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Acute and Long-Lasting Neurological Symptoms in SARS CoV-2 Infected Patients

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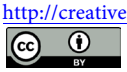

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Abstract

There have been reported a large number of neurological symptoms in CoV-2 infected patients after the COVID-19 outbreak was declared in January 2020. Cases reports as well as series of COVID-19 patients have shown a wide variety of neurological symptoms such as stroke, encephalomyelitis, polyradiculoneuropathy and other neurological conditions. Despite the fact, a high incidence of neurological symptoms have been reported during the COVID-19 pandemic, the proportion of them in acute and in a more chronic phase has not been exactly described in most of the papers published until now. We described in this article the neurological symptoms in a series of COVID-19 patients during the acute phase of infection while they were admitted into the hospital and subsequently the persisting neurological symptoms showed in the following 6 months in the outpatients' evaluation once they were discharged from the hospital in the province of Catalonia-Spain from January to June of 2020.

Keywords

CoV-2, Neurological Symptoms, CoV-2 Europe, Neurological Sequeles

1. Introduction

There have been reported more than 55 million CoV-2 infected patients around the world causing more than 2 million deaths during the COVID-19 pandemic from January 2020 to the date according to the World Health Organization among others [1] [2]. Most of the COVID-19 patients during this pandemic have shown minimal respiratory symptoms with a total health recovery in ap-

proximately 2 weeks [3], however approximately 10% of them have shown severe respiratory symptoms (SARS) showing bilateral interstitial pneumonia requiring in most of the cases ventilatory support and intensive care therapy [4] [5]. Unfortunately, there has been reported high mortality in the most severe group of CoV-2 patients who show respiratory insufficiency and also showing a high prevalence of neurological symptoms and sequels in those patients who eventually leave the intensive care units. Epidemiologically, Spain has been one of the most affected European countries during this COVID-19 pandemic in terms of incidence, prevalence and mortality rates, particularly the province of Catalonia, nevertheless affecting almost homogeneously all the country. We described in this article the acute and long lasting neurological symptoms in a Serie of SARs-CoV-2 patients admitted in 2 hospitals in the province of Catalonia (West Valles county), Spain.

2. Patients and Methods

The neurological teams of two different hospitals from the Valles county (Barcelona, Catalonia) with a high index of bed occupation of CoV-2 patients (CST Terrassa), evaluated all the CoV-2 patients and their medical records during the acute phase (admitted into the hospital) and during the following 6-month in the outpatients' neurological consultation from March to November 2020.

Patients were consecutively included into our protocol once they were admitted into the hospital due to CoV-2 infection. All their medical records were checked over and carefully determined for possible neurological symptoms.

All the CoV-2 patients with possible neurological symptoms underwent to a neurological evaluation during the admission into the hospital and subsequently all of them were visited at 3 and 6 months evaluations in the outpatient neurological visit once discharged from the hospital. Additionally, all the medical records of the CoV-2 infected patients admitted into the hospital were periodically reviewed in order to detect possible neurological symptoms which could be not detected in other medical specialties.

Patients were submitted to a complete neurological evaluation. The anamnesis was directed to determining neurological symptoms which have been already described in other COVID-19 patient series such as Hyposmia, cognitive state, nerve peripherical disorders, headache and stroke. Furthermore, the physical examination was performed to determine any kind of neurological deficit. All necessary neurological tests were carried out according to the clinical practice such as MRI, Lumbar puncture, EEG, EMG and other neurophysiological tests were also carried out.

The data (clinical and paraclinical tests) were recorded at the baseline evaluation and compared to the clinical and paraclinical findings at the 6-month evaluation.

A descriptive statistical analysis was used in this follow-up. The size of the sample was assumed for the population of our region (500.000 Inhabitants). The index of CoV-2 infections ranged from 750 - 1000 cases by 100.000 inhabitants

in the time of the follow-up.

The baseline neurological evaluation included: Anamnesis, physical examination, minimental state scale, attentional disorders scale (ADHD Rating Scale).

MIDAS migraine scale and monthly attacks migraine dairy were performed to all the patients and at the 3- and 6-month evaluations all the patients were submitted to the same evaluation included the same clinical scales additionally all the necessary tests were performed in the acute as well as in the chronic phase according to the real clinical practice

3. Definitions

We defined **severe affected** COVID-19 patients, those who showed less than 90% oxygen saturation and/or alteration of arterial gases parameters.

Severe acute respiratory syndrome (SARS) was defined as a viral respiratory disease of zoonotic origin caused by severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1).

Attention deficit disorder (ADD) was defined as a neurological disorder that causes a range of behavior problems such as difficulty attending to instruction, keeping up with assignments, following instructions, completing tasks and social interaction.

We defined an **acute confusional state** as a syndrome characterized by disturbed consciousness, cognitive function or perception, which has an acute onset and fluctuating course. It usually develops over 1 - 2 days.

All the patients infected with the CoV-2 virus with neurological symptoms were included and registered in a database and compared to their premorbid clinical condition, finally they were evaluated between 3- to 6-month after being discharged from the hospital and compared with the basal evaluation.

4. Results

We found 250 COVID-19 infected patients admitted into the hospitals from March to November 2020. 154 of them (61.4%) showed at least 1 neurological manifestation.

We divided our findings into 7 neurological manifestations groups:

1) Migraine episodes; 2) Cognitive disorders; 3) Acute confusional state; 4) Attentional disorders; 5) Peripheral neurological disorders; 6) Stroke and cerebrovascular disease and 7) Hyposmia/hypogeusia

86 out of 150 (57.3%) patients showed an attentional disorder disease (ADD). 68 patients showed hyposmia/ageusia (45.3%). 48 patients showed a nerve peripherical compression, mainly paresthesic meralgia (32%). migraine episodes 52 (34.6%). Cerebro-vascular diseases 11 (7.3%) (Table 1).

Attentional disorder:

86 COVID-19 patients (57.3%) showed clinical criteria of an attentional disorder (ADD) when they were admitted into the hospital, aged from 44 to 76, 18 women and 28 men. 62 of them (75%) severely affected with respiratory insufficiency

Table 1. Results of neurological manifestations in COVID-19 patients.

Acute and long-lasting neurological manifestation N= 154 (61.4%)		
Manifestations	**N**	**%**
Confusional state	19	12.6%
Attentional disorders	86	57.3%
Hiposmia/Ageusia	68	45.3%
Paresthesic meralgia	48	32%
Migraine and headache	52	34.6%
Cerebro vascular disease	11	7.3%

and 42 (48.8%) of them required intensive care therapy and endotraqueal intubation. None of them showed ADD previous to COVID-19 infection.

38 of them (44%) were strongly affected for the social and Laboral activities because the ADD and they persisted with symptoms at the 6-month outpatient evaluation. 19 patients showed a confusional state during the acute phase (12.6%) however all of them recovered their pre-morbid state (Table 2).

Hyposmia/ageusia:

68 COVID-19 patients (45.3%) in Table 3 showed ageusia/hyposmia and 52 of them (82%) only hyposmia, they referred hyposmia/ageusia at the beginning of symptoms associated with the COVID-19 infection. 60 (72%) of them were severely affected needing respiratory insufficiency and endotraqual intubation. 44 (88%) of them referred partial recovery of symptoms after COVID-19 diagnosis at the 6 months evaluation. However, 22 (12%) of them referred to persisting symptoms at 6-month evaluation.

Peripheral symptoms:

48 patients (32.4%) in Table 4 showed peripheral neurological symptoms. 28 of them (58.3%) showed a not disturbing femoral-cutaneous nerve compression (paresthesic meralgia), all of them were placed in prone position in order to improve dyspnea and respiratory insufficiency. 22 patients (52%) persisted with paresthesic meralgia at the 6 months evaluation. 4 patients showed an acute polyradiculoneuropathy Gillan Barre-type who responded adequately to Intravenous immunoglobulin. Finally, 4 patients showed a facial peripherical palsy with a total recovery in the following 2 months after the beginning of COVID-19 symptoms.

Migraine and headache:

52 out of 250 patients (20.8%) in Table 5 showed an increase in the migraine episodes (mean 14 monthly episodes) during the acute phase of COVID-19 infection, posteriorly these patients kept showing an increase in the monthly episodes (mean 8 monthly episodes) in the following 6-month outpatient evaluation as shown in Table 6. 36 (69.2%) of them with clinical criteria of sporadic migraine also experienced an increase in the frequency of monthly episodes mainly while they were admitted into the hospital in the acute phase and later showing a clear clinical improvement once they were discharged from the

Table 2. Attentional disorder in COVID-19 patients.

Characteristics	N = 86 (57.3%)
Age	Mean 57 (range 44 to 80 yo)
Gender F/M	(38)/(48)
Respiratory insufficiency	62 (75%)
Intensive care therapy and endotraqueal intubation	42 (48.8%)
Previous ADD	0
Affectation in social and laboral activities	38 (44%)

Table 3. Hyposmia/ageusia in COVID-19 patients.

	N = 68	Hyposmia/Ageusia 45.3%
Only hiposmia	56	82.3%
Respiratory insufficiency	60	72.6%
Intensive care therapy and endotraqueal intubation	60	72.6%
Recovery of hyposmia/ageusia	44	88%
Persisting hyposmia/ageusia	22	12%

Table 4. Peripheral neurological symptoms in COVID-19 patients.

	N = 48	Peripheral symptoms 32.4%
Meralgia paresthesica	28	58.3%
Prone positions for respiratory insufficiency	40	83.3%
Acute polyrradiculophaty	4	8.3%
Facial palsy	4	8.3%

Table 5. Migraine and tensional headache in COVID-19 patients.

	N = 52	Migraine and headache (20.8%)
Sporadic migraine patients	36	69.2%
Chronic migraine patients	14	26.9%
Migraine status patients	4	7.7%
Acute tensional headache	16	30.8%
Monthly Migraine episodes (mean)	14	(6 - 18 attacks)

Table 6. Acute and persisting neurological symptoms in COVID-19 patients at 6 months follow up.

N = 150	Migraine	Attentional disorders	Hyposmia/ hypogeusia	Stroke	Guillan Barré	Facial palsy	Confusionnal state	Paresthesic meralgia
Inpatients	52	86	68	11	4	2	19	48
Outpatients	22	38	22	-	0	0	0	22
% recovery	42.3	44.1	32.3	-	100	100	100	48

hospital; 4 of them showed a **Status Migrainous** requiring dexamethasone 6 mg every 8 hours and triptans to improve the severity of the pain. All of them improved at 6-month evaluation in the outpatient neurological clinic. 6 patients showed tensional headaches who experienced a total release of pain when they were discharged from the hospital.

5. Discussion

SARS-CoV-2 is proposed to cause damage to the Central Nervous System (CNS) by a surge of inflammatory cytokines (mainly Interleukin-6), called Cytokine Storm Syndrome (CSS), in the same way as many neurotropic viruses are assumed to induce the production of IL-6 from glial cells, resulting in cytokine storm syndrome.

This concern is also supported by the neurotropism previously documented in other human coronaviruses, including the 2002-2003 SARS-CoV-1 outbreak [6].

ADD was the most common neurological symptom showed for our COVID-19 patients in this follow up; Frequently, most of them were severely affected by respiratory insufficiency and ventilatory support was needed in the majority; Probably a psychological effect could explain the ADD showed for our COVID-19 patients more than a direct injury on the CNS caused by the CoV-2; In fact, it is well-known that Psychiatric sequels, including anxiety, depression, and post-traumatic stress disorder (PTSD) are also prevalent among both ICU survivors and their family members [7] [8]; Furthermore, it has been reported severe psychological sequels in COVID-19 patients with different levels of clinical outcomes for some authors [9]; Besides, psychological disorders such as depression, anxiety and confusional states can frequently cause an ADD in our personal experience.

Hyposmia/ageusia was another common symptom in our COVID-19 patients; Curiously, this symptom was not related to the severity of COVID-19 infection, observing a relatively mild-affected patients showing hyposmia in acute phase and persisting hyposmia at the 6-month evaluation; However, we want to remark that most of them showed a total recovery of these symptoms at 6-month evaluation, Nevertheless they referred no hyposmia/ageusia previous to COVID-19 infection was contracted; Probably the virus can use the olfactory nerve as an entrance to the body as other viruses use to do it [10] However, there is not a clear neurotropic behavior of CoV-2 virus supported by a strong scientific evidence by now, nevertheless some basic and clinical studies are needed to clarify this issue. Particularly, we recently reported a case of a patient with a severe **Opsoclonus/myoclonus syndrome** related to COVID-19 infection who showed no proofs (Cranial MRI, spine fluid, PCR etc.) which could support a direct effect of COVID-19 on the CNS [11].

Our COVID-19 patients showed an increasing in the Migraine monthly attacks (mean = 14), most of them were episodic migraine patients who experienced an increment of their migraine attacks in the acute phase of the infection during admission into the hospital, therefore showing a worsening in their

monthly migraine attacks dairies as well as in MIDAS scale scores; however they showed a clear improvement once they were discharged from the hospital at the 6-month evaluation. As an important comment, those patients responded very well to **TRIPTANS** and other **NSAIDs** as Dextaketoprophen and intravenous paracetamol and 4 of them showed a **Status Migrainous** who relieved in all the cases with intravenous dexamethasone. We think the viral infection and the inflammatory cytokine storm could precipitate the increment in the migraine attacks and migraine status of our COVID-19 patients.

Paresthesic meralgia was frequently showed for our COVID-19 patients; they showed a clear clinical manifestation and the EMG confirmed the diagnosis in all the cases, most of them were admitted in the intensive care unit with ventilatory support for a long period of time (mean = 4 weeks), therefore we related this neurological symptom to the prono-position that they were placed in the intensive care unit in order to improve dyspnea and the respiratory insufficiency. Curiously just only 42% of them showed a clinical recovery at the 6-month evaluation.

4 COVID-19 patients showed clinical and EMG criteria of acute polyradiculoneuropathy (Guillain Barré) who improved substantially after intravenous immunoglobulin with a similar outcome when compared to other acute polyradiculoneuropathy patients not affected by COVID-19 infection so all of them showed a 100% recovery at the 6-month evaluation. Some acute polyradiculoneuropathy patients have been reported during COVID-19 infection, however not a direct effect of the CoV-2 has been scientifically shown in these patients. Finally just only 4 patients showed facial peripherical palsy in the acute phase of COVID-19 patients infection during admission into the hospital and again they showed a good outcome showing a total recovery at 1 month after COVID-19 diagnosis and they kept asymptomatic at the 6-month evaluation.

6. Conclusions

154 out of 250 (61.4%) of the CoV-2 infected patients showed some neurological manifestation in the acute phase infection during hospital admission as well as some long lasting clinical manifestation at the 6-month evaluation after discharged from the hospital from March to November 2020 during the COVID-19 pandemic.

COVID-19 patients with respiratory insufficiency showed more neurological symptoms than those with less systemic symptoms. ADD was the most common symptom in the acute phase as well as in the following 6-month after the COVID-19 infection was contracted in our COVID-19 patients; persisting ADD was more frequently seen in patients who were admitted into the ICU for respiratory insufficiency; depression and anxiety and the post traumatic syndrome could explain the ADD in those patients.

Hyposmia/ageusia was the second most common neurological symptoms as well as nerve peripherical compression (Paresthesic meralgia).

We finally conclude that, during the COVID-19 pandemic, it is crucial to be aware of the possible neurological complications of the disease. We think that much more scientific evidence is needed to affirm a direct effect of CoV-2 on central or peripheral nervous system. Due to the high similarities of SARS-CoV-2 with other human coronaviruses such as SARS-CoV or Middle East Respiratory Syndrome (MERS)-CoV, reviewing the neurological involvement also associated with these coronaviruses will provide an idea about the long-term complications of COVID-19; Nevertheless, an indirect and immuno-mediated effect, triggered by the CoV-2, seems to be a possible pathophysiological explanation of the neurological symptoms.

This study represents a descriptive and a good follow up of COVID-19 patients with neurological manifestations during a 6-month period of time, describing the neurological manifestation in the COVID-19 infection in the acute phase and posteriorly in a more chronic phase at 6-month, however we are aware about the limitations of this study because the difficulty during the chaos that we faced during this period of time, probably we unintentionally didn't included some COVID-19 patients with neurological manifestations and a precise follow up was honestly difficult because the restrictions of mobility imposed for the government in our country during the pandemic. We are also aware that some interesting issues are missed in our follow up such as a serological-clinical correlation in our COVID-19 patients therefore we think that better designed studies are needed to get a better understating of the neurological manifestations in the acute phase of COVID-19 infection as well as the long-lasting neurological symptoms in a more chronic phase.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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