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Psychomotor agitation, anxiety disorders, trauma-related disorders: a review of clinical manifestations in COVID-19

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Summary

Introduction. The aim of our study is to highlight psychiatric clinical features due to the SARS-CoV-2 infection, providing insights from the new environmental circumstances resulting from the global pandemic.

Materials and Methods. We conducted a review of the most recent literature involving psychiatric consequences of COVID-19, particularly focusing on psychomotor agitation, anxiety disorders, trauma-related disorders and the main guidelines for the treatment of such consequences.

Results. A great variety of psychiatric correlates is involved in the present pandemic, with a relatively wide distribution.

Discussion and Conclusions. We believe that promoting studies that could explore the epidemiological distribution of psychiatric and psychological dysfunctional responses to the global situation may be useful. Furthermore, the possible influence that SARS-CoV-2 may exert on specific psychiatric diseases claims further attention. Future research with this specific focus may help a more timely and correct management of the infection, as well as the implementation of actions to protect public health.

Key words: COVID-19 pandemic, SARS-CoV-2 infection, ACE2 receptor, Psychomotor agitation, Anxiety Disorders, and Trauma-Related Disorders

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the Coronavirus Severe Acute Respiratory Syndrome - CoronaVirus - 2 (SARS-CoV-2) that belongs to the family of Coronaviridae, genus Betacoronavirus and is a virus with a single-stranded RNA genome with positive polarity [1].

SARS-CoV-2, despite having a possible different origin, has a similarity to SARS-CoV for over 70% of the genome, since both use spike glycoprotein to bind to the ACE2 receptor (present in large quantities in the respiratory tract and also in the gastrointestinal tract) and infect the host, but SARS-CoV-2 possesses a 10-20 times greater binding affinity, justifying the high infectivity compared to its predecessor SARS-CoV, which caused an epidemic in 2002, of much more limited geographical and temporal extent [1].

The virus has human-to-human transmission capacity through droplets (respiratory droplets generated by coughing or sneezing, with a journey of 1-2 meters which then deposits on surfaces) or by direct or indirect contact with secretions [2]. If there are favorable conditions, the virus can remain on surfaces for few days but is destroyed in a minute by commonly used disinfectants such as sodium hypochlorite or hydrogen peroxide [2,3].

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Clinical manifestations of COVID-19 may encompass different levels of severity, with a variable course ranging from mild symptoms to an acute respiratory distress syndrome (ARDS), also causing in some cases Multi-Organ Failure Syndrome (MOFS) leading to death [4,5]. Among possible presentations of COVID-19, psychiatric symptoms were also reported, e.g. psychotic symptoms [6], anhedonia [7], anxiety [8], psychomotor agitation [9]. Furthermore, psychiatric manifestations that may be reactive to the current pandemic and to the SARS-CoV-2 infection are in fact increasingly widespread in our daily practice in hospital and at local level, and currently represent one of the greatest challenges in the medical field. Among these an increase of symptoms relate to anxiety, including pandemic fear and ruminations about this, severe insomnia and suicidal thoughts, has been highlighted [10]. Noteworthy, mental health was pointed out as a priority during the current emergency situation by the World Health Organization (WHO), with a call for a comprehensive approach to this issue in order to address mental health needs [11]. As a consequence, in this review we will outline the main clinical aspects of the infection caused by Coronavirus (COVID-19) in the field of mental health, also evaluating the possible impact on psychiatric services and evaluating possible intervention strategies.

Materials and Methods

We carried out a research on Pubmed/MedLine using the main keywords “COVID-19” and/or “SarS-Cov 2” variously combined with “Psychomotor Agitation”, “Anxiety”, “Anxiety Disorders”, “Post-traumatic Stress Disorder”, ”Trauma-related disorders”.

Results

We present our results divided into chapters of interest concerning major psychiatric aspects highlighted during the pandemic: Psychomotor Agitation, Anxiety Disorders, Stress-related or trauma-related disorders.

Psychomotor agitation

Psychomotor agitation is a heterogeneous concept, mainly defined a set of non-specific, unconnected behaviors that can endanger the safety of the patient or caregivers and hinder the treatment process [12,13].
It is generally considered to be a cognitive and motor state characterized by excessive or inappropriate motor or verbal activity, marked emotional arousal, very marked internal restlessness or tension, high reactivity to internal and external stimuli, and irritability, which can lead to aggression and violence [14]. While it is difficult to estimate the overall prevalence of agitation episodes in subjects affected by psychiatric disorders due to the lack of epidemiological studies, it is widely recognized that agitation is a common phenomenon in both medical and psychiatric emergencies [15].

In a patient suffering from COVID-19, agitation, confusion or both may result from the underlying clinical condition, from medical complications, from treatment or from the medical environment, e.g. intensive care [12]. Possible causes are pain and discomfort from endotracheal intubation, fever, electrolyte imbalances, acidosis, hypoxia, hypotension, sepsis and shock, organ failure, sedative use, sleep deprivation, fear of dying, anxiety about unpleasant medical procedures, mechanical ventilation, the presence of a genitourinary catheter, and the possible establishment of delirium [12]. Additional triggers for the development of psychomotor agitation can be accidental rupture of ventilators, shortness of breath, loneliness, immobilization [12].
In such circumstances, it is appropriate to set up pharmacological therapy with psychotropic drugs to avoid the appearance of behavioral disorders induced by psychomotor agitation, which can complicate the treatment of SARS-CoV-25 infection. Many psychotropic drugs share the same metabolism with cytochrome P450 of antiviral drugs, therefore the choice of the drug must be made considering these possible interactions. Sedatives and hypnotics such as oxazepam and lorazepam are not metabolized by cytochrome P450 and are therefore quite safe when used in combination with antivirals, althoughtit is to consider that their use is contraindicated during respiratory distress. The same is true for some antipsychotics such as olanzapine and mood stabilizers such as valproic acid, which are thus considered safe [16].

Anxiety Disorders

We will examine anxiety disorders starting from the assumption that psychological factors play a vital role in the success of public health strategies (risk communication, hygiene practices and social distancing, antiviral therapy and, where possible, vaccination) used to manage epidemics and pandemics. Health anxiety is indeed important in influencing the success or failure of each of these strategies. Pandemics include not only the spread of physical disease, but also the spread of what is perhaps the real pathogen of mass reactions: anxiety, which at times, if also propagated through social media, can become “viral” [17].
This great epidemiological impact is evidenced by a study where a sample of 1,210 adults from 194 cities in China during the SARS-CoV-2 pandemic was interviewed to asses he psychological impact of the virus spread. Among those, 53.8% declared a moderate or severe psychological impact of the pandemic, 28.8% reported moderate to severe anxiety symptoms, and 8.1% disclosed moderate to severe stress levels [17].
When facing a major emergency like the present one, personal reactions may be heterogeneous, as well as the defense mechanisms that can be implemented: at one end of the spectrum, some people may deny the risks, sometimes not following health-related behavioral recommendations (hygiene practices, social distancing, vaccination,

when available), whilst on the other end of the spectrum many people may react with intense anxiety or fear that are sometimes even exagerrated [18].

Excessive health anxiety, as present in psychiatric disorders such as Hypochondria, Illness Anxiety Disorder and Somatic Symptom Disorders is common, with an estimated lifetime prevalence of 6% in the general population [18]. It is therefore easy to understand how subjects are prone to excessive worries concerning health risks, thus becoming particularly anxious during a pandemic period [19].

Additionally, patients with already known psychiatric conditions are at increased risk of developing comorbid anxiety exacerbations; this phenomenon is especially accentuated if such patients are already being treated for anxiety disorders [20].

In a psychodynamic context, anxiety can be defined as "fear without an object", even though the object of anxiety "exists, but it is indefinite and indefinable"[16]. It is perhaps possible to hypothesize that, in such situation, the anxious subject could try to link his or her mood to some representation or idea with a pessimistic content, which could find an easy expression, in this historical moment, in anxiety about an "indefinite and indefinable", apparently invisible pathogen, possibly threatening his or her health [21].

In order to provide an overview of possible scenarios, we drew up the following list of behaviors, possibly being the obvious sign of clinically relevant anxiety:

- resorting to repetitive medical checks and seeking excessive reassurance, which could lead to management problems by the healthcare system [22], e.g., in the early stages of the swine flu pandemic, a British government diagnostic website was unable to keep up with the demand for information, crashing as thousands of people simultaneously attempted to access it [23];
- excessive avoidance, with social withdrawal, of stimuli / sources related to infection, including people, places, things, animals. Emblematic are the cases of abandonment / killing of domestic dogs and cats, sometimes brutally killed, on the occasion of the SARS virus pandemic and the fear of being avoided by others if one becomes ill [24-26];
- extreme attempts at "decontamination", with the risk of more extreme behaviors than simple hand washing. As evidenced from the news of 44 people who died and 218 hospitalized for industrial alcohol poisoning in the provinces of Khuzestan and Alborz in Iran, after the news was spread that drinking alcohol could fight COVID-19 [27];
- civil unrest, riots, mass panic, looting sometimes occur during pandemics although the most common behaviors are of a solidarity type, as the threat of the disease evokes acts of mutual aid among the members of a community in crisis. Even in our country (Italy), after the first weeks of the first lockdown, there was a growing fear that the emergency situation and the stress secondary to isolation, and in general to the restrictions in place, could lead to riots and civil revolts, especially in some areas characterized by worse socio-economic status [28,29];
- tendency to excessive buying, which taken to an extreme can have negative consequences for the individual and his community [30];
- sleep disturbances, which can be both a consequence of stress and risk factors for the development of PTSD. In a study conducted on 170 individuals in self-isolation, low levels of "social capital", as defined by Portes and Lynch, ("a collection of actual or potential resources that include social trust, belonging and social participation") were associated with increased levels of anxiety and stress [30]. Anxiety was associated with stress and reduced sleep quality, and the combination of anxiety and stress reduced the positive effects of social capital on sleep quality. Similarly, out of 180 healthcare professionals involved in the treatment of COVID-19 patients, anxiety levels were significantly associated with stress, and negatively influenced work efficiency and sleep quality [31-33].

In order to reduce the social impact of the current environmental stressor and reduce the impact of anxiety disorders, it would be appropriate to pay greater attention to vulnerable groups, including psychiatric patients, to strengthen and improve accessibility to medical resources of the public health system, also establishing a strategic national coordination plan for psychological first aid services, which could be potentially provided through telemedicine [34].

Trauma-related disorders

In the DSM-5, a traumatic or stressful event means a serious threat to the psychophysical integrity of the person [32]. Exposure can be direct or indirect, therefore the individual can experience the threat firsthand or be in physical or emotional proximity to the victim; those who are exposed to repetitive observation of raw details of the event are also included. Post-Traumatic Stress Symptoms (PTSS) are considered as such because their first manifestation in the individual is temporally related to the event and had not manifested before it [35].

The two disorders differ in the temporal criterion, respectively for the persistence of symptoms beyond one month from the event (they tend to present themselves about three months later), and for the onset of the same between three days and within the month following the event. It should not be underestimated that this diagnostic category includes Adjustment Disorders, psychic manifestations characterized mainly by marked suffering, disproportionate to the severity of the stressful event, which produce a significant impairment in social, work or family functioning of the individual, and which may cause a deflection of mood and / or anxious symptoms [35,36].

Simplifying a lot, we could say that patients affected by the SARS-CoV-2 virus, in particular those who have been

in the Intensive Care Units (ICU), should be considered directly exposed to a traumatic or stressful event, which was a threat to psychophysical integrity. The general population is exposed to psychological distress, not only for measures of social distancing, but also for the variable perception of risk [36,37].

Contradictory information (easily accessible on social media) exposes subjects to greater distress, because it increases uncertainty about the future and the consequent fear of the unknown and leads to greater levels of anxiety both in the "healthy" population and in those with previous mental health problems [37,38].

Qualitative and quantitative data on the impact of mental health is currently available, despite limitations due to research being carried out in the short period of time from the beginning of the epidemic until today, whilst literature relating to previous Coronavirus infections, as well as other epidemics and experiences in the Intensive Care Unit, offers numerous contributions to be referred to by analogy of circumstance [39-42].

The following individuals should be considered more vulnerable and exposed to the risk for developing emotional responses(to quarantine or isolation, to the perceived risk of getting sick, or to the spread of the disease with its consequences: (1) infected individuals (hospitalized and/or quarantined), their families and their colleagues; (2) individuals with previous morbidity (organic or psychic); (3) healthcare professionals, especially doctors and nurses, who directly worked with affected patients [39].

In various studies conducted following an epidemic, the incidence of PTSD varies from 14% to 59% of survivors in the Intensive Care Units (ICU); in line with the literature supporting the classification systems, PTSD can occur up to three years later (on average) after the traumatic event [38]. Some studies highlight its appearance even in those who have been in quarantine, with an increasing incidence according to the longer duration of quarantine. In the general population, the incidence is between 4% and 41% [20-43].

Additional risk factors can be the following: female gender, low socioeconomic status, interpersonal conflicts, frequent use of social media and decreased resilience and social support. Fear of getting infected, frustration, boredom, inadequate support and information, economic losses, and stigma can also contribute to the onset of PTSD. Therefore, variables that should be taken into account are both the ones that were present prior to the epidemic (not least, the existence of previous trauma), and the ones related to the disease (severity, hospital or home treatment, quarantine and / or isolation), as well as psychosocial variables [44,45].

The absence of a support system for mental health, as well as the shortage of properly trained professionals, may amplify the risk of persistent psychological distress and progression of psychopathology [46,47].

In the short term, first-line psychological help should be provided to patients: interventions must be aimed at assessing the most critical needs, reducing stress and reactions to pain, supporting positive thoughts about the future and teaching mindfulness-based techniques to reduce stress levels and hyperarousal (e.g. deep breathing, progressive muscle relaxation, and guided imagery). Coping with anger and reducing anger-driven behaviors are also important therapeutic goals. The global picture relating to mental health is inevitably influenced not only by local culture, political and economic factors, but also by the presence of previous and / or concomitant traumatic events [48].

Addressing the psychological aspects of social distancing likely offers benefits in the long term, through a lower incidence of PTSD, anxiety, depression, or substance abuse, but it could also motivate participation and promote adherence to treatment [49].

Another major aspect that should be considered concerns health professionals, towards whom preventive measures may be represented by the support from supervisors and colleagues, such as clear communication about decisions, directives, and risks [49]. It is important to encourage the transmission of skills by means ofwith mentoring systems, which also promote a sense of support and interconnectedness, while reducing stigma [49]. It may also be useful to promote work in groups and moral-building activities, as it would be useful to promote shared moments of gratification and appreciation in which the efforts that the whole staff is carrying out should be verbally acknowledged [49]. It would be adequate to reduce overtime shifts, encourage shifts that allow rest and temporary relief from obligations (also preventing burnout) [49]. Mindfulness and relaxation techniques can prove to be self-help tools that health professionals could pass on to patients. For those who have religious communities of reference, ad hoc initiatives by the guides of these realities are protective and supportive [50,51].

As for PTSD treatment, where diagnosed, it should be timely and, based on the evidence available to date, the first choice should be Trauma-Foucsed Cognitive-Behavioral Therapy (TF-CBT) to reduce pessimistic and catastrophic thoughts about the future. An alternative is represented by Eye Movement Desensitization and Reprocessing (EMDR) therapy [52]. If these therapeutic modalities are not available, pharmacological treatment may consist of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepineprhine Reuptake Inhibitors (SNRIs), which should be maintained for 6-12 months to prevent recurrence and relapse of symptoms [53]. Quetiapine may also be considered, either as monotherapy or as adjunctive therapy. Alpha-adrenergic antagonists such as prazosin can be used for sleep abnormalities and nightmares, either alone or in combination with an antidepressant [52].

Discussion and Conclusions

Although only some of the psychopathological manifestations that were most highlighted during the pandemic have been reviewed in this paper, we can assert that most populations of subjects suffering from psychiatric diseas-

es can potentially present an increased risk of relapse in this particular historical moment [20]. From a psychopathological point of view, the current COVID-19 pandemic represents a new form of trauma. It has been compared to natural disasters such as earthquakes or tsunamis but, in these cases, the emergency was localized, limited to a specific area and to a specific time, and people could escape if they had the chance. In all of these circumstances the enemy was easily recognizable, while in the pandemic the "threat" can be anywhere and can be carried by the person close to us. This destabilizing environmental condition has led to some psychiatric patients an alteration in reactive judgment skills, with the assumption of risky behaviors and great difficulty in following the measures aimed at mitigating the spread of the epidemic [20].

It is therefore useful to promote initiatives aimed at acquiring epidemiological information: adequate knowledge of the distribution of risk allows for the implementation of preventive actions in terms of public health, including the protection of mental health [46,47].

In fact, it is crucial to increase the resources dedicated to mental health services and facilitate access to them, also by exploiting the use of telepsychiatry [53], which makes it possible to overcome the obstacles caused by fiduciary isolations or ascertained patient's infection, thus removing the geographical barriers between patients and operators [54]. Through the use of telepsychiatry, the effectiveness of which has now been widely proven [55], the number of patients that can be reached increases, as can be guessed, and with it the possibility of making early diagnoses and promptly setting appropriate therapies. In a period like this, opening up and relying on alternative ways of doing and building treatment paths means knowing how to respond to the concrete adversities of the moment and thus also encourage the patient to adhere to a reality plan [55].

Moreover, providing educational materials that inform the public of common stress reactions can help scale reactions and emphasize hope, resilience, and healing [49]. Recommendations for the development of positive coping strategies should be readily accessible (e.g., a dedicated website describing the warning signs of pandemic-related mental health problems). Social media, despite of the previously mentioned risks, can play a useful role in helping to share and disseminate information sources [50].

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