The infection with severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) can lead to a new disease called long-COVID or post-acute COVID-19 syndrome (PACS). Symptoms generally appear to improve over time, but in some individuals, they may persist for years. Long/post-COVID evidently represents a heterogeneous nosological entity, despite similar or overlapping symptoms between patients, and clear diagnostic criteria are yet to be established. The neurologic manifestations of long-COVID, also known as “neuro-long COVID,” may be particularly debilitating and contribute to a significant proportion of the morbidity and disability. The authors from the United States investigated the age-related differences in neurological symptoms, neurological examination findings, self-rated quality of life, and cognitive performance in patients affected by neuro-long COVID. They hypothesized that older individuals may be more severely affected.

It seems that SARS-CoV-2 exploits various neuroinvasive strategies and pathways to enter the central nervous system (CNS), such as the infection of the nasal olfactory epithelium and axonal transport along the olfactory nerve, retrograde axonal transport, the invasion through the impairment of the blood-brain barrier, and using infected hematopoietic cells as

"Trojan horses" (haematogenic pathway). A recent study has shown that the neurotoxin-like region of the SARS-CoV-2 interacts with nicotinic acetylcholine receptors (nAChRs), which have important physiological functions, including mediating the cholinergic excitatory neurotransmission, synchronization of neuronal activity, and regulation of essential physiological functions such as cognition, arousal, sleep, fatigue, anxiety, nutrition, central processing of pain, attention, and behavior (aggression, mood, and impulsivity). This study discovered that the target for the SARS-CoV-2 glycoprotein is the α7 nAChR, one of the common nAChRs in the CNS, linked to hyperactivity, aggression, anxiety, and depression. Furthermore, the neurotoxin-like region of SARS-CoV-2 exerted an opposing, bimodal, and concentration-specific effect on the α7 nAChR: a high concentration of the neurotoxin-like region of SARS-CoV-2 significantly inhibited α7 nAChR and reduced acetylcholine potency, whereas low concentrations potentiated acetylcholine-induced currents.
https://discovermednews.com/sars-cov-2-and-nicotinic-acetylcholine-receptors/

In addition, numerous data have demonstrated the participation of nicotinic acetylcholine receptors in aging and neurodegeneration. These processes affect two main CNS nicotinic acetylcholine receptor subtypes, α7 and α4β2. It was suggested that the loss of these receptor subtypes during normal aging is one of the reasons for the cognitive impairments and the pathogenesis of age-related neurodegenerative diseases. (Utkin YN. Aging Affects Nicotinic Acetylcholine Receptors in Brain. Cent Nerv Syst Agents Med Chem. 2019: 19(2):119-124.)

About the study

This cross-sectional study enrolled 1,300 patients with a history of clinical manifestations of COVID-19 confirmed by SARS-CoV-2 reverse transcription polymerase chain reaction or rapid antigen test, and/or by subsequent positive SARS-CoV-2 total antibodies (before COVID-19 vaccinations) or anti-SARS-CoV-2 nucleocapsid antibodies (before or after COVID-19 vaccinations), and with persistent neurological symptoms lasting ≥6 weeks after COVID-19 onset.

Patients were categorized into the two neuro-long COVID groups: hospitalized or non-hospitalized for acute COVID-19. All patients were evaluated by a neurologist, either in person or by video-based telehealth visit. Parts of the neurologic examination (full cranial nerve exam, muscle strength, tone, reflexes, and sensation) were limited during telehealth visits, but full neurologic exams were performed during in-person visits.

Patients filled out questionnaires based on the Patient-Reported Outcome Measurement Information System (PROMIS), including cognitive functions, fatigue, sleep disturbance, anxiety, and depression. A more detailed assessment of cognitive functions was performed using the National Institute of Health (NIH) Toolbox (version 2.1) that evaluates processing speed (Pattern comparison processing speed test), attention (Flanker inhibitory control and attention test), executive functions (Dimensional change card-sorting test), and working memory (List-sorting working memory test).

Results

According to their age, 1,300 neuro-long COVID patients were divided into younger (18–44 years), middle-aged (45–64 years), and older (65+ years) groups. Younger and middle-aged individuals accounted for 71% of the neuro-long COVID group hospitalized for acute COVID-19, and 91% of neuro-long COVID patients who were not hospitalized for acute COVID-19. The mean age of the hospitalized neuro-long COVID patients was 55.6 years and of the non-hospitalized patients 46.2 years.

In both neuro-long COVID groups, hospitalized or non-hospitalized for acute COVID-19, age-related differences in the prevalence of comorbidities such as hypertension, dyslipidemia, and cancer were observed. Significant age-related differences in the prevalence of pre-existing autoimmune diseases, type 2 diabetes, other endocrine disorders, chronic kidney diseases, and cardiovascular and peripheral vascular diseases were found in the non-hospitalized neuro-long COVID patients only.

Age-related differences in the neuro-long COVID manifestations

The younger individuals with neuro-long COVID had more prevalent neurologic and non-neurologic symptoms. Age-related differences were found for headache, chest pain, and dysautonomia in both groups, for numbness/tingling, dysgeusia, anosmia, and depression/anxiety in the non-hospitalized patients with neuro-long COVID, and for blurred vision and insomnia in the hospitalized patients with neuro-long COVID. Higher prevalences of these symptoms were observed in the younger individuals diagnosed with neuro-long COVID.

On the contrary, abnormal neurological examination was more prevalent among older neuro-long COVID patients. Age-related differences were observed in gait disturbances in both groups, abnormal general neurological examination in the neuro-long COVID group hospitalized for acute COVID-19, and sensory and motor dysfunction in non-hospitalized

patients. Higher prevalences of these findings were observed in the older group.

Quality of life assessment was based on the PROMIS questionnaire. There were no age-related differences in quality of life in the the neuro-long COVID group hospitalized for acute COVID-19. However, age-related differences in fatigue and sleep disturbance were found in the neuro-long COVID patients who were not hospitalized for acute COVID-19, reflecting lower self-rated quality of life in younger patients.

NIH Toolbox assessment revealed that age-related differences in executive functions were borderline among hospitalized patients. In the neuro-long COVID patients who were not hospitalized for acute COVID-19, age-related differences in executive function and working memory were significant. Importantly, the worst performance was found in the younger group.

Conclusion

This study showed that younger and middle-aged patients diagnosed with neuro-long COVID were more affected than older patients, regardless of the severity and hospitalization status of acute COVID-19.

Younger and middle-aged patients had more prevalent neurological symptoms, and they reported lower quality of life in domains of fatigue and sleep disturbance than older patients with neuro-long COVID. Younger and middle-aged patients with neuro-long COVID who were not hospitalized for acute COVID-19 also had poorer cognitive performance and executive functions than the older group. However, older patients had a higher prevalence of abnormal neurological examination, likely due to pre-existing comorbidities.

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