Chapter

"Neurocovid": An Analysis of the Impact of Covid-19 on the Older Adults. Evolving Psychological and Neuropsychological Understanding

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Abstract

When SARS-CoV-2 began to spread, older adults experienced disproportionately greater adverse effects from the pandemic, including exacerbation of pre-existing physical and cognitive frailty conditions. More severe complications, higher mortality, and concerns about disruptions to their daily routines and access to care. Knowledge about the impact of COVID-19 on the brain is rapidly accumulating and this is reflected in the increasing use of the term "*neurocovid*". Co-involvement of the central and peripheral nervous system had already been observed in SARS patients, but COVID-19 seems to invade it with greater affinity than other coronaviruses. This chapter provides an overview of the expanding understanding of the multiple ways in which COVID-19 affects the human brain, discuss the likelihood of long-term sequelae of neurocovid, and their implications for cognitive functions and behaviors in the elderly.

Keywords: COVID-19; SARS-CoV-2, neurocovid, long term pandemic fatigue, mechanisms of brain damage, brain dysfunction, neurology, neuropsychology, neuropsychiatry, cognitive dysfunctions, mood changes, anxiety, depression, social isolation, frailty, elderly, older adults

1. Introduction

Europe is a country that is getting older every day. An increasingly significant number of people find themselves in a condition of vulnerability and are at greater risk of suffering a functional loss and/or loss of autonomy [1, 2]. These conditions have been accentuated during the health emergency due to the current pandemic situation [3].

The elderly population has been burdened with a higher incidence and mortality of infection: the older adults have been shown to contract the infection in a more severe clinical form and this is especially true in Europe which, having, after Japan, the highest percentage of elderly people, has paid a very high toll in terms of mortality [3]. More than 95 per cent of the deaths involved people over the age of 60, and 50 per cent of all deaths were aged ≥80 [4].

The disease did not strike indiscriminately; it was mainly the elderly with serious concomitant chronic diseases (cardiovascular diseases, respiratory diseases, diabetes, neurodegenerative diseases, oncological diseases, etc.) who paid the highest price in terms of mortality [3, 4]. A particular incidence of fatal events has occurred among people living in social and health care residences throughout Europe [3, 4]. It is reasonable to assume that the virus has affected residential care facilities because of the community life that takes place there, affecting people already suffering from frailty and polypathology, so that the damage caused by the virus has been superimposed on that caused by coexisting diseases.

Considering the above, social distancing measures severely penalized the elderly, since they needed to be isolated as they could act as healthy carriers for the community and, if they became ill, would produce extraordinary pressure on intensive care [4].

The Covid-19 pandemic has also brought to light the concept that it is above all the frail elderly who are at high risk of functional, cognitive and psycho-social disabilities that make it difficult for the elderly to return to their pre-infection condition: this is the key to interpreting the relationship between the elderly and the coronavirus infection.

This inference is derived from what is observed about the global population. It seems increasingly likely that the majority of all those infected wills experience chronic sequelae of the disease, resulting in disability or diminished quality of life, a phenomenon now described as "*long-covid*" [5, 6]. Indeed, COVID-19 survivors can suffer from persistent symptoms after recovering [5], especially related to organ damage, post viral syndrome, and post-critical care syndrome [6]. Long-covid is characterized by breathlessness, chest tightness, cough, fatigue, myalgia, palpitations, sleep disorders and difficulty to focus [5, 6]. Anxiety and depression were also reported [5].

The SARS-CoV-2 pandemic has rekindled attention on the possible neurovirulence of this virus and the possible involvement of the central nervous system and peripheral nervous system [7, 8]. The spectrum of central and peripheral nervous systems disease in COVID-19 patients is much broader than previously thought. Some form of "*neurocovid*" appears to occur in up to 30% of positive patients. It is therefore a phenomenon that deserves to be carefully investigated and evaluated when screening and monitoring short- and long-term patients, especially the elderly.

2. Aging, frailty, and COVID-19

Aging is a natural phenomenon involving a progressive physiological transformation of the human body and of neuropsychological and behavioral functions [1, 2]. The aging phenomenon, in addition to the growing quantitative data on the total population, is characterized by the different attributes that qualitatively characterize this process and transition. In fact, elderly life is structured by different levels of independence and dependence of individuals with respect to both primary family networks and secondary networks of assistance and care [1, 2].

The conceptualization of frailty is presented as an attempt to define this heterogeneity of conditions. Frailty is a condition of marked vulnerability to adverse events caused by a reduction in the functional reserves of multiple systems of the body due to the aging process and chronic polypathology. It is a condition that represents a risk factor for disability, hospitalization, institutionalization, and death [1–3]. At first, frailty appeared in the literature with a distinctly bio-medical or clinical meaning [9], but in the last decade it has acquired bio-psycho-social

connotations as well as medical ones. Starting from the works of Gobbens et al. [10] and Van Campen [11], it is preferred to define frailty as a condition of vulnerability at a bio-psycho-social level. Today we prefer to speak of frailty in the plural. There are functional, cognitive, psycho-social, clinical, and - finally - economic frailty. These different dimensions interact together in moments of greatest difficulty. The definition of "frail elderly" therefore refers to a person who, faced with a stressful event -such as the SARS-CoV-2 pandemic - is unable to respond adequately, and therefore succumbs, with an increased risk of adverse events: mortality, disability and worsening of his/her general condition.

An increasingly significant number of older people are in a frail state, making this a hot topic. Physical and cognitive frailty have proved more useful than ever in understanding the impact of the SARS-CoV-2 pandemic on the elderly population and in guiding the principles of vaccine clinical trials [3]. Indeed, not only frail older people are particularly vulnerable to serious or life-threatening infections, but the age-related dysregulation of the immune system (due to immunosenescence and inflammaging) results in poorer responses to vaccination [3].

3. Neurological presentations of COVID-19: the polyform entity of neurocovid

Psychiatric and neurological complications were reported during the SARS epidemic in 2003 [11].

Apart from depression, anxiety disorders and suicidal ideations, fear for survival, and fear of infecting others; across all timeframes, stigmatization, reduced quality of life, psychological distress, and posttraumatic stress symptoms were reported [11]. Moreover, cases of organic hallucinosis (visual and auditory hallucinations), deliriums of persecution, temporo-spatial disorientation and hypomanic disorder were reported. In some cases, these manifestations have been classified as secondary to steroid therapy. Isolated cases of fatal Coronavirus OC43 encephalomyelitis in the face of little pulmonary involvement [12] and generalized tonic–clonic convulsion in patients with infection and cerebrospinal fluid positivity for SARS-CoV [13] have also been described.

Recent data suggesting that the COVID-19 virus also reaches the central nervous system [7, 8, 14]. It has been shown that (like SARS-CoV) COVID-19 virus exploits the receptor for the angiotensin converting enzyme 2 (ACE2) to enter cells. This discovery made it possible to investigate the expression of ACE2 in the neurological tissue and to determine the possible contribution of neurological tissue damage to morbidity and mortality caused by COVID-19 [7, 14].

The neuroinvasiveness, neurotropism and neurovirulence of the COVID-19 has been demonstrated [7]. Pathological studies suggest a direct route of neuroinvasion via haematogenous diffusion and retrograde transport by the olfactory nerve. Retrograde transport via the vagus and olfactory nerves remains hypothetical [7].

In most cases, COVID-19 would not make a direct attack on vulnerable structures. This would explain why various manifestations of the nervous system are favorable to immune suppression or immune modulation [8].

Direct affection of the central nervous system is uncommon and may result in meningitis/encephalitis [8, 15, 16], manifesting as headache, seizures, confusion, ataxia, pyramidal signs, or impaired consciousness. Direct affection of the peripheral nervous system includes hyposmia or hypogeusia [8].

Neurological disease due to the immune reaction against the COVID-19 embraces acute disseminated encephalomyelitis; acute, haemorrhagic, myoclonus; necrotizing encephalopathy [17, 18]; cytokine release syndrome (a new nosographic

entity characterized by aphasia, behavioral alterations, central hypothyroidism, cerebellar ataxia, coma, confusion, cranial nerve palsy, dysautonomia, pyramidal signs, and tremor) and mononeuritis [19]; myositis [20]; cerebral vasculitis; delirium; psychosis; transverse myelitis [21]; cranial nerve palsy; Guillain-Barre syndrome [22]. Neurological long-term complications may be also secondary to affection of the heart or the kidneys [8]. Cardiac involvement may be responsible for cardioembolic, ischemic stroke, or ischemic stroke due to hypotension [8].

The COVID-19 pandemic continues to affect millions of people globally, with increasing reports of neurological manifestations but limited data on their incidence and associations with outcome. Two recent papers report the presence of neurological symptoms in 36.2% [23] and 80% [24] of patients hospitalized with COVID-19. Neurocovid is a polymorphic entity [25]. More than seventy different symptom combinations have been reported in the literature. Symptoms of a general nature seem to be present in almost all patients, often with abnormal laboratory tests [25]. The timing of symptoms varies from early states (anosmia, headache, myalgia) to later stages (altered mental status, neuromuscular disorders, seizures, stroke) [25]. Some neurological symptoms may persist (such as anosmia or headache), while others may cause persistent disability (such as stroke or polyneuropathy) [25].

4. Brain imaging findings and new classification system

The existence of alterations in brain structure as a result of SARS-CoV-2 infection appears to be well established [26, 27], even in subjects whose only symptom was anosmia [28]. Post-mortem structural MRI examinations revealed brain parenchymal abnormalities, subcortical micro and macro hemorrhages, cortico-subcortical oedema, non-specific deep white matter changes and asymmetrical olfactory bulbs [29]. Similar evidence is also found in hospitalized patients [30–33]. The most common neuroimaging findings include cortical signal abnormalities on fluid-attenuated inversion recovery images, associated with leptomeningeal enhancement or cortical diffusion restriction [26], which may reflect autoimmune or infectious encephalitis, hypoglycaemia, hypoxia, or seizures [34]. Acute demyelinating lesions have also been depicted [35–38].

Starting from the observation that different neurobiological processes and mechanisms may lie behind the onset of neurocovid, a three-stage MRI classification system to categorize patients has been recently proposed [39]:

- *Neurocovid Stage 1*: Viral damage is limited to epithelial cells of the nose and mouth with temporary loss of smell and taste.

- *Neurocovid Stage 2*: Inflammation floods from the lungs through the blood stream, leading to blood clots that prompt small and large strokes.

- *Neurocovid Stage 3*: The inflammation damages the blood–brain barrier. Inflammatory markers and viral particles infiltrate the brain, causing confusion, coma, encephalopathy, and seizures.

5. Aging, COVID-19, and neurocovid

Frailty elderly are more prone to cognitive impairment and SAR-CoV-2 infection [3]. Preexisting comorbidities (i.e., cerebrovascular, and cardiovascular

diseases, diabetes, hypertension, obesity, malignancy, and respiratory diseases) seem to be predictor of disease severity and neurological complications [40]. Moreover, elderly individuals with pre-existing neurological diseases are susceptible to more severe forms of COVID-19 infection and higher mortality rates [40, 41]. Indeed, it is now established that older people with Alzheimer's and Parkinson's diseases exhibit independent association with the rate of change in both physical frailty and cognitive impairment [42], placing these individuals at higher risk of COVID-19 disease severity [40]. Specifically, patients with Parkinson's disease are vulnerable to infection due to advanced age, bulbar symptoms, respiratory dysfunction, frailty and cognitive impairment. Similarly, patients with Alzheimer's disease and major neurocognitive disorder are at increased risk of infection and adverse events [43].

Elderly patients aged 65 years or older are known to have higher rates of neurological complications [40]. Commonly reported neurological dysfunctions include dizziness, confusion, fatigue, and headache. They may experience also atypical presentations such as falling or postural instability. Other neurological complications include cerebrovascular disease, cognitive impairment and neuropsychiatric disease [40]. Altered mental status and epilepsy have been also reported [25].

Older patients are particularly vulnerable to the psychological burden of COVID-19 [40]. Disturbed sleep, moderate to severe depression and anxiety have been reported [44]. Loneliness related to quarantine and social isolation has had a significant impact on mental health outcomes in the elderly [45], especially for those with chronic neurological diseases and neurocognitive disorder [46]. Quarantine comes to induce a rapid increase in behavioral and psychological symptoms in ~60% of patients and stress-related symptoms in two-thirds of caregivers [46]. The most common symptoms included agitation, anxiety, apathy, irritability, and sleep disturbances [46]. Similarly, a worsening of symptoms was observed in 67.5% of Parkinson's patients during the quarantine period [47].

6. Implications for neurocognitive and neuropsychiatric disorders

COVID-19 causes high levels of acute respiratory distress, hypoxia, and proinflammatory cytokines - all of which contribute to the onset of cognitive decline in the elderly [26]. It therefore seems reasonable that cardiovascular and cerebrovascular disease secondary to infection may contribute to an increased long-term risk of cognitive decline and major neurocognitive disorders in recovered individuals [26, 48, 49].

After the SARS pandemics, one in five infected individuals reported memory problems [50]. Likewise, the current pandemic situation appears to have resulted in a dysexecutive syndrome in one in three individuals who have been hospitalized [50]. Poor memory, attention and speed of information processing impairments have commonly been reported with COVID-19 [39, 51].

This could lead to a vicious circle whereby impaired cognitive abilities may cause poor occupational and functional outcomes for individuals recovered from COVID-19 that precipitate or exacerbate mental health concerns, and poor mental health may likewise contribute to cognitive dysfunction [52].

Abnormalities in the mental status (defined as a severe change in personality, behavior, cognition, or consciousness) have been reported [39, 53], in line with what happened previously with the SARS pandemic [26]. COVID-19 patients experienced a high level of post-traumatic stress symptoms and a significantly higher level of depressive symptoms [39, 54]. In the post-illness phase, the point prevalence of post-traumatic stress disorder seems to be around 32%, depression

and anxiety disorder both around 15% [50]. Patients with pre-existing psychiatric disorders reported a worsening of their symptomatology [54].

Viral infections of the brain may have an impact on the risk of AD or Parkinson's disease [26]. Olfactory deficits (hyposmia/anosmia) are among the sentinel symptoms of COVID-19 infection [55] and are characteristic of neurodegenerative disorders [56–58]. Indeed, anosmia is associated with high levels of interleukin-6, an inflammatory mediator causally implicated in brain disorders and which action is blocked by tocilizumab as part of COVID-19 treatment [59].

To date, the mechanisms by which neurological abnormalities result from SARS-CoV-2 infection have yet to be fully established. Nevertheless, the contribution resulting from direct effects of SARS-CoV-2 on neuronal function and survival or glial reactivity, exaggerated cytokine responses or anti-neuronal antibodies are all likely, as are sequelae of cerebrovascular accidents [26]. The data available to date suggest an increase in neuropsychiatric and neuropsychological long-term sequelae, including cognitive decline, motor impairment, and affective and psychotic disorders [26].

7. Management and treatment of neurocovid in elderly patients

Treatment of neurocovid is currently based on existing evidence-based treatment for specific neurologic conditions in conjunction with systemic treatment of COVID-19 infection (i.e., antivirals, corticosteroids, and immunomodulators) [25, 40].

The contagion is associated with neuropsychiatric symptoms [60] and it is recommended to set up a baseline mental status examination for all hospitalized COVID-19 old patients [61].

Delirium management has long been a priority in the care of older adults [25]. Every hospitalized older person should be considered at high risk for developing delirium, and prevention should be optimized [58]. Non-pharmacologic interventions include patient-centered care with adequate hydration and sleep, optimization of hearing and vision, early mobilization, frequent re-orientation, reduction of social isolation and regular visits, connecting patients with their families, and minimization of unnecessary lines, tubes, polypharmacy, and precipitating medications [61, 62]. Low-potency neuroleptics and alpha-2 adrenergic agents may be useful [60].

Neurologists, geriatricians and neuropsychologists must be involved at an early stage and be prepared to handle the peculiarities of neurocovid. It is advisable to have patients undergo neuropsychological assessment even 6–8 months after their discharge from hospital, especially if cognitive problems, slowness in processing information or poor attention persist [39].

Patients with below cut-off test scores should be evaluated for rehabilitation and cognitive enhancement interventions. This would reduce the risk of facilitating an earlier/rapid age-related cognitive decline [3, 39].

8. Conclusions

The high probability of long-term neurological and neuropsychological consequences of COVID-19 indicates the importance of continuous surveillance for neuroimmune and neurodegenerative disorders in infected individuals, especially the elderly [7]. Until an effective treatment is discovered, or the expected global population-wide vaccination coverage is achieved, clinicians need to be alert to neurocovid [25].

Researchers have postulated several explanations for the severity with which COVID-19 occurs in the elderly and the increased mortality rate in this population group. Age-related epigenetic changes, inflammasome activity, covalent modifications of human and viral proteins, etc. are all possibilities currently being explored by scientists [63]. Future research will lead to a full understanding of the key factors leading to the vulnerability of the elderly population, especially about the intersection of aging, vulnerability to infection and alterations in cognitive-behavioral patterns. A neurocognitive approach could prove extremely useful for this purpose. It seems particularly appropriate to deepen our knowledge of the deleterious effects of SARS-CoV-2 and COVID-19 infection on the central and peripheral nervous system (in both structural and functional terms), and to assess through predictive medicine how these effects may contribute to the chronic burden of disease in the coming years. Notably, key questions need to be answered about the impact of the risk of cognitive decline in old age, Alzheimer's disorder, Parkinson's disorder and other neurodegenerations. In addition, a change of pace in the observation of the various conditions of elderly life can make it possible to construct complementary health and welfare interventions that have the characteristic of elasticity and immediacy to be placed alongside the traditional ones - above all in response to phenomena such as neurocovid.

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Conflict of interest

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