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NEUROPSYCHOLOGICAL CONSEQUENCES OF COVID-19: CURRENT APPROACH AND CLINICAL RECOMMENDATIONS

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SUMMARY

Nearly two years into the pandemic, a large body of data has emerged on how COVID-19-positive patients function with the viral infection. It is now known that the virus targets the central nervous system(CNS). As a result, in addition to the expected common health complaints, patients display cognitive and emotional problems. Cognitive deficits should be expected particularly in patients who have arrived at an intensive care unit as a result of respiratory failure, in patients suffering from comorbid neurodegenerative diseases and respiratory conditions, as well as in the elderly. However, these may also occur in patients with moderate to mild symptoms as well as in those of a younger age. The cognitive impairment has an unknown profile. Given the hypothesised hippocampal vulnerability to the SARS-CoV-2 virus, one might expect particular difficulties with memory, attention, information processing, and executive functions. With varying neuropsychological and emotional problems, convalescents in trying to return to their social, family and professional life require professional psychological assistance. The role of neuropsychologists is here crucial. Indeed, many patients will require a detailed, multifaceted neuropsychological diagnosis that will form the basis for subsequent neuropsychological rehabilitation. An early detection of neuropsychological manifestations could modify the risk of subsequent irreversible impairment and further neurocognitive decline.

Key words: elderly, chronic pulmonary diseases, cognitive dysfunction, neurodegenerative diseases, mental health, emotional functioning, brain fog, global pandemic, psychosocial factors, neuropsychological diagnosis, neuropsychological rehabilitation, hypoxia, infection of SARS-CoV-2, NeuroCOVID 19, long COVID

INTRODUCTION

In December 2019, the first reports came from China about cases of pneumonia caused by a previously unknown coronavirus, SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*), responsible for a disease called COVID-19 (coronavirus disease 2019). Since then, the pandemic has spread worldwide, affecting people's physical and mental health as well as quality of life. The first confirmed infection of SARS-CoV-2 and hospitalization in Poland was announced on March 4th 2020, and the first confirmed fatality on March 12th. The increase in infections led to the first lockdown-type control measures – with the closing of schools, universities, kindergartens, offices, shopping malls, as well as widespread cancellation of public events. These restrictions were strengthened several days later, with limitations being placed on non-family gatherings, the closure of beauty salons, parks, beaches,a curfew being imposed on minors restricting them to their homes, and limited access to public health services. During the course of the pandemic, even further numerous restrictions were imposed affecting the everyday life of Polish citizens and raising Poles' objections, including the limiting of religious gatherings, funerals and weddings, closure of hotels, restaurants, limiting of the public transportation capacity etc., and the imposition of the obligation to wear masks. Not with standing the restrictions, in Poland up to Oct 26th 2021, over 2.9 million cases of COVID-19 had been diagnosed with over 76.5kdeaths (Worldmeters.info).

After nearly two years of the pandemic, the main symptoms have been identified. Beyond the respiratory system also digestive, circulatory and nervous system are often targeted by the virus. Hence, COVID-19 is considered to be a multi-organ disease. Viruses enter body cells through ACE2 receptors. These receptors are found in multiple organs of the body, including in the lungs, heart, liver and intestines. They also appear in the central nervous system.

After entering the body, The SARS-CoV-2 virus infects people through the S (spike) protein that binds with the peptidase angiotensin-converting enzyme 2 (ACE-2) receptors, and, as a consequence, penetrates into the cells (Matheson & Lehner, 2020). The virus infects other organs by attacking cells with the same receptors, enabling the virus to cause damage outside the respiratory system. Furthermore SARS-CoV-2 infection followed by a contraction of COVID-19 can lead to respiratory failure, and therefore to hypoxemia and hypoxia, which intensifies the risk of irreversible organ devastation (Matheson & Lehner, 2020; Wiersinga et al.,2020).

Risk factors for severe infection of SARS-CoV-2 include advanced age (Garg et al., 2020), male gender (Boye et al., 2021; Garvin et al., 2020), and medical comorbidities such as hypertension, and diabetes – even identified as an independent risk factor for COVID-19 complications (Cummings et al., 2020; Oliveira et al., 2020; Boye et al., 2021) – obesity (Cummings et al., 2020), smoking (Reddy et al., 2020), and chronic pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) (Baker et al., 2021; Guan et al., 2020; Lippi & Henry,

2020; Young et al., 2020) or obstructive sleep apnea (OSA) (Baker et al., 2021; Maas et al., 2021). Interestingly – most of the listed factors overlap significantly with the at-risk groups for MCI and cognitive decline (Baumgart et al., 2015).

The SARS-CoV-2 virus is considered to have a neotropic capability, which means it can easily migrate from one site to another within the body and replicate in the brain. Histopathological examination of the brains of deceased COVID-19 patients indicate the potential of SARS-CoV-2 to infiltrate the central nervous system (Coolen, et al., 2020; Solomon et al., 2020). Moreover, the outcomes of neuroimaging studies conducted by various research centers around the world confirm the prevalence of brain abnormalities linked to the course of infection of SARS-CoV-2 . A systematic review of 26 articles (including 21 case reports, and 5 cohort studies) noted that about a third of acute/subacute COVID-19 patients referred for neuroimaging show brain abnormalities suggestive of a COVID-19-related etiology. Abnormalities were noted in the bilateral medial temporal lobes, frontal, occipital, parietal, and temporal lobes. Changes were also registered in the insular cortex, subinsular regions, cingulate gyri, cerebral peduncle and internal capsule, the thalamus, midbrain, pons, parahippocampal gyri and basal ganglia, as well as the splenium of corpus callosum, olfactory nerves/bulb, and gyrus rectus (Egbert et al., 2020). In a Chinese study, changes were mainly observed in olfactory cortices, hippocampi, insulas, the left Rolandic operculum, left Heschl's gyrus and right cingulate gyrus (Lu et al.,2020).Observed changes in the brain were found to correlate with memory loss.It remains uncertain whether these changes in the brain persist over time, butit is highly likelyinfection ofSARS-CoV-2 is responsible for resulting brain lesions. Evidence for this is supplied by a careful investigation of studies, excluding those instances in which subjects were likely to have suffered from pre-existing brain lesions associated with conditions unrelated to COVID-19.

It is still unclear whether the effects of SARS-CoV-2 infection on the brain are indirect (mediated by oxygen starvation of the brain and/or the body's extreme inflammatory response in severely affected patients) or direct (mediated by the virus' invasion into the brain). There are at least four possible pathogenic mechanisms that may account for the detrimental effect of contraction of COVID-19 on the CNS:

- systemic inflammation,
- peripheral organ dysfunction (liver, kidney, lung),
- direct viral encephalitis,
- cerebrovascular changes.

In response to the infection, the body activates immunological processes with the release of cytokines and chemokines. In the case of the most severe course of the disease, a hyperactive immune response is observed – a "cytokine storm", which causes a multisystem failure in the body. Among the symptoms, headache, arthralgia, fever, or even delirium paresis and seizures are listed. This prolonged activation of the immune system (Mehta et al., 2020) and cytokines ability to cross the blood-brain barrier, may cause a deterioration in the functioning of the

CNS. However, the incidence of some organ damage is too high to be attributed only to the cytokine storm. Therefore, other hypotheses are considered. Another potential cause is the phenomenon of molecular mimicry, in which the immune system confuses the antigens of the SARS-CoV-2 virus with structurally similar proteins present in the CNS, and, as a result, destroys both (Vlachoyiannopoulos et al., 2020). This autoimmune mechanism probably leads to the destruction of neurons and its neuropsychological consequences.

Many other plausible hypotheses for the cognitive decline caused by the contraction of COVID-19 are discussed. One of them focuses on the basic claim that the brain and its functioning largely depends on the state and efficiency of other, non-nervous, systems. In this context, disturbances in the functioning of the respiratory system – difficulties with breathing, persistent cough or reduced respiratory surface of the lungs – directly lead to brain hypoxia.

On the other hand, viral infections can cause cognitive symptoms through direct viral effects on the CNS or through indirect phenomena. Therefore, researchers postulate the theory that neurons become infected after SARS-CoV-2 has entered the brain via the ACE2 receptors (widely expressed in the CNS) via a route that is not yet understood. One of the suspicions in this area falls on the olfactory neurons or crossing of the blood-brain barrier in the hypothalamus or pituitary gland (Song et al., 2021; Wu et al., 2020) or the olfactory epithelium (Kerslake et al., 2020) or any pathway for the spread of other human coronaviruses (Cheng et al., 2020). These routes include the hippocampus, hypothalamus, brainstem and neurotransmitter pathways.

Song et al. (2021) found that infected cells take up more oxygen and nutrients to produce viral proteins, preventing these nutrients from being delivered to neighboring (uninfected) neurons. This may lead to degradation from malnutrition and hypoxia. Therefore, it is not the result of the virus's actions, but the outcome of the infection's course of action that causes the greatest destruction. This is why the direct viral infiltration is probably not the main mechanism of CNS damage.

Another hypothesis is based on research showing that the coronavirus interferes with the function of the renin-angiotensin system (RAS), which controls the levels of bradykinin and may cause the so-called "bradykinin storm" (Garvin et al., 2020). Consequently, an increased risk of inflammation, blood clots, strokes and brain damage, which are symptoms seen in the most severely ill patients, occurs. Leaks from blood vessels also trigger COVID-19 symptoms in the nervous system and brain, as bradykinin is likely to increase the permeability of the blood-brain barrier, therefore causing dizziness, seizures, delirium, or even strokes. However researches findings concerned the SARS-CoV-2 crossing the blood-brain barrier are inconclusive (MacQueen & MacQueen, 2021). Authors suggest that one of the reasons are the ethical problems surrounding the autopsy of COVID-19 patients and too little viral RNA findings in samples that were legally obtained for studies.

Therefore it is best to assume that in most cases neurological manifestations of COVID-19 arise from a combination of the above. As a result, patients in re-

covery from infection of SARS-CoV-2 may present neurological, neuropsychological and emotional problems in addition to other well-known conditions.Based on previous research, coronaviruses can cause demyelination, neurodegeneration, and cellular senescence, which accelerate brain ageing and exacerbate neurodegenerative pathology (Desforges et al., 2014; Lane & Hosking, 2010). It has been also reported that most of COVID-19 patients had common complaints such as poor concentration, declined memory, and insomnia, as well as anxiety and depression symptoms, indicating cognitive impairments after the SARS-CoV-2 infection (Sheng et al., 2005).

According to the first-hand evidence from Wuhan, 36.4% of COVID-19 patients presented neurological symptoms such as dizziness, headache and impaired consciousness during hospitalization. The percentage and extensiveness were higher in patients suffering severely (Mao et al., 2020). It is currently estimated that neurological symptoms occur more commonly and affect 36% to 84% of patients (Holmes et al., 2020; Mao et al., 2020). These include mild symptoms like headaches, loss of smell and taste, tingling sensations, dizziness, nausea and severe fatigue, as well as more severe outcomes such as aphasia, strokes and seizures, fluctuating consciousness, thrombosis, and encephalopathies (Ellul et al., 2020; Gupta et al., 2020;Mao et al., 2020;Varatharaj et al., 2020). A UK study found that out of 125 patients hospitalised for infection of SARS-CoV-2, 62% had suffered a cerebrovascular event, with ischaemic strokes predominating (57 patients, 74%). It has been established that these complications affect elderly patients in particular, no doubt due to the condition of their central nervous system (Varatharaj et al., 2020).

As a result of infection, a set of cognitive impairments happen, so-called “COVID brain fog”, which, according to some data, occurs in up to 81% of those infected (Graham et al., 2021) and may persist from several weeks (Theoharides et al., 2021) to several months (Graham et al., 2021). Its characteristics include a deterioration in physical and mental activity, extreme fatigue, a sense of lightheadedness, attention, memory and communication skills impairment, as well as a sense of “foggy” consciousness and depressed mood (Ocon, 2013). Patients liken it to the dizziness experienced before losing consciousness or feeling light-headed. They manifest problems with performing even uncomplicated activities, accompanied by a feeling of being lost (Kaseda & Levine, 2020). The reported symptoms are similar to those seen in people with concussion, as well as with chronic fatigue syndrome (CFS), which is a common contraction of COVID-19 complication (Morley, 2020). CFS is characterized by at least six months of chronic fatigue, both physical and mental, accompanied by mild cognitive impairment (MCI) (Ocon, 2013). In addition, there are studies confirming the effect of COVID-19 on sleep-related disorders (Morin & Carrier, 2021), which may result in chronic fatigue during the day and, as a result, problems with attention, memory, thinking, planning and language processes.

Most of the reports on the incidence of neurological complications are for patients hospitalised for SARS-CoV-2 virus infection. The published articles are

often case reports and clinical experiences. However, there is little information on patients with mild to moderate forms of the disease. Many questions have still remain unanswered, for example: how common are neurological complications? Which patient group is most at risk? What are the long-term consequences? The most important question, however, is: what is the impact of CNS infection on the cognitive and emotional functioning and daily life of patients? These are particularly troublesome, for they determine the patient's ability to function, affecting his/her perception of their past, present, and future life. They hinder daily routines, while also making it difficult to cope with responsibilities and everyday-life situations and professional roles. At the same time, they promote social withdrawal, while also being a barrier to treatment, rehabilitation, and a major problem in family life and other relationships. Last but not least, they are a determining factor of the patient's quality of life.

However, the cognitive manifestations associated with the severity of a novel coronavirus (SARS-CoV-2) infection are unknown.Therefore, scientists are now facing the challenge of explaining the hypothesised COVID-related cognitive difficulties. It is undeniable that cognitive functioning as affected by COVID-19 requires empirical research and theoretical studies. This is important from a theoretical point of view (seeking to determine specific features of and gaining more knowledge about mental functioning), but also from a practical point of view (formulating a complete model of functioning, developing reliable and accurate measurement tools, preventive programmes, and strategies of neuropsychological therapy that favour adaptation and quality of life improvement for patients).

The general aim of the present article was to present the current state of knowledge on the specificity of cognitive functioning of COVID-19 patients, as well as providing preliminary recommendations for clinical neuropsychologists, for diagnosis and rehabilitation. The article also includes excerpts from interviews with COVID-19 patients with cognitive dysfunctions in order to better understand their situation.

A web-based comprehensive search of peer-reviewed journals was conducted based on a variety of key terms: brain fog, COVID-19, coronavirus, long COVID, COVID brain fog, hypoxia, cognitive dysfunction, mental health, respiratoryillness, neuroinvasion, global pandemic. Articles were chosen based on relevance to the current topic. Databases searched included Google Scholar, PubMed, and EBSCOhost Web (Academic Research Source eJournals, Academic Search Ultimate, APA PsycArticles, APA PsycInfo, MEDLINE).

Cognitive dysfunctions in COVID-19 patients

Clinical reports indicate that, besides commonly known difficulties, patients in recovery may present cognitive problems, such as trouble concentrating, remembering, attention, and performing routine activities (Almeria et al.,2021; Hampshire et al., 2020; Miskowiak et al., 2021; Zhou et al., 2020). Executive dysfunctions, including attention deficits, disorientation, and difficulties with following verbal instructions were also common (Almeria et al., 2021; Helms et al.,

2020; Raman et al., 2021). The observed executive functioning deficits are similar to HIV-associated neurocognitive disorder, which has known associations with increased inflammation and immune activation (Hellmuth et al., 2021; Yuan et al., 2015). On the other hand, Kaseda and Levine (2020) classify cognitive impairment and other neurological symptoms diagnosed in patients with the contraction of COVID-19 as a consequence of post-traumatic stress disorder (PTSD). Some cognitive disorders are probably just temporary symptoms, but a common mistake made by convalescents is making a decision too early to return to work or school, without a sufficiently long recovery period after the disease.COVID-19 survivors tend to refuse psychological or psychiatric help, assuming that they are able to cope with the difficulties themselves, despite severe, even PTSD symptoms (Pąchalska & Nowaczyk, 2021). As a consequence, such patients face problems with resuming their professional activity at the level at which they performed their duties before the infection.

Interestingly, patients themselves report that cognitive symptoms significantly impair their daily functioning, affecting work and family life. Greater objective cognitive impairments were associated with more subjective cognitive difficulties, absenteeism, lower work function and poorer quality of life (Miskowiak et al., 2021). We have made numerous clinical observations which confirm that it is particularly difficult for patients to return to work. Many of them have complained of feelings of confusion, uncertainty, and difficulty with routine activities. One of the respondents, a computer programmer by profession, stated: "*I work much longer hours but I'm unable to complete simple tasks. I no longer see code. I feel like I can't deal with anything anymore*."

Concentration problems are particularly troublesome for many patients. How serious is the scale of the problem is shown by a US survey study (> 1500). Difficulty concentrating and focusing was experienced by more than 50% of patients and was the fourth most reported longterm symptom after the contraction of COVID-19 (Lambert & Survivor Corps, 2020).

It is estimated that patients who experience cognitive impairment following infection of SARS-CoV-2 may account for between 20% and 65% of all cases, with deficits also affecting those presenting mild to moderate symptoms and young patients alike(Almeria et al., 2020; Belluck, 2020; Dinakaranet al., 2020; Miskowiak et al.,2021; Nalleballe et al., 2020; Woo et al., 2020). For example, a study by Woo et al. (2020) included 18 mostly young patients 20– 105 days after recovery from mild to moderate disease. As established,14 (78%) patients reported sustained mild cognitive deficits, while short-term memory, attention and concentration were particularly affected by COVID-19.Interestingly recent findings also suggest that the risk of persistent symptoms after COVID-19 is not necessarily associated with its initial severity (Jacobson et al., 2021).

Still, the most significant risk factor for cognitive impairment is represented by severe symptoms of COVID-19, requiring mechanical ventilation.The literature on cognitive ability following acute respiratory distress syndrome (ARDS) shows that those who have spent time in intensive care (a population that over-

laps with ARDS) are known to experience lasting cognitive impairment. It is estimated that up to 78% of people with ARDS had cognitive problems a year post-discharge and approximately 50% at two years. Self-reported everyday memory failures, such as forgetting medication and appointments, have been found to persist in patients five years post-discharge (Wolters et al.,2013). Therefore, it is to be expected that lasting cognitive impairment likely to occur frequently in people who have had severe forms ofCOVID-19, even without obvious neurological presentation in acute stages.

Little is known about this pattern and the severity of cognitive impairment after COVID-19 in relation to the disease variables. Based on the hypothesised hippocampal vulnerability to the SARS-CoV-2 virus, one might expect particular difficulties with memory, attention, information processing, and executive functions. However, it is highly likely that cognitive functioning patterns in patients will be more heterogeneous. It is also unclear whether complications will persist and for how long.The newest research (Aknin et al., 2021; Jacobson et al., 2021; Liu et al., 2021) and everyday clinical practice indicate the existence of long-term persistent symptoms and functional impairment that is commonly referred to as “long COVID”. It lasts for 3–4 months after COVID-19 diagnosis, whether or not the patient was hospitalized. Among it symptoms “profound fatigue” is widely recognized, as well as other typical COVID-19 symptoms includinga cough, breathlessness, muscle and body aches, chest heaviness or pressure, palpitations, fever, headache, and pins and needles. A common feature is the relapsing nature of the illness and cognitive impairment, especially memory loss. It is therefore highly likely that cognitive dysfunctions will persist in patients long after recovery.The pathological mechanisms of cognitive impairment are also unknown.

One should pay attention to inflammatory processes, higher D-dimer levels – a marker of thrombosis during acute illness –and restricted oxygen delivery to the brain (Zhouet al., 2020; Miskowiak et al., 2021). The relationship between more cognitive impairments and poorer pulmonary function suggests that reduced oxygen delivery to the brain may play a particularly important role in patients’ cognitive impairments. In keeping with this interpretation, poorer verbal memory and lower psychomotor speed are correlated with higher D-dimer levels – a marker of thrombosis or pulmonary coagulation disorder, which may suggest vascular consequences cerebrally, perhaps with hypoxia of the brain or direct damage from micro-embolisms. This would explain the pronounced impairments in verbal learning and memory, which depend on the integrity of the hippocampus, a region off the brain highly susceptible to hypoxia (Hota et al., 2007). Importantly, these putative pathogenic processes may not be specific to COVID-19; hypoxia has been highlighted as a common cause of cognitive decline in acute respiratory distress syndrome that is associated with cerebral atrophy (Hopkins et al., 2005) and a degree of verbal memory and executive function impairments (Hopkins et al., 2005). It is assumed that hypoxia due to acute respiratory failure is a strong predictor of persistent cognitive deficits over time (Wolters et al., 2013; Ritchie et al., 2020).

There have been a small number of scientific studies focusing on the cognitive functioning of patients after infection of SARS-CoV-2. Most have been conducted remotely or by telephone with small respondent samples. The studies have been conducted mainly on patients with severe symptoms and who were hospitalised for COVID-19. These types of patients should be interpreted in the context of potentially confounding factors, such as hospitalization, isolation and medication. Generally speaking the main problem facing the current research is the lack of a uniform methodology. This is, of course, mainly dictated by the pandemic situation itself, but the question remains how to compare the results of patients in followup if one study is conducted on patients who are hospitalized, another, referring to cognitive functions over the phone, while others to a very limited population or even a case study? Two aspects related to COVID-19 incidence should also be noted, which are quite largely overlooked in the research relating to psychological and neuropsychological functioning. One of them is the issue of the treatment used to combat the illness, the other – the morbidity of children and adolescents. The lack of an unequivocal therapeutic procedure and, in line with the current status, of a registered effective COVID-19 drug with a known effect on the central nervous system, significantly hampers the possibility of drawing unequivocal conclusions from the individual studies. Regardless of whether they were carried out in the place of treatment or residence, and regardless of the age of the respondents – we cannot be sure whether the pharmacotherapy used did not affect the obtained results. In summary, the picture of the cognitive functioning of patients after the contraction of COVID-19 produced by previous studies seems to be somewhat simplified.

For example, in the case of the Chinese (Zhou et al., 2020), 29 recovered patients were examined (from 30 to 64 years). Patients with a history of mental disorders, or current treatment for mental illnesses, wereexcluded.COVID-19 patients exhibited cognitive dysfunction in maintaining sustained attention. The findings indicated that cognitive impairments exist even in patients that have recovered from COVID-19. According to the researchers, cognitive impairments might be possibly linked to the underlying inflammatory processes (Zhou et al., 2020).

On a larger scale, internet-based testing of cognitive functions in > 84,000 people with suspected or biologically confirmed COVID-19 revealed even broader cognitive impairments ranging across memory, attention and executive functions after recovery from COVID-19when controlling for age, sex, education levels and pre-existing comorbidity (Hampshire et al., 2020). Broader cognitive impairments have also been shown in Danish studies (Miskowiak et al., 2021). The study examined 29 COVID-19 patients 3–4 months after theirhospital discharge. The COVID-19 patients exhibited cognitive impairments across their verbal learning,executive function and working memory. According to the researchers, cognitiveimpairments were associated with the degree of long-termpulmonary dysfunction and respiratory symptoms and with the D-dimer levels during acute illness, suggesting a potential link to restricted oxygen delivery to the brain. Restricted oxygen delivery to the brain is also implicated by Spanish researchers

(Almeria et al., 2021).Patients that required oxygen therapy during hospitalization had cognitive impairment. This could be explained by the continuous hypoxia caused by pulmonary disease related to the SARS-CoV-2 infection. In addition, researchers also indicate a potential SARS-CoV-2 invasion into the CNS. Patients presenting neurological symptoms such as headache, anosmia, or dysgeusia had lower scores in memory, attention and executive function subtests as compared to asymptomatic patients.

It should be emphasized that in all the presented studies an attempt was made to exclude patients with previous known cognitive impairment, any central nervous system or psychiatric disease.Nevertheless, the cognitive effects of viral infection may be much more severe for patients with comorbid neurodegenerative diseases such as vascular dementia, Alzheimer's disease and multiple sclerosis, or in patients at an advanced age.The infection of SARS-CoV-2 will contribute to the exacerbation of pre-existing degenerative neuropathologies. Evidence strongly suggests that patients surviving the contraction of COVID-19 are at high risk for subsequent development of neurological disease and in particular Alzheimer's (Heneka et al., 2020) or Parkinson's disease (Pereira, 2020).

Aged people – one of the highest risk groups for severe manifestations of COVID-19 –are a particularly vulnerable group. One mechanistic explanation common to the effects of old age preexisting dementia and SARS-CoV-2 infection is a suppressed neurotrophic expression of the ACE-2 which plays a protective role, inhibiting cognitive impairment (Li etal., 2020). In addition, the elderly typically develop neurodegenerative or cerebrovascular disease and often have underlying MCI, commonly hypertension, diabetes mellitus, obesity and organ damage from smoking. This overlap argues that there is a compelling need for prospective neurological and neuropsychological surveillance and care.For example, in a study conducted in the United Kingdom, out of 125 patients (mean age 71 years) hospitalised for infection of SARS-CoV-2, significant cognitive deficits (resembling dementia) were reported in 6 patients (Varatharaj et al., 2020). At this point, we would like to describe the case of our patient who, after contracting COVID-19, experienced a significant cognitive decline. Deficits were evident in objective neuropsychological testing as well as in the subjective perception of the patient and her family. In particular, the patient noticed a considerable deterioration in the power of her memory. She also reported she was finding it increasingly difficult to cope with tasks that involved complex planning. It had become a particularly acute problem for the respondent to find the right items when shopping and to prepare dinner for the whole family. It is also clear that cognitive disabilities after COVID-19 are associated with her quality of life. She was of the opinion that her problems were clearly exacerbated by the illness.

Patients with pulmonary diseases are also at risk, especially theCOPD and OSA patients (Lippi & Henry, 2020) experience an approximately 5-8-fold greater risk for SARS-CoV-2 infection compared to a similar population not affected by these comorbidities. In both diseases cerebral hypoxia is the leading symptom. COPD is a group of progressive lung diseases, especially emphysema and

chronic bronchitis, in which patients experience continuous daily hypoxemia (Bailey et al., 2021). At the same time, OSA is a disorder characterized by intermittent night-time hypoxemia caused by brief cessations of breathing during sleep. Reductions in grey matter in COPD patients are found in the cingulate cortex, hippocampi, and amygdala (Esser et al., 2016), as well as limbic and paralimbic structures (Zhang et al., 2012). The latter are positively correlated with PaO2 and negatively associated with disease duration. The rapid rate of cognitive decline in patients with severe COPD, when compared to those with milder COPD (Hung et al., 2009) or even healthy controls, resembles an accelerated dementative process (Witkowska, 2011). Among the cognitive deficits, impairments in executive functioning, attention, psychomotor speed, and memory are observed (Dodd et al., 2010). Meanwhile due to widespread reductions in grey and white matter, also hypometabolism and hypoperfusion across a number of brain regions estimated at 24%–89%, individuals with OSA experience some degree of cognitive impairment (Antonelli-Incalzi et al., 2004; Findley et al., 1986). Researchers point to the executive dysfunctions, attention, psychomotor speed, and verbal memory deficits. Lung damage and the resulting COVID-19-induced hypoxemia probably indirectly contribute to neuronal damage and subsequent cognitive decline (Baker et al., 2021). Interestingly, the patients with COVID-19 ARD Scan show hypoxemia despite the absence of severe lung damage (Gattinoni et al., 2020). This “silent hypoxaemia” requires intubation and prolonged mechanical ventilation.

Effect of psychosocial factors on cognitive functioning

The global pandemic has contributed to a major lifestyle change affecting many people’s mental health. The pandemic has intensified isolation, loneliness, and anxiety. Many people have experienced financial difficulties related to the global economic crisis, and traumatic life events such as the death of friends and relatives. Chronic stress has become commonplace – even for young people.In a study of young adults, 29% of respondents indicated experiencing “high” or “very high” levels of stress, a percentage figure that far exceeds that of pre-pandemic levels (Mazza etal., 2020). In addition, prolonged home isolation or hospitalisation (promotes the aggravation of depressive disorders, increases anxiety, stress, and leads to the development of PTSD symptoms (Agarwal et al., 2020; Pąchalska & Nowaczyk, 2021). Most generally, a pandemic affects mental health by contributing to an increase in the variety of psychopathological disorders.

One situation seems to be particularly difficult for COVID-19 survivors. Not infrequently, patients experience stigma, guilt, anger, depression, sleep disorders, PTSD, and adaptation or anxiety disorders (Bowman et al., 2021). Nevertheless, fluctuations in COVID-19 patients’ mental condition cannot be explained solely by adaptive factors. It is difficult to decide whether mental changes associated with infection of SARS-CoV-2 are reactive and therefore a response to the disease, its complications, isolation, and stress, or whether they are a result of infectious factors and CNS damage. On the one hand, contraction of COVID-19

should be regarded as a psychologically difficult situation that favours the development of psychopathological disorders. On the other hand, the bulk of data suggests that these disorders should not be considered solely as a reaction to illness. Mood swings, anxiety and fatigue have been observed even in recovering patients with mild symptoms of COVID-19 (BPS, 2020) and are common after recovery from the infection of SARS-CoV-2, especially in those with pre-existing mental illness (Holmes et al., 2020; Bowman et al., 2021). A large-scale study found that 75% of people hospitalized with COVID-19 experience symptoms for at least six months after recovery, including fatigue, depression and sleep difficulties (Huang et al., 2021). The symptoms can occur after mild illness and across all ages, while the severity of persistent symptoms is often related to the severity of symptoms during the acute illness phase (Townsend et al., 2020). In addition,psychiatric disorders have been also reported in patients following previous HCoV and MERS-CoV epidemics (Jeong et al., 2016; Kim et al.,2018). For example, 70.8% of confirmed patients who survived infection of MERS-CoV exhibited psychiatric symptoms, including hallucinations and psychosis, and 40% received a psychiatric diagnosis during their hospital admittance (Kim et al., 2018).

Psychiatric symptoms such as depression, adaptation or anxiety disorders, PTSD, and insomnia, lower immunity, hinder recovery (Kim & Su, 2020) and could play a role in subjective cognitive complaints (Almeria et al., 2021). Almeria et al. (2021) showed higher scores in anxiety and depression in patients with cognitive complaints. The clinical management of these patients, including patient isolation, lack of personal protective equipment (PPE) resulting in reduced staff contact, lack of family/visitors, and long-term ventilation/sedation, not only places them at high risk for subsequent cognitive deficits, butthese findings emphasize also the importance of an early detection of anxiety and depression in order to avoid later cognitive complaints in COVID-19 patients. A French study (Gouraud et al., 2021) explored the associations of objective cognitive performances and psychological distress with self-reported cognitive complaints in100 COVID-19 survivors and a set of standardized methods were used to examine neuropsychological functioning (Digit Symbol Substitution Test, Semantic Verbal Fluency Test, Mini Mental State Examination, MMSE) and psychological distress (Hospital Anxiety and Depression Scale, HADS). None of the objective neuropsychological test scores was significantly associated with cognitive complaints, which basically means that cognitive complaints should be considered as potentially signaling anxiety or depression symptoms as they are associated with psychological distress, independently of objective neuropsychological status. On the other hand, the researchers limited the selection of tests for cognitive functioning to only three short methods, including MMSE, with the widest diagnostic spectrum. This method is considered to be only a basic cognitive screening test, not able to capture specific cognitive impairment, especially in young and middle-aged adults. Therefore, systematic neuropsychological assessments of ambulatory COVID-19 patients is suggested.

A feeling of loneliness is particularly debilitating and contributes to the severity of cognitive impairment.Loneliness is associated with feelings of helplessness, powerlessness, and vulnerability. As established, COVID-19 quarantines have the potential to further isolate people resulting in negative psychological effects including post-traumatic stress symptoms, confusion, anger, and loneliness (Brooks et al., 2020; Morlett Paredeset al., 2020).Loneliness is especially difficult for the elderly. The literature describes the case of an elderly man whose isolation alone due to the COVID-19 pandemic affected his cognitive degradation (Padala et al., 2020). In a functionally independent and physically active older adult with mild cognitive impairment, there was worsening in their depression and anxiety symptoms associated with the restrictions of COVID-19. Functional decline was also noted, as assessed by Instrumental Activities of Daily Living (Padala et al., 2020).

The role of psychosocial factors in the etiology of cognitive impairment in COVID-19 survivors is significant. They are expected to play an additional role in long-term cognitive disturbances and quality of life, especially psychopathological symptoms or syndromes that may coexist and be linked to objective cognitive difficulties.

Neuropsychological diagnosis and rehabilitation

Considering the prevalence of mental disorders among COVID-19 patients, their heterogeneous profile and significant impact on daily activities, it is necessary to develop post-standards of symptom management and ensure that qualified personnel is available to patients. Contact with a neuropsychologist should be an important part of acute inpatient treatment (if the patient's condition allows for it). It is important that neuropsychological diagnosis and rehabilitation become a common intervention for patients with COVID-19, also, after recovery. It is especially important for people with the risk of developing cognitive changes after COVID-19. A detailed, multifaceted, and in-person neuropsychological diagnosis using standardized methods of examination is necessary. Most often simple screening tests have been used, which do not do justice to the sufferers' mental functioning patterns. For example, patients with cognitive difficulties may occasionally succeed in achieving normal scores due to the nature of the particular screening tool. At the same time, many of them require a detailed, multifaceted neuropsychological diagnosis. The assessment should cover cognitive domains (especially attention, executive functions, memory, speed of information processing), psychosocial functioning – especially depression, adaptation or anxiety disorders, and PTSD – and their impact on everyday functioning.

Another problem is a lack of strict neuropsychological and neurological protocols. It is said that magnetic resonance imaging (MRI) may detect early symptoms of true neurological involvement or allow differentiation from toxic and metabolic CNS effects in severely ill COVID-19 patients. This is especially so in light of post-mortem studies that showed evidence of inflammation and neuronal loss but did not confirm the virus infiltration of the CNS (von Weyhern et al.,

2020), and negative results of lumbar puncture CSF (cerebrospinal fluid) examinations. Consequently a longitudinal approach to neurological, neuropsychological and neuropsychiatric diagnostics is advised.

There are no methods of rehabilitation specific to the population of COVID-19 patients, but as recommended by Łojek etal. (2021) techniques used in patients with brain injuries, especially after hypoxia, stroke and encephalopathy, may be useful. Similar to COPD-hypoxic patients (Kozora et al., 1999), we can predict that oxygen therapy will positively impact the cognitive performance of COVID-19 patients. Another innovative method of neurorehabilitation suggested in the literature is the use of EEG neurofeedback, goal-oriented cognitive training (CT) (Łuckoś et al., 2021) and individually tailored anodal Transcranial Direct Current Stimulation (tDCS) (Pąchalska et al., 2021; Pąchalska & Nowaczyk, 2021). Neurofeedback is said to has a positive effect on various disorders, including the contraction of COVID-19 and it uses the basic protocols related to the processes of operant conditioning. This protocols effectiveness is promising in the reduction of neurocognitive dysfunctions and long-term side effects after the infection of SARS-CoV-2. Whereas tDCS was especially effective in treatment of at least threeCOVID-19 survivors reported in the following case studies. The first one was the49-year old paramedical whose ERPs wave pattern reflected the PTSD neuromarker (Pąchalska & Nowaczyk, 2021). Another was the 23-year old student with a chronic associative prosopagnosia (face blindness)after infection with SARS-CoV-2 followed by a contraction of COVID-19 and a right hemisphere stroke (Pąchalska et al., 2021). The neurorehabilitation of the latter patient was combined with a Symbolic Art Therapy (Pąchalska et al., 2021). And the third one was the patient with a newly diagnosed Parkinson's disease followed by an infection with the SARS-CoV-2 virus, contracting of NeuroCovid 19, and long COVID (Pąchalska et al., 2022). All mentioned case studies prove virtues of tDCS in treatment of different variations of neuroCOVID, but also emphasize the necessity of customization of the treatment. In other words neuropsychological rehabilitation should be tailored to each patient's individual needs and goals.It is increasingly important to exercise cognitive abilities in order to develop compensatory strategies. It is important to reinforce daily activity, teach the patient to develop new interventions and motivations, and solve increasingly difficult tasks that stimulate brain function, hence Łuckoś et al. (2021) suggestion of CT. All these activities contribute to the build-up of what is known as a 'cognitive reserve'. The hypothesised brain reserve and cognitive resources counteract the neuropathological processes that impair the cognitive performance of patients (Mori et al., 1997), allowing for at least partial compensation for COVID-19 disease-related cognitive decline. The sources of cognitive deficits, however, should not be found solely in purely biological factors. Numerous studies indicate that lifestyle, stress, isolation, and loneliness impair mental functioning. Thus, when analysing the mental condition of a patient after COVID-19, one should think outside the purely medical context and look at the patient's overall emotional and psychosocial functioning.

Limitations

The article was written during the pandemic and at the time of the emergence of new research and, as such, is not exhaustive of the studies which continue to be published in the subject literature. As a result, a great obstacle was the selection of texts based on methodologically correct research, and not non-empirical articles or case studies, which are quite common with this topic.Some of the methodological difficulties related to the implementation of correct neuropsychological researches are the consequences of limited access to patients due to various pandemic restrictions in different countries or even institutions. We can predict the negative consequences of COVID-19 epidemics on the CNS based on the similarity of this viral infection to other known disease entities, or observing the destruction of other systems as a result of the disease. It does not change the fact that longitudinal neuropsychological research is still highly advised, as well as continuous control of people with potential long COVID.

Further research is needed to understand the association between the severity of the viral illness and subsequent cognitive dysfunction.Cognitive impairment is likely to be due not only to the behavioural consequences of incident neurological disorders directly related to the virus, but also secondary to damage to other body organs, psychiatric disorders and the worsening of pre-existing cognitive difficulties.Description and understanding of the long-term consequences contraction of COVID-19 (especially cognitive impairments) and their mitigation are needed. It is highly probable that the current coronavirus outbreak will not be thelast.This is the third coronavirus epidemic in 10 years (with SARS, MERS, and COVID-19). Therefore, it is necessary to bring together specialists in many fields, including neurologists, neuropsychologists, and psychiatrists to better understand the disease and its impact on the patient.

CONCLUSIONS

The results of studies and our own observations confirm that patients in the process of recovery from COVID-19 will require careful neuropsychological diagnostics and rehabilitation. Caring for patients with cognitive impairment is extremely important because of longer-term cognitive dysfunction impacting on the ability to return to everyday functioning.It is also important to raise awareness of the potential for post-onset problems as a result of contraction of COVID-19. Neuropsychological care should be provided to all those infected – both those with a mild case ofCOVID-19, in whom it may happen that sub-clinical disorders such as mild cognitive dysfunction or selective cognitive dysfunction may easily go undetected or be attributed to psychological reactions to the fear and social upheaval generated by the pandemic – as well as high-risk groups such as patients with coexisting neurodegenerative diseases, or the elderly. This is especially important as infection of SARS-CoV-2 will contribute to the exacerbation of pre-existing degenerative neuropathologies such as vascular dementia, or Alzheimer's and Parkinson's disease. Therefore, as suggested by MacQueen

and MacQueen (2021), it is imperative to also consider the pre-existing health condition of the patient. Making assumptions that all symptoms exhibited by a COVID-19 patient are solely attributable to SARS-CoV-2 infection might be significantly misleading. However, it should be remembered that there are risks of neuropsychological symptoms in individuals affected both directly and indirectly by contraction of COVID-19.

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