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NEUROTROPISM AND NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH COVID-19

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SUMMARY

Background: *The Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2). Beyond the most common clinical features of COVID-19, mainly represented by respiratory symptoms, other systems may be interested by the infection. Among these, through a neurotropic pathway, the central nervous system (CNS) may be affected by the virus, leading to developing neuropsychiatric symptoms. Particularly, this study focuses on neurological symptoms determined by the Sars-CoV-2 infection, as well as on the underlying pathogenetic processes.*

Methods: *For the present review, we followed a narrative approach. A literature search was carried out concerning the neurological consequences of COVID-19. Papers were screened, focusing on the clinical manifestations interesting the CNS and on their possible role in the early diagnosis of the disease.*

Results*: We display the most significant neurological clinical manifestations of COVID-19. Common neurological manifestations (ageusia, anosmia, and encephalitis) are first described. Subsequently, we provide a focus on delirium and its possible pathogenetic and clinical correlates. Delirium is not only a possible resultant of the COVID-19 neurotropism, but it may also be precipitated by a number of environmental factors that assume further relevance during the pandemic.*

Conclusions: *Neuropsychiatric symptoms, and particularly delirium, can help identifying the infection at an early stage. Tailored treatments should be identified in order to prevent complications.*

Key words: *neurotropism – delirium - SARS-CoV-2 - COVID-19*

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the Coronavirus Severe Acute Respiratory Syndrome - CoronaVirus - 2 (SARS-CoV-2), leading to an unprecedented health emergency. SARS-CoV-2 has a similarity to SARS-CoV for over 70% of the genome, but it presents a 10-20 fold greater binding affinity, thus justifying the higher infectivity of the virus (Lai et al. 2020). The SARS-CoV-2 is transmitted through respiratory droplets or by direct or indirect contact with secretions (Guo et al. 2019). The virus can remain on surfaces for few days but is destroyed rapidly by commonly used disinfectants (Guo et al. 2019; Li et al. 2019).

Clinical manifestations of COVID-19 are heterogeneous and may encompass different levels of severity, with a wide spectrum of manifestations ranging from mild symptoms to an acute respiratory distress syndrome (ARDS), causing in some cases Multi-Organ Failure Syndrome (MOFS) (Huang et al. 2019, Wang et al. 2020).

Apart from the most common clinical features of COVID-19, some systems that may be critically interested by the infection are still overlooked in clinical practice and understudied in research settings. Among these, the central nervous system (CNS) may be affected by the virus due to its neurotropism, leading to neuropsychiatric manifestations.

Indeed, it is now well known how the Angiotensin Converting Enzyme 2 receptor (ACE2r) mediates the entry of SARS-CoV-2 (and other Coronaviruses) into the host cells (Lai et al. 2020). This receptor is expressed on the cell surface of heart, kidneys and testicles that have been found as initial sites of Angiotensin Converting Enzyme 2 (ACE2) expression (Lai et al. 2020). However, its presence has also been confirmed at the endothelial and neuronal level. In the CNS, immunohistochemistry of the ACE2r did not show neuronal or glial positivity, but instead confirmed its presence at the cerebral vessels level (Guo et al. 2020). In addition, during the attacking mechanism against the host some viral proteins intervene, as well as host proteins such as cathepsin L and CD-147 that are widely present in the CNS (Guo et al. 2020). The presence of SARS-CoV was also confirmed in post-mortem neurons and glial cells of deceased patients based on autopsy findings (Guo et al. 2020). Although blood spread is a well-known pathway for viral spread at the systemic level, it has been hypothesized that the virus could also proceed from the periphery to the CNS through retrograde neuronal transport and synaptic connections, particularly through the afferences of vagal nerves (Guo et al. 2020, Li et al. 2020). Moreover, with the evidence of the presence of SARS-CoV-2 in the gastrointestinal tract, it has been hypothesized that its neuroinvasive potential could include first the enteric nervous system and then the vagal one, until reaching, finally, the CNS (Guo et al. 2020, Lechien

et al. 2020). In the present narrative review, we focus on the neurological manifestations of SARS-CoV-2, particularly anosmia, ageusia, and encephalitis. Furthermore, we concentrate on delirium and its medical management in hospital settings, also considering the new peculiar characteristics imposed by the pandemic.

The study aims to highlight the neurological manifestations determined by the Sars-CoV-2 infection, as well as the underlying pathogenetic processes. A literature search was carried out concerning the neurological consequences of COVID-19, and their possible role in promptly promoting the detection of the infection itself. We thus highlighted the impact of the various neurological manifestations of COVID-19 within the current pandemic and their possible consequences.

METHODS

The present review was conducted following a narrative approach. A literature search was carried out using the biomedical databases of Pubmed and MedLine, variously combining the following keywords: "COVID-19", "SarS-CoV-2", "Neurotropism", "Ageusia", "Anosmia", "Encephalopathy", and "Delirium". Papers published between January 2020 and October 2021 were screened for inclusion. Both research analyzing the pathogenetic pathways leading to neuropsychiatric symptoms and describing neurological clinical manifestations of COVID-19 was deemed eligible. Only papers in English and Italian language were considered.

RESULTS

We display the results divided in two chapters representing the most highlighted clinical manifestations of COVID-19. After describing common neurological manifestations (ageusia, anosmia, and encephalitis), we will focus on delirium and its possible pathogenetic and clinical correlates.

Neurological symptomatic manifestations

Studies carried out in Europe observed that several subjects infected with SARS-CoV-2 had serious olfactory and gustatory dysfunctions that were not associated with rhinorrhea or nasal obstruction. Originally, none of these subjects had been suspected of COVID-19, especially since many of them did not present cough, fever, or other systemic symptoms. Faced with numerous reports of these symptoms, studies have been conducted in order to characterize olfactory and gustatory disorders in infected subjects (Meng et al. 2020). In one of the largest multicenter studies conducted (Li et al. 2020), 375 COVID-19 patients (85.6% of the total) had infection-related olfactory dysfunction (Hwang et al. 2020). Among these, 284 (79.6%) patients were anosmic and 73 (20.4%) were hyposmic. Phantosmia and parosmia affected 12.6% and 32.4%, respectively, of patients throughout the course of the disease (Guo et al. 2020). Olfactory dysfunction appeared before (11.8%), after (65.4%), or simultaneously with the appearance of general symptoms (22.8%) (Guo et al. 2020). Olfactory dysfunction was demonstrated in 247 (63.0%) patients with a clinically resolved infection (absence of general symptoms) even after resolution of symptoms (Guo et al. 2020).

As for taste alterations, a total of 342 patients (88.8%) reported taste disorders, which were characterized by an impairment of the four basic tastes: salty, sweet, bitter, and sour (Guo et al. 2020). Olfactory and gustatory disorders remained unchanged over the illness course in 72.8% of patients, while they fluctuated in 23.4% of patients (Guo et al. 2020). There was no significant association between comorbidities and the development of olfactory or gustatory dysfunctions (Guo et al. 2020). Females were more likely to be affected by hyposmia or anosmia than males. Similar results have been found for gustatory dysfunction (Guo et al. 2020).

As for the etiopathogenesis of both symptoms a relevant role has been hypothesized to be played by the neurotropism of the virus. Indeed, high ACE2r expression has been found on the epithelium of the tongue, and animal studies have shown ACE2r expression in the nucleus of the solitary tract, which could explain the central cause of dysgeusia and a possible neuro-invasive pathway through both local vagal axonal and continuous retrograde transport (Lechien et al. 2020).

Another neurological manifestation documented in the context of COVID-19 is encephalitis, an inflammatory process affecting the cerebral parenchyma and the surrounding tissues. The clinical manifestations of encephalitis involve alteration of mental state, headache, behavioral abnormalities, in association with possible focal neurological signs. Meningitis can also be caused by SARS-CoV-2 infection (Lechien et al. 2020), as well as signs of meningoencephalitis. Furthermore, many subjects with COVID-19 may present with an altered mental state due to metabolic toxic processes caused by hypoxia, electrolyte imbalances, and multiple organ failure, without necessarily presenting the direct involvement of the CNS (Huaxia et al. 2020). The management of such clinical manifestations is complicated by the inability to distinguish the underlying pathogenetic process (infectious or toxic-metabolic) only on the basis of the symptoms (Meng et al. 2020).

Delirium

Delirium is an acute neurocognitive disorder, which is usually reversible and tends to fluctuate throughout the day, often with exacerbation during night hours, in relation to the decrease in external stimuli (American

Psychiatric Association 2013). Three forms of delirium can be distinguished depending on the level of psychomotor activity: hyperactive, characterized by the presence of agitation and restlessness; hypoactive, in which the subjects appear slowed down and lethargic; mixed, where activity levels can swing between the other two clinical manifestations or be normal. The etiopathogenesis of delirium mainly relies on cerebral metabolic suffering, which can be determined by several causes. Particularly, delirium can be induced by nutritional deficiencies and imbalance, medications and their abrupt discontinuation, intoxications, and several medical conditions, including infectious diseases. Furthermore, precipitating environmental factors may be identified (Hwang et al. 2020). During the pandemic, specific precipitating factors may be related to the extraordinary measures adopted by the different Governments to confine the COVID-19 spread. Particularly, the widespread use of face masks may have hindered the possibility of fixing hearing impairments through the reading of lips, and the decreased availability of caregivers could have led to more serious difficulties in maintaining orientation in hospital settings (Inouye et al. 1990).

During SARS-Cov-2 infection, as well as in other infections, fever and hypoxia can act as a trigger for delirium. This means that the emergence of an acute confusional state, especially in an elderly person, could represent a “red flag” and suggest the presence of the infection. Impaired consciousness can actually represent an early symptom of COVID-19 and appear even before the onset of fever. Therefore, relating to the current pandemic, the clinical significance of delirium, which can underlie a Coronavirus infection, should not be underestimated (Hwang et al. 2020).

The diagnosis of delirium is essentially clinical. This evaluation is associated with the execution of a series of instrumental and laboratory investigations aimed at identifying the underlying cause. The adoption of validated screening tools is useful for practical purposes. Among them, the most widespread is the Confusion Assestment Method (CAM), which allows to formulate the diagnosis of delirium based on the positivity to the studied criteria (Inouye 2003). However, CAM requires specific training, in the absence of which its reliability is considered unsatisfactory (Inouye 2003).

The screening tool that can be used with good reliability having more objective scores is the "4AT", which does not require specific training, is administered quickly, and can be easily applied in the various contexts of care (Bearn et al. 2018). This scale allows to evaluate even those subjects who would not be able to carry out more analytical cognitive tests due to psychomotor agitation or, on the contrary, drowsiness (Bellelli et al. 2014). Delirium is enlisted among the urgent neuropsychiatric conditions for which the World Health Organization suggests the presence of experienced and qualified personnel in general hospitals (WHO 2020).

Regarding the management of subjects presenting with delirium, the standard measures normally used for the non-pharmacological treatment, as well as for prevention, may not be applicable in case of subjects being isolated due to SARS-CoV-2 infection. The isolation itself can represent a precipitating factor and can also exacerbate the neuropsychiatric symptomatology of delirium once it appears. Given the high contagiousness of the virus, it is also considered inappropriate to facilitate reorientation by the presence of family members (British Geriatric Society et al. 2020).

Several proposals for treating delirium during the current pandemic were made (Pini & Pacciardi 2020; Pinna et al. 2021). In COVID-19 related hyperkinetic delirium, first-line therapy with oral risperidone is recommended at a dosage between 0.25 and 1 mg / day. In case of ineffectiveness, intramuscular promazine between 25 and 150 mg/day is proposed in the second instance (INMI 2020). If the patient is suffering from cognitive impairment tiapride between 50 and 300 mg/day can be administered (INMI 2020).

It should also be considered that the presence of delirium affects the clinical management of subjects suffering from COVID-19. In fact, delirium is one of the conditions that require caution when initiating systemic steroid therapy (Zhao et al. 2020). The presence of delirium, therefore, modifies the risk-benefit ratio of the additional prescription of steroidal anti-inflammatories (Nicastri et al. 2020).

Furthermore, it should be underlined how other specific treatments prescribed for the infection may increase the risk of delirium. In particular, an augmented risk of delirium was demonstrated in subjects with neuropsychiatric disorders following the introduction of hydroxychloroquine sulfate into therapy (Keyhanian et al. 2021).

CONCLUSIONS

It is useful to promote studies that explore the wide spectrum of clinical manifestations determined by SARS-CoV-2, in addition to the most well-known respiratory diseases. This could lead to a greater and more complete awareness of the systemic organic damage mediated by viral infection. SARS-CoV-2-related neuropsychiatric manifestations, and particularly delirium, can help both identifying the infection at an early stage. Specific treatments should target these symptoms in order to improve clinical outcomes and allow a better overall management of subjects affected by COVID-19.

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Patrizia Moretti conceived and designed the review;

Francesca Brufani Valentina Pierotti, Giorgio Pomili, Agata Di Buò, Cecilia Giulietti, Vivjana Tanku & Massimo Claudio Bachetti performed the literature search;

Francesca Brufani, Valentina Pierotti, Giorgio Pomili & Filippo Masini wrote the first draft of the manuscript;

Giulia Menculini & Patrizia Moretti corrected the first draft of the manuscript;

Alfonso Tortorella supervised all phases of the study design and writing of the manuscript.

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