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Neuropsychological disorders after COVID-19. Urgent need for research and clinical practice

Zaburzenia neuropsychologiczne po COVID-19. Pilne potrzeby w zakresie badań i praktyki klinicznej

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Abstract

Purpose: Numerous studies suggest that infection with coronavirus SARS-CoV-2, which causes acute respiratory distress syndrome and COVID-19 illness, can lead to changes in the central nervous system (CNS). Consequently, some individuals with SARS-CoV-2 infection may also present the symptoms of neuropsychological disorders. The goals of this literature review is the synthesis of various perspectives and up-to-date scientific knowledge as well as the formulation of initial recommendations for clinical practice.

Views: According to current state of knowledge, numerous SARS-CoV-2 infection-specific and nonspecific risk factors exist for brain damage, which might lead to neuropsychological impairments in individuals who have recovered from COVID-19. The emerging evidence suggests significant behavioral and cognitive deficits in COVID-19 survivors, which are present in the early phase after recovery and persist for several months. Neuropsychological disturbances can potentially include a wide spectrum of disorders, yet deficits of attention, memory, executive functions, language and visuospatial orientation are among most commonly identified. The relationship between cognitive impairment, emotional disturbances and severity of COVID-19 symptoms needs to be submitted to further research.

Conclusions: The scientific knowledge resulting from neuropsychological empirical studies during the COVID-19 pandemic allows for a postulate of an urgent evidence-based systematic neuropsychological research to be conducted among COVID-19 survivors. More than anything, the recovered individuals must be provided with adequate neuropsychological help in the form of neuropsychological diagnosis, monitoring and rehabilitation.

Key words: clinical practice, neuropsychological impairment, COVID-19, brain disorders.

Streszczenie

Cel: Wiele badań wskazuje na to, że zakażenie koronawirusem SARS-CoV-2, wywołujące zespół ostrej niewydolności oddechowej i chorobę COVID-19, może prowadzić do zmian w ośrodkowym układzie nerwowym (OUN). W konsekwencji u części osób zakażonych SARS-CoV-2 i chorych na COVID-19 mogą pojawić się obok innych również objawy zaburzeń neuropsychologicznych. Celem niniejszej pracy przeglądowej jest podsumowanie koncepcji i dotychczasowych badań na ten temat oraz sformułowanie wstępnych wskazań dla praktyki klinicznej.

Poglądy: Zgodnie z dotychczasową wiedzą istnieje wiele specyficznych i niespecyficznych dla COVID-19 czynników ryzyka uszkodzeń mózgu oraz w konsekwencji powstawania zaburzeń neuropsychologicznych u osób, które przeszły tę chorobę. Pierwsze prace opisujące

zachowanie i zdolności poznawcze u osób po COVID-19 wskazują na istotne deficyty zarówno w niedługim czasie od wyzdrowienia, jak i w kilka miesięcy później. Trudności neuropsychologiczne mogą potencjalnie obejmować bardzo szerokie spektrum zaburzeń, jednak najczęściej opisuje się deficyty uwagi, pamięci, funkcji wykonawczych, językowe, orientacji przestrzennej. Związek pomiędzy trudnościami poznawczymi a zaburzeniami emocjonalnymi, a także głębokością objawów COVID-19 wymaga dalszych badań.

Wnioski: Jest wystarczająco dużo przesłanek opartych na ugruntowanej wiedzy naukowej z zakresu neuropsychologii oraz danych empirycznych z badań nad COVID-19, aby apelować o pilne rozpoczęcie systematycznych badań neuropsychologicznych osób po COVID-19. Konieczne jest także objęcie tych chorych odpowiednią pomocą neuropsychologiczną w postaci diagnozy, monitorowania i rehabilitacji neuropsychologicznej.

Słowa kluczowe: praktyka kliniczna, zaburzenia neuropsychologiczne, COVID-19, dysfunkcje mózgu.

INTRODUCTION

The COVID-19 pandemic was announced in March 2020 [1]. The new disease is caused by coronavirus SARS-CoV-2 (SARS – *severe acute respiratory syndrome*) [2] with a typical symptomatology including fever, cough, fatigue and muscle pain [3]. Contrary to the initial perceptions, SARS-CoV-2 does not only attack lungs and the respiratory system, but also many other important organs, including the CNS [2]. Outcomes of neuroimaging studies conducted by various research centers around the world confirm the prevalence of brain abnormalities, linked to the course of infection in patients with COVID-19 [4]. Brain structural abnormalities, associated with COVID-19 (after cautious exclusion of other causes) were found in 124 out of 361 (34%) patients examined. The most frequent brain abnormalities were noted as white matter (WM) hyperintensities (on MRI scans) or hypodensities (on CT scans). These changes indicate decreased WM density in COVID-19 patients, compared to the normal range of WM density. This type of brain abnormalities accounts for approx. 76% of all brain structural changes described [4]. So far, these abnormalities are described as diffused, that is not specific to any particular brain structure, and are observed in bilateral medial temporal lobes [5]; frontal, occipital, parietal and temporal lobes [6-10]; insular cortex, cingulate gyri [8]; cerebral peduncle and internal capsule [11]; thalamus [5, 7, 12]; midbrain [5]; pons [7, 11]; parahippocampal gyri and basal ganglia [12]; splenium of corpus callosum [11, 13]; olfactory nerves/bulb [14, 15]; and gyrus rectus [5]. Even though it remains uncertain whether these brain changes persist over time, their observed prevalence, scope and localization allow for speculation about the risk of various neuropsychological dysfunctions in patients who underwent COVID-19.

An additional challenge with the long-term neurological and neuropsychological consequences of COVID-19 is the evidence that infection-induced parenchymal inflammation may increase the long-term risk of developing Alzheimer's disease [16] or Parkinson's disease [17].

The recognition of risks associated with COVID-19 impacted and mobilized the neuropsychology community worldwide. Numerous published appeals call for urgent systematic neuropsychological research and development of clinical practice, i.e., diagnostics, neuropsychological rehabilitation and psychotherapy, in order to provide professional care to people who may need it after COVID-19 [18-21].

In response to these needs, the article aims to review the current state of knowledge regarding neuropsychological deficits that may result from SARS-CoV-2 infection and the related disease, and to formulate initial recommendations for clinical practice. It also includes a description of COVID-19-specific and non-specific risk factors of brain changes and neuropsychological dysfunction, the results of up-to-date research and recommendations for neuropsychological diagnosis and rehabilitation for COVID-19 survivors. A critical review of empirical research and reviews related to the CNS complications of COVID-19, published before March 2021, was conducted by searching PubMed, PubMedCentral, Google Scholar and bioRxiv.

RISK FACTORS OF NEUROPSYCHOLOGICAL CHANGES IN COVID-19

COVID-19 is a disease with many risk factors of brain dysfunction and neuropsychological disorders in both acute and chronic phases and with potential chronic disability [22]. These factors can be divided into specific and non-specific to COVID-19.

Specific risk factors

Risk factors specific to COVID-19 that can lead to dysfunction or death of neurons within the CNS, and consequent neuropsychological disorders include:

- cerebral hypoxia,
- vascular changes,
- neuronal damage.

Cerebral hypoxia

SARS-CoV-2 enters the body through the respiratory tract, attacks bronchi and lungs, leading to severe changes

in these organs and, consequently, to hypoxia of the entire organism, including the brain [23]. Additionally, the severe course of COVID-19 infection often affects people with concomitant bronchopulmonary diseases, which is associated with the intensification of pulmonary changes and systemic hypoxia.

Notably, severe course of the COVID-19 infection is often observed in individuals with comorbid bronchopulmonary diseases, which is associated with intensified pulmonary changes and systemic hypoxia. Hypoxia resulting from various conditions (e.g., progressive obstructive pulmonary disease, obstructive sleep apnea, cardiac arrest or cerebral arteries occlusion) is known to be linked to the CNS changes and cognitive consequences (e.g., distorted focus, memory, thinking, visuospatial orientation) that may be further accompanied by emotional disorders, such as anxiety, depression, symptoms of posttraumatic stress disorder [24, 25]. Cognitive difficulties can persist over two years after the hypoxic event, regardless of the patient's emotional state [26]. Neuropsychological deficits following hypoxia typically require long-term neuropsychological rehabilitation and can present various intensity and scope, from severe, generalized to selective, cognitive deficits [27]. Similar cognitive impairments and emotional disorders are currently observed in patients in the early phase and up to 3 months after severe respiratory disorders due to COVID-19 [28].

Vascular changes

Patients with COVID-19 may further experience inflammatory changes in blood vessels and arterio-venous thrombotic complications that may involve CNS. Hypercoagulation alone poses an increased risk of stroke which, in turn, leads to neurological and neuropsychological symptoms [29, 30]. Hypercoagulability and hyperinflammation observed in patients with severe course of COVID-19 may contribute to delirium and other disturbances of consciousness that are associated with chronic cognitive difficulties, following the recovery from the disease [2, 31].

Neuronal damage

The intranasal route via the olfactory nerves is hypothesized as one of the main neuronal pathways for SARS-CoV-2 for direct entry into the brain [3, 32]. The anatomical organization of olfactory nerves and the olfactory bulb in the nasal cavity and forebrain effectively make it a channel between the nasal epithelium and the CNS. Previous studies conducted after the respiratory coronavirus infected nasal cells concluded that it could reach the entire brain and CSF through the olfactory nerve and olfactory bulb causing inflammation, demyelinating reactions and neuronal death. It is suggested that through the olfactory bulb, SARS-CoV-2 may target the deeper parts of the brain, including the thalamus and brainstem, causing the collapse of the respiratory and cardiorespiratory centers [14]. The resulting inflammation (encephalitis) can lead to delirium, generalized cognitive deficits, and severe long-term neuropsychological changes [31, 32]. Empirical data suggest that through direct neural pathways SARS-CoV-2 can also enter hippocampus amygdala, causing memory impairment and emotional dysfunctions [33, 34].

Nonspecific risk factors

The group of nonspecific risk factors, nonetheless related to COVID-19, includes iatrogenic factors and other risks related to the patient's individual characteristics.

Iatrogenic factors

Numerous studies show that long-term cognitive impairment may occur as a result of the critical condition of a patient requiring hospitalization at the intensive care unit (ICU) in the course of any severe somatic disease [26]. Even though intensive care treatment (e.g., ventilator, large quantities of strong sedative medication) saves lives of critically ill patients, it also carries the risk of complications, such as cognitive difficulties that persist post-recovery. Social isolation, particularly the lack of direct contact with relatives and being cut off from emotional support which is known to facilitate recovery, are yet another adverse iatrogenic factor. Unfortunately, ensuring such contact is particularly difficult during the pandemic [22, 35]. Importantly, many indications point out to neuropsychological deficits being underdiagnosed even in hospitalized patients. It is, after all, strongly emphasized in case of encephalopathy or stroke victims that the fact that they do not present any visible deficits, being capable of "walking and talking" at the time of discharge from the hospital, does not necessarily translate into their neuropsychological functioning being fully intact [29, 36].

Individual characteristics

Demographic and health-related factors comprise a distinct class of risk factors of neuropsychological impairment in the COVID-19 survivors. Among them of particular importance are older age, high blood pressure, diabetes, obesity, smoking tobacco/cigarettes, and comorbid conditions such as oncological, coronary, neurological or psychiatric [22]. This class of factors in itself is an indicator of a higher risk of developing mild cognitive impairment – MCI [37]. At the same time, these factors are also the risks linked to a more severe course of the COVID-19 disease [38].

Older age and premorbid neurodegenerative conditions (such as Alzheimer's disease, mild cognitive impairment and Parkinson's disease) are especially linked to a possible lasting cognitive impairment in the COVID-19

survivors [39]. One mechanistic explanation common to the effects of old age preexisting dementia, and SARS-Cov-2 infection is the suppressed neurotrophic expression of the angiotensin-converting enzyme 2 (ACE-2) which plays a protective role, inhibiting cognitive impairment [40]. Thus, the intersecting effects of old age and chronic, pre-existing medical conditions, especially from the dementia spectrum, can be hypothesized in COVID-19 survivors [39]. There is also an accumulating epidemiological evidence suggesting that SARS-CoV-2 survivors without premorbid dementia are at a higher risk of the subsequent development of neurological diseases, particularly Alzheimer's disease [16]. In response to the urgent need to understand the chronic neuropsychiatric sequelae in COVID-19 survivors, the Alzheimer's Association with the guidance from WHO, and representatives from over thirty countries, formed an international consortium with special attention given to the underlying biological factors that may contribute to post-COVID-19 dementia development [41]. While these research efforts are in progress, the literature available suggests that the possible acceleration in cognitive manifestations, long-term cognitive decline and the underlying pathogenic mechanisms are likely multifactorial, and remain to be determined in older adults with or without neurodegenerative conditions who survived COVID-19 infection [39].

Furthermore, psychiatric symptoms such as depression, adaptation or anxiety disorders and post-traumatic stress disorder (PTSD),which are intensified amid the COVID-19 pandemic, may also contribute to cognitive problems [42-44]. Especially, in the light of the current debate on bidirectional causality between PTSD and neurocognitive impairment [45], one can speculate about an increased prevalence and/or adverse maintenance of PTSD symptoms in the COVID-19 survivors that present neurocognitive decrements. This possible feedback loop hypothesis could further suggest elevated risk of neurocognitive difficulties in COVID-19 survivors suffering from PTSD symptoms. As neurocognitive deterioration constitutes one of the core features of PTSD through its associations with altered brain connectivity [45], neurotransmitter and neuroendocrine activity [46] these mechanisms may pose additional challenge to differentiate the etiology of cognitive impairment in COVID-19 survivors [47] and may be expected to play additional role in long-term cognitive disturbances.

Additionally, individuals exhibiting smell and taste impairments in the course of COVID-19 are at an elevated risk of physiological dysregulation of ingestive behavior that can lead to poorer health outcomes, anorexia, weight loss and low albumin levels [48]. Even though the role of the SARS-CoV-2 neuroinfection vs. malnutrition in direct neuropsychological dysfunction remains to be "elucidated", evidence from other neuroinfectious and neurodegenerative diseases suggests a more direct link with cognitive deterioration, where anosmia and aguesia are proposed as possible early biomarkers of disease progression and severity [49]. Amidst COVID-19-related lockdowns and quarantine restrictions, increased disparities in food security, food literacy, diet quality (especially in terms of immuno-supportive nutrients) and management of food intake can contribute to nutrition-related risks, with adverse consequences for neuropsychological consequences of the disease expected particularly in socioeconomically, educationally, and environmentally disadvantaged populations [50, 51].

DATA FROM CLINICAL RESEARCH

Initial scientific reports on the impact of COVID-19 on the CNS structure and function originated in China even before the announcement of the COVID-19 pandemic by the World Health Organization [14]. Shortly after, numerous reports confirmed the possibility of the COVID-19 patients presenting neurological and neuropsychiatric syndromes or symptoms including encephalitis, meningitis, transverse myelitis, epileptic seizures, cerebral hemorrhagic and ischemic strokes, headache and dizziness, anosmia and ageusia, Guillain-Barré syndrome, as well as delirium, distorted consciousness, agitation, lethargy and frontal lobe syndrome, with symptoms such as verbal perseverance and imitation behavior [11-13].

According to the data provided by Helms *et al.* [9], 33% of patients who underwent the ICU treatment for COVID-19 (i.e., 15 out of 45 patients, on average 63 year old) at the time of discharge from the hospital presented symptoms from a spectrum of executive disorders, including attention deficits, disorientation, and difficulties with following verbal instructions. For example, these patients could not give the correct answer to a question like "Do two pounds weigh more than one pound?" or lift two fingers, first in one hand and then in the other.

Varatharaj *et al.* [52] discussed the results of dementia screening tests in the UK population of patients with COVID-19. Based on a sample of 125 hospitalized COVID-19 patients, the authors discussed the symptoms of neurological or neuropsychiatric disorders, with cerebral vascular changes (77/125 [62%]), other neurological symptoms (9/125 [7%]) or with altered mental status related to the CNS inflammation or neuropsychiatric syndromes (37/125 [29.6%]). Patients from this particular cohort ranged in age between 23 and 94 (mean = 71). Unfortunately, the neuropsychological functioning of this cohort, especially the patients with cerebral vascular lesions resulting from COVID-19, was not thoroughly evaluated on discharge from the hospital. Data revealed that the criterion of "dementia-like syndrome" was met by six patients that were classified into the subgroup with altered mental status and neuropsychiatric disorders (6/37 [26%]).

There is, however, a systematic increase in the number of neuropsychological studies indicating the presence of significant cognitive impairment in the COVID-19 survivors. For example, Zhou *et al.* [23] disseminated the results of their study in 29 hospitalized COVID-19 patients (mean age = 47 years) vs. 29 controls (mean age = 42), which excluded patients who could have presented cognitive disorders due to factors other than COVID-19 (e.g., previous neurological or mental disorder, other diseases, learning disabilities). The clinical group was assessed relatively soon post recovery, i.e., after the second negative SARS-CoV-2 test result. The authors implemented a battery of screening tests that enabled remote neuropsychological assessment. Outcomes of their study showed a statistically significant reduction in the ability of sustained attention in the COVID-19 survivors as compared to the control group. Severity of cognitive impairment in the COVID-19 survivors was positively correlated with the rate of inflammation at the time of hospital admission (as measured by the concentration of C-reactive protein CRP; $r = 0.5\text{-}0.4$) [23].

Another neuropsychological research into COVID-19 was presented by Almeria *et al.* [28]. The authors presented a cohort of 35 hospitalized COVID-19 patients (mean age = 47, SD = 8.9), including 20% of patients who required ICU medical care, 66% received oxygen, while the remaining 14% of patients showed mild COVID-19 symptoms. The study excluded individuals over 60 years of age, patients with premorbid neurological or mental illnesses, cognitive impairment or other risk factors of cognitive disturbances. Qualified participants were examined using a standardized neuropsychological tests battery in face-to-face contact between 10 and 35 days after hospital discharge. Results below 2 standard deviations from the mean (that indicate significant reduction compared to the norm) were found in 19 out of 25 neuropsychological indices. Problems were most frequently noted on the following tests: the Trail Making Test Part B, the Digit Symbol Modalities Test, and the Phonetic Fluency Test. These tests requires engagement of attention, working memory, executive functions, visuospatial orientation, motor skills, and verbal memory [28].

The analysis of data from the nationwide online intelligence test on a sample of over 48,000 people that was carried out by the British Broadcasting Corporation in the UK also suggests that the functioning of the COVID-19 survivors in multiple cognitive domains may be impaired as compared to individuals who were not infected with SARS-CoV-2 [53]. Significant decline was found in performing cognitive tasks of working memory and executive functions, primarily in patients with confirmed coronavirus infection ($n = 361$) who had been hospitalized ($n = 147$). Patients showing more severe respiratory disorders and in greater need of medical intervention due to the COVID-19 presented lower cognitive performance after the disease. However, Hampshire *et al.* (2020) hypothesize that cognitive disturbances related to the COVID-19 may also affect individuals who suffered from SARS-CoV-2 infection at home and did not require medical attention. The authors suggest the inflammatory origins of brain dysfunction. In fact, there are new studies suggesting possible neurological and cognitive complications in patients after mild COVID-19, without the need for hospitalization [54], but these data require further systematic investigations.

The presence of cognitive impairment even three months after recovery from mild to moderate COVID-19 in young people was described by Woo *et al.* [33]. The study included 18 middle-aged (mean age = 42), COVID-19 survivors, who did not reveal subsequent medical complications after recovery, and 10 control individuals (mean age = 38.4). The hospitalized patients comprised 61% of the clinical group and their condition was assessed as mild to moderate. Patients who needed the ICU treatment were not included in the study. The remaining 33% received medical care at home throughout the course of the COVID-19 disease, while 6% did not require any medical attention. Cognitive and emotional testing was performed using the over-the-phone interview and standardized neuropsychological screening tools, while controlling for the examination conditions to a maximum possible extent. The COVID-19 survivors performed worse on objective tests for short-term memory, attention, verbal learning, semantic memory, and word update readiness as compared to non-infected individuals. Most of the clinical group (78%) also reported fatigue, lack of energy, mood lability, difficulties in logical thinking, and sound aversion. Anxiety, depression and severity of the COVID-19 symptoms were not significantly related to cognitive outcomes [33].

More recent neuropsychological studies have confirmed these findings and further suggested that difficulties with memory, executive function, attention, inhibition, verbal fluency or visuospatial orientation persist in the COVID-19 survivors for many weeks after recovery [55-58]. Many individuals who recovered from COVID-19 report feeling symptoms of anxiety, depression, and difficulties in falling asleep even six months after the acute phase of SARS-CoV-2 infection [3]. The persistence of these disturbances and their possible impact on the quality of life in the COVID-19 survivors require further scientific exploration.

In summary, according to the data presented, it is possible that due to COVID-19 at least one third of patients whose condition was severe and who experienced neurological and/or neuropsychiatric disorders, especially the elderly and those with various comorbidities and individual risk factors, may suffer from long-term neuropsychological impairments that require neuropsychological assistance. The hypothesis that some people after mild

COVID-19, who did not require hospitalization may also experience neurological changes and cognitive impairment should not be rejected. However, these conclusions need further in-depth investigations.

NEUROPSYCHOLOGICAL DIAGNOSIS AND REHABILITATION

COVID-19 is a major challenge for all clinicians, including neuropsychologists. The key is therefore the cooperation of various specialists caring for the patient, exchange of information and the results of specialist examinations. To prevent neuropsychological disorders, including late cognitive decline in population of COVID patients, treatment and controlling for neurological and other risk factors is urgently needed. The contribution of neuropsychology to the diagnosis and rehabilitation of the COVID-19 survivors should be considered in relation to the severity of the course of the disease, health-related consequences, and subsequent treatment phases. Contact with a neuropsychologist should be part of acute inpatient treatment if the patient's condition allows for it. Also, after recovery from the active phase of the disease patients should be seen in rehabilitation departments, outpatient diagnostics and – in the case of possible complications – in other specialist departments, such as neurology or psychiatry.

It is recommended to diagnose the neuropsychological status of people after COVID-19 with the risk of developing cognitive changes as soon as possible and, if required, introduce early rehabilitation interventions [59, 60]. When the patient's condition and the epidemic situation allow it, a comprehensive in-person neuropsychological assessment using standardized methods of examination, based on the Polish norms, is strongly recommended. Assessment should cover cognitive domains (general intellectual level, speed of information processing, attention, memory, executive functions, speech and language, motor and psychomotor skills, visual-spatial orientation, social cognition) and emotional functioning (depression, anxiety, PTSD). In a situation where a comprehensive evaluation is not possible, it is also recommended to use screening methods, bearing in mind their psychometric limits (e.g., low sensitivity and specificity of the Mini Mental State Examination) [61].

Listed below are standardized tests with the Polish norms selected from a much larger set of methods recommended for neuropsychological assessment in individuals after COVID-19 [62]: the Wechsler Adult Intelligence Scales, the California Verbal Learning Test, the Wisconsin Card Sorting Test, the Ruff Figural Fluency Test, the Verbal Fluency Test, the Color Trails Test, the Mini Mental State Examination, the Beck Depression Inventory. These methods are characterized by a high, well established value for neuropsychological evaluation of populations with brain disorders, including neuroinfectious diseases [63].

A comprehensive functional diagnosis should be the starting point for neuropsychological rehabilitation, tailored to the individual needs and capabilities of the patient. There are no methods of rehabilitation specific to the population of COVID-19 patients, therefore the approaches and techniques used in patients with brain injuries are recommended, especially after hypoxia, stroke and encephalopia [64, 65]. A holistic approach may be of particularly high value. It not only comprises the training in the area of a disturbed function, but also looks after the patient's individual needs and goals, and accounts for addressing the impact of deficits on coping with activities of daily living. It also considers maladaptive beliefs, which becomes critical, as these may increase during the COVID-19 pandemic [64, 65].

In the COVID-19 pandemic, diagnostic testing and in-person rehabilitation are not always possible. Amid the pandemic, neuropsychologists took steps to incorporate remote methods, which have been more readily used in a broader medical services context (telemedicine) [65, 66]. Despite teleconsultation-related concerns, the use of audio- or videoconferencing for the purposes of neuropsychological assessment is advancing [67]. Guidance was sought from professional organizations and several of them issued recommendations for practice amid the COVID-19 pandemic, including the COVID-19 Pandemic Health System REsilience PROGRAM (REPROGRAM), Inter-Organizational Practice Committee (IOPC) [68], and the NeuroCOVID-19 International Neuropsychological Society Special Interest Group [62][1].

Due to the lack of a complete picture of neuropsychological disorders related to COVID-19, it may be tempting to diminish the importance of patients' subjective functioning or addressing them solely in terms of depressed mood, anxiety disorders, delusions or post-traumatic reactions. On the other hand, the possibility of psychopathological symptoms or syndromes that may coexist and be linked to objective cognitive difficulties should not be disregarded. In light of the above, clinical neuropsychologists should be more open to consider symptoms reported by patients and their families and to explore these rather than trying to fit them into the diagnostic criteria. Vigilance and openness to learning about

[1] The NeuroCOVID-19 Research Group (https://www.the-ins.org/sigs/) investigates neuropsychological consequences of SARS-CoV-2 infection. The group operates within the International Neuropsychological Society (INS) and brings together more than 80 experts from over 20 countries. The group developed recommendations for conducting international research on neuropsychological consequences of the COVID-19. These recommendations harmonize research methodology and facilitate future comparisons of research outcomes between different countries [62]. The authors of the current article are the Members of the NeuroCovid Research Team at the Faculty of Psychology, University of Warsaw, that closely collaborate with the INS Research Group.

the nature of the reported difficulties can facilitate the determination of the patient's actual mental problems as well as the assessment of their impact on everyday functioning. Such approach also provides an opportunity to establish positive relationship with a patient and helps to prevent iatrogenic disorders e.g. mood disorders, reluctance toward using healthcare services due to sensed rejection, being misunderstood or underestimated which is often due to the lack of sufficient knowledge on the part of specialists or preconceived ideas about the nature of the patient's difficulties or possible therapy options.

In conclusion, it should be highlighted that it is currently difficult to estimate the real extent and persistence of neuropsychological disorders in the population affected by COVID-19. In-depth epidemiological studies are needed to address this issue. However, we have the means and methods that can be readily used in the current health care system in order to provide individuals in need with access to professional neuropsychological help.

Conflict of interest/Konflikt interesu

Absent./Nie występuje.

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References/Piśmiennictwo

1. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (Accessed: 20.02.2021).
2. Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. Ann Neurol 2020; 88: 1-11.
3. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-232.
4. Egbert AR, Cankurtaran S, Karpiak S. Brain abnormalities in COVID-19 acute/subacute phase: a rapid systematic review. Brain Behav Immun 2020; 89: 543-554.
5. Virhammar J, Kumlien E, Fällmar D, Frithiof R, Jackmann S, Sköld M, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. Neurology 2020; 95: 445-449.
6. Anzalone N, Castellano A, Scotti R, Scandroglio AM, Filippi M, Ciceri F, et al. Multifocal laminar cortical brain lesions: a consistent MRI finding in neuro-COVID-19 patients. J Neurol 2020; 267: 2806-2809.
7. Afshar H, Yassin Z, Kalantari S, Aloosh O, Lotfi T, Moghaddasi M, et al. Evolution and resolution of brain involvement associated with SARS- CoV2 infection: a close clinical – paraclinical follow up study of a case. Mult Scler Relat Disord 2020; 43: 102216.
8. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. Radiology 2020; 297: E232-E235.
9. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020; 382: 2268-2270.
10. Radmanesh A, Raz E, Zan E, Derman A, Kaminetzky M. Brain imaging use and findings in COVID-19: a single academic center experience in the epicenter of disease in the United States. Am J Neuroradiol 2020; 41: 1179-1183.
11. Zoghi A, Ramezani M, Roozbeh M, Darazam IA, Sahraian MA. A case of possible atypical demyelinating event of the central nervous system following COVID-19. Mult Scler Relat Disord 2020; 44: 102324.
12. Fischer D, Threlkeld ZD, Bodien YG, Kirsch JE, Huang SY, Schaefer PW, et al. Intact brain network function in an unresponsive patient with COVID-19. Ann Neurol 2020; 88: 851-854.
13. Hayashi M, Sahasi Y, Baba Y, Okura H. COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. J Neurol Sci 2020; 415: 116941.
14. Li CW, Syue LS, Tsai YS, Li MC, Lo CL, Tsai CS, et al. Anosmia and olfactory tract neuropathy in a case of COVID-19. J Microbiol Immunol Infect 2021; 54: 93-96.
15. Petrescu AM, Taussig D, Bouilleret V. Electroencephalogram (EEG) in COVID-19: a systematic retrospective study. Neurophysiol Clin 2020; 50: 155-165.
16. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther 2020; 12: 69.

17. Pereira A. Long-term neurological threats of COVID-19: a call to update the thinking about the outcomes of the coronavirus pandemic. Front Neurol 2020; 11: 308.
18. Arenivas A, Carter KR, Harik LM, Hays KM. COVID-19 neuropsychological factors and considerations within the acute physical medicine and rehabilitation setting. Brain Inj 2020; 34: 1136-1137.
19. Cothran TP, Kellman S, Singh S, Beck JS, Powell KJ, Bolton C J, Tam JW. A brewing storm: the neuropsychological sequelae of hyperinflammation due to COVID-19. Brain Behav 2020; 88: 957-958.
20. Devita M, Bordignon A, Sergi G, Coin A. The psychological and cognitive impact of Covid-19 on individuals with neurocognitive impairments: research topics and remote intervention proposals. Aging Clin Exp Res 2021; 33: 733-736.
21. Koterba CH, Baum KT, Hamner T, Busch TA, Davis KC, Tlustos-Carter S, et al. COVID-19 issues related to pediatric neuropsychology and inpatient rehabilitation – challenges to usual care and solutions during the pandemic. Clin Neuropsychol 2020; 34: 1380-1394.
22. Baker HA, Safavynia SA, Evered LA. The 'third wave': impending cognitive and functional decline in COVID-19 survivors. Br J Anaesth 2021; 126: 44-47.
23. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.
24. Rzadkiewicz M. Dysfunkcje poznawcze w przebiegu wybranych przewlekłych schorzeń układu oddechowego. In: Jodzio K, Nyka WM (eds.). Neuropsychologia medyczna. Wybrane zagadnienia. Sopot: Wydawnictwo Arche; 2008, p. 67-88.
25. Yerlikaya D, Emek-Savas DD, Bircan Kurşun B, Öztura I, Yener GG. Electrophysiological and neuropsychological outcomes of severe obstructive sleep apnea: effects of hypoxemia on cognitive performance. Cogn Neurodyn 2018; 12: 471-480.
26. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. Chest 2006; 130: 869-878.
27. Wilson BA, van Heugten CM. Anoxia. In: Wilson BA, Winegardner J, van Heugten CM, Ownsworth T (eds.). Neuropsychological Rehabilitation. The International Handbook. London: Routledge Taylor and Francis; 2017, p. 74-77.
28. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: clinical predictors leading to neuropsychological impairment. Brain Behav Immun Health 2020; 9: 100163.
29. Van Dijk EJ, de Leeuw FE. Recovery after stroke: more than just walking and talking again. If you don't look for it, you won't find it. Eur J Neurol 2012; 19: 189-190.
30. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395: 1417-1418.
31. Davis DHJ, Muniz-Terrera G, Keage HAD, Stephan BCM, Fleming J, Ince PG, et al. Association of delirium with cognitive decline in late life: a neuropathologic study of 3 population-based cohort studies. JAMA Psychiatry 2017; 74: 244-251.
32. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767-783.
33. Woo MS, Malsy J, Pöttgen J, Seddiq Zai S, Ufer F, Hadjilaou A, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. Brain Commun 2020; 2: fcaa205.
34. Cheng Q, Yang Y, Gao J. Infectivity of human coronavirus in the brain. EbioMedicine 2020; 56: 102799.
35. Rabinovitz B, Jaywant A, Fridman CB. Neuropsychological functioning in severe acute respiratory disorders caused by the coronavirus: Implications for the current COVID-19 pandemic. Clin Neuropsychol 2020; 34: 1453-1479.
36. Easton A, Hodgson J. Encephalitis. In: Wilson BA, Winegardner J, van Heugten CM, Ownsworth T (eds.). Neuropsychological Rehabilitation. The International Handbook. London: Routledge Taylor and Francis Group; 2017, p. 69-73.
37. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 2015; 11: 718-726.
38. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020; 395: 1763-1770.
39. Alonso-Lana S, Marquié M, Ruiz A, Boada M. Cognitive and Neuropsychiatric Manifestations of COVID-19 and Effects on Elderly Individuals with Dementia. Front Aging Neurosci 2020; 12: 588872.
40. Li Z, Xu X, Yang M, Feng J, Liu C, Yang C. Role of angiotensin-converting enzyme 2 in neurodegenerative diseases during the COVID-19 pandemic. Aging 2020; 12: 24453-24461.
41. de Erausquin GA, Snyder H, Carrillo M, Hosseini AA, Brugha TS, Seshadr S; CNS SARS-CoV-2 Consortium. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. Alzheimers Dement 2021; 17: 1056-1065.
42. Fujii Y, Kitagawa N, Shimizu Y, Mitsui N, Toyomaki A, Hashimoto N, et al. Severity of generalized social anxiety disorder correlates with low executive functioning. Neurosci Lett 2013; 543: 42-46.
43. Scott JC, Matt GE, Wrocklage KM, Crnich C, Jordan J, Southwick SM, et al. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. Psychol Bull 2014; 141: 105-140.
44. Gambin M, Sękowski M, Woźniak-Prus M, Wnuk A, Oleksy T, Cudo A, et al. Generalized anxiety and depressive symptoms in various age groups during the COVID-19 lockdown in Poland. Specific predictors and differences in symptoms severity. Compr Psychiatry 2021; 105: 152222.

45. Esterman M, Stumps A, Jagger-Rickels A, Rothlein D, DeGutis J, Fortenbaugh F, et al. Evaluating the evidence for a neuroimaging subtype of posttraumatic stress disorder. Sci Transl Med 2020; 12: eaaz9343.
46. Quinones MM, Gallegos AM, Lin FV, Heffner K. Dysregulation of inflammation, neurobiology, and cognitive function in PTSD: an integrative review. Cogn Affect Behav Neurosci 2020; 20: 455-480.
47. Kaseda ET, Levine AJ. Post-traumatic stress disorder: a differential diagnostic consideration for COVID-19 survivors. Clin Neuropsychol 2020; 34: 1498-1514.
48. Meunier N, Briand L, Jacquin-Piques A, Brondel L, Pénicaud L. COVID 19-induced smell and taste impairments: putative impact on physiology. Front Physiol 2021; 11: 625110.
49. Rebholz H, Braun RJ, Ladage D, Knoll W, Kleber C, Hassel AW. Loss of olfactory function – early indicator for Covid-19, other viral infections and neurodegenerative disorders. Front Neurol 2020; 11: 569333.
50. Belanger M J, Hill MA, Angelidi AM, Dalamaga M, Sowers JR, Mantzoros CS. Covid-19 and disparities in nutrition and obesity. N Engl J Med 2020; 383: e69.
51. Lamarche B, Brassard D, Lapointe A, Laramée C, Kearney M, Côté M, et al. Changes in diet quality and food security among adults during the COVID-19-related early lockdown: results from NutriQuébec. Am J Clin Nutr 2021; 113: 984-992.
52. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020; 7: 875-882.
53. Hampshire A, Trender W, Chamberlain SR, Jolly A, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19 relative to controls: an N=84,285 online study. medRxiv 2020; preprint. DOI: 10.1101/2020.10.20.20215863.
54. Del Brutto OH, Wu S, Mera RM, Costa AF, Recalde BY, Issa NP. Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: a longitudinal study nested to a population cohort. Eur J Neurol 2021. DOI: 10.1111/ene.14775 [Online ahead of print].
55. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. J Infect 2021; 82: 378-383.
56. Ortelli P, Ferrazzoli D, Sebastianelli L, Engl M, Romanello R, Nardone R, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: insights into a challenging symptom. J Neurol Sci 2021; 420: 117271.
57. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine 2021; 31: 100683.
58. Whiteside DM, Oleynick V, Holker E, Waldron EJ, Porter J, Kasprzak M. Neurocognitive deficits in severe COVID-19 infection: case series and proposed model. Clin Neuropsychol 2021; 35: 799-818.
59. Sozzi M, Algeri L, Corsano M, Crivelli D, Daga MA, Fumagalli F, et al. Neuropsychology in the times of COVID-19. The role of the psychologist in taking charge of patients with alterations of cognitive functions. Front Neurol 2020; 11: 573207.
60. Zarrabian S, Hassani-Abharian P. COVID-19 pandemic and the importance of cognitive rehabilitation. Basic Clin Neurosci 2020; 11: 129-132.
61. Stańczak J. MINIMENTAL – Krótka Skala Oceny Stanu Umysłowego (MMSE). Warszawa: PTP; 2010.
62. Cysique LA, Łojek E, Ching-Kong Cheung T, Cullen B, Egbert AR, Evans J, et al. Assessment of neurocognitive functions, olfaction, taste, mental, and psycho-social health in COVID-19 in adults: recommendations for harmonization of research and implications for clinical practice. J Int Neuropsychol Soc 2021. DOI: 10.1017/S1355617721000862 [Online ahead of print].
63. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological Assessment. 5th ed. Oxford: Oxford University Press; 2012.
64. Wilson BA, Winegardner J, van Heugten CM, Ownsworth T (eds.). Neuropsychological Rehabilitation. The International Handbook. London: Routledge Taylor and Francis Group; 2017.
64. Szepietowska EM, Daniluk B. Rehabilitacja neuropsychologiczna. Ujęcie holistyczne. Lublin: Wydawnictwo UMCS; 2018.
65. Marra DE, Hoelzle JB, Davis JJ, Schwartz ES. Initial changes in neuropsychologists clinical practice during the COVID-19 pandemic: a survey study. Clin Neuropsychol 2020; 34: 1251-1266.
66. Bilder RM, Postal KS, Barisa M, Aase DM, Cullum CM, Gillaspy SR, et al. InterOrganizational practice committee recommendations/guidance for teleneuropsychology (TeleNP) in response to the COVID-19 pandemic. Clin Neuropsychol 2020; 34: 1314-1334.
67. Rochette AD, Rahman-Filipiak A, Spencer RJ, Marshall D, Stelmokas JE. Teleneuropsychology practice survey during COVID-19 within the United States. Appl Neuropsychol Adult 2021. DOI: 10.1080/23279095.2021.1872576 [Online ahead of print].
68. Postal KS, Bilder RM, Lanca M, Aase DM, Barisa M, Holland AA, et al. Inter Organizational Practice Committee guidance/recommendation for models of care during the novel coronavirus pandemic. Arch Clin Neuropsychol 2021; 36: 17-28.