifestation more frequent in SARS-CoV-2-positive patients compared with controls was headache; however, its frequency was lower if matched with a previously published paper [5].

Hyposmia and hypogeusia are considered typical manifestations of COVID-19 infection [12]. In our cohort, although their frequency was similar to previously reported studies [5], only hyposmia was more frequent compared with controls. Probably hypogeusia could have been underestimated during clinical interview, or its presence is more frequent in mild or not hospitalized COVID-19 patients [12].

The frequency of seizures and stroke was higher and lower, respectively, compared with published data [5]. Considering ischaemic stroke, the lower frequency with respect to the literature may depend on the population considered (old patients hospitalized in non-intensive units), since this complication occurs more often in patients with severe disease [5,13] or in young cases [14]. Furthermore, in our experience ischaemic stroke was more frequent in the control group. The inhomogeneity of the two populations with regard to mean age and other possible stroke risk factors (such as cancer or chronic renal failure) may explain the results of our study. Although stroke may be a consequence of SARS-CoV-2 infection, older patients also have higher cardiovascular comorbidities and higher rates of stroke [5,13–14].

On the other hand, peripheral nervous system involvement seems more frequent in SARS-CoV-2 infection. So far, several cases of Guillain-Barré syndrome have been reported suggesting that the virus may have a role [15,16]. Muscle could be one target of the virus too [17]: muscular symptoms were more common amongst SARS-CoV-2-positive patients and creatine kinase level was higher compared with controls. Unfortunately, to avoid contamination, muscle magnetic resonance imaging and electromyography have not been performed in these cases, so there are not enough data to speculate about the pathogenesis of muscular involvement.

In conclusion, three main pathogenic mechanisms could be hypothesized in COVID-19: a direct invasion of the nervous system by the virus, a possible immune-mediated damage or abnormal production of pro-inflammatory cytokines [3,18–20]. Considering

inflammatory markers, in our cohort only CRP was more elevated in SARS-CoV-2-positive patients compared with control. Unfortunately, samples for D-dimer and IL-6 were not available for the entire cohort and these data could explain the lack of difference in these laboratory values. It is not clear which mechanism is responsible for neurological manifestations in COVID-19 but immune-mediated mechanisms may play a role in the development of neurological disturbances. Further studies with a longer follow-up are needed to assess the incidence of SARS-CoV-2-related para-infectious disorders involving the nervous system and the extent of neurological sequelae of the pandemic.

At present, COVID-19 has been declared a global pandemic but our understanding of the disease is still limited. Given that COVID-19 patients can manifest neurological symptoms and signs, neurologists need to be involved, alert and prepared.

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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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