ANALYSIS OF RISK FACTORS FOR NEUROLOGICAL COMPLICATIONS OF SARS-COV-2 INFECTION: FOCUS ON CHRONIC FATIGABILITY

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ANALYSIS OF RISK FACTORS FOR NEUROLOGICAL COMPLICATIONS OF SARS-COV-2 INFECTION: FOCUS ON CHRONIC FATIGABILITY (Abstract): **Aim:** Chronic fatigue syndrome is a long-term neurological manifestation that significantly affects the quality of life of patients. Its etiology is incompletely known, although it can occur after various infections including COVID-19, and the associated risk factors are not fully defined. The aim of the current study was to evaluate neurological manifestations in long-COVID and to identify potential risk factors for these complications. **Materials and methods:** We performed retro - prospective study on patients with history of COVID-19 infections. Patients were assessed up to 3 years after infection. Clinical and neurological investigations, brain imaging, analysis of inflammatory markers, levels of vitamin B_{12}, folic acid and vitamin D were carried out. Neurocognitive status was assessed using a validated semiquantitative scale. **Results:** In 132 eligible patients, 41.67% of cases developed chronic fatigability. Other neurological manifestations associated with Long-COVID were dizziness (29.17% cases), and memory impairment (25% cases). The deterioration of the neurocognitive status 1 year after infection was significantly correlated with the patient's age ($p<0,0001$), serum vitamin D ($p=0.015$), as well as vitamin B12 ($p=0.006$). **Conclusions:** Chronic fatigability is a common neurological complication of COVID-19 infection. Older people, those with low vitamin D and vitamin B12 levels, have higher risk of developing this syndrome. The COVID-19 infected patients need multiple investigations and a multidisciplinary approach to prevent these long-term complications. **Keywords:** RISK FACTORS, NEUROLOGICAL COMPLICATIONS, SARS-COV-2, INFECTION, FATIGABILITY.

INTRODUCTION

More than three years after the COVID-19 pandemic began, accumulating evidence highlights how SARS-CoV-2 infection has impacted patients' quality of life. Initially, it was considered that the new coronavirus had only respiratory tropism; however, later real - world data showed that it produces a wide range of symptoms, including neurological ones. Moreover, the persistent complications following SARS-Cov-2 infection are extremely varied. For this reason, a series of clinical manifestations have been correlated with the infection and classified as the Long–COVID complication.

In fact, several forms of post-COVID-

19 complications have been identified and defined so far and included in this umbrella term of Post COVID-19 conditions (1). Center for Disease Control and Prevention (CDC) defines this complication as Long COVID that "include a wide range of ongoing symptoms and conditions that can last weeks, months, or even years". According to the CDC, the symptoms of Long COVID should be improved within 3 – 6 months (2).

The World Health Organization (WHO) later provided a definition for Post COVID-19 condition, describing it as "the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months and with no other explanation" (3).

Clinical sequelae of COVID-19 include respiratory (lung fibrosis), cardiovascular (thrombosis, myocarditis, arrhythmias), metabolic (diabetes), dermatologic (alopecia), renal, and neurological complications (4). Neurological manifestations of Long COVID include fatigue, "brain fog," sleep disturbances, mood disorders, cognitive dysfunction, anxiety, depression, and stroke (5). Their prevalence is uncertain but may reach 50% worldwide. Reported risk factors described in other studies include female sex, comorbidities, lack of COVID vaccination, obesity (increased) BMI, with women more frequently experiencing headache, stress, concentration difficulties, and fatigue (6).

In this context, we conducted a retro-prospective study to evaluate neurological manifestations of Long COVID and potential risk factors.

MATERIALS AND METHODS

We performed a retro-prospective study which included patients with history of SARS-CoV-2 infections. Patients were hospitalized and evaluated in Sf. Parascheva Clinical Hospital of Infectious Diseases Iasi and Equilibrium Clinic between 2021-2024.

The study was approved by the Ethics Committee of the hospital, the Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy Iasi. The data was collected in agreement to ensure data protection. The informed consent was obtained from the patients or their legal representatives before the inclusion in the study.

Eligible patients met the criteria: written informed consent obtained from the patient or their legal representative, patients aged over 18 years with history of SARS-CoV2 infection, patients evaluated up to 3 years after COVID-19 infection. Patients with history of chronic fatigue syndrome before COVID-19 infection or with incomplete data were excluded.

Data collection. Data collected from medical records included demographics (age, sex), medical and medication history, SARS-CoV-2 infection details (severity, reinfections, treatment, outcome), laboratory findings (complete blood count, biochemistry, inflammatory markers, serum vitamin D, folic acid, vitamin B_{12}), neurological evaluation, and cerebral CT. Neurological status was assessed with the extended SCGI scale, covering cognition, affective state, sleep, fatigue, headache, motor and sensory function, balance and coordination, functional autonomy, and quality of life. Each domain was scored 0–3, with total scores categorized as mild (0–10), moderate (11–20), or severe (21–30). This is an interim analysis of data obtained one year after infection. Therefore, only

data up to this time point have been collected and analyzed.

Statistical analysis. Normally distributed data are presented as means ± standard deviations, and nonnormally distributed data are reported as medians and ranges). The chi-squared test was performed for the single-factor analysis of count data, and the Kruskal-Wallis was performed for the single-factor analysis of non-normally distributed data. Pearson correlation coefficients were used for correlation between different variables. A p-value ≤0.05 was considered statistically significant. Statistical analysis was performed using XLSTAT software version 1.3, 2025 (Lumivero, USA).

RESULTS

Of a total of 183 patients, 132 eligible cases were included in our analysis. Of these, 41.67% cases were males. The mean (St. dev.) age was 49.43 (±18.98) years in females and 57 (±15.51) years in males (fig. 1).

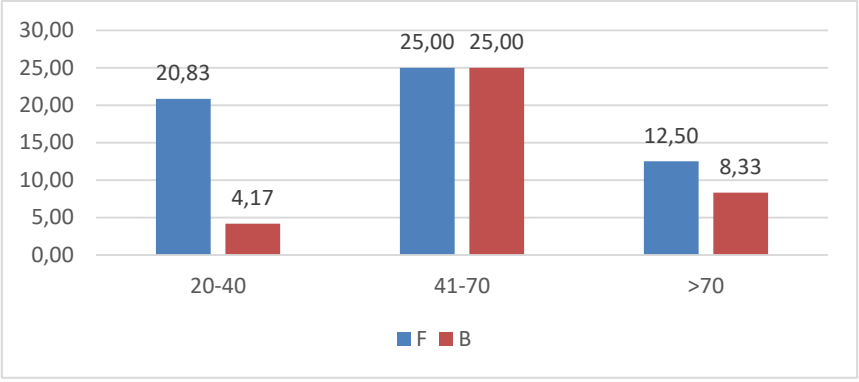

Fig. 1. Demographic data - gender repartition by age group (%)

Almost 67% of cases described associated disorders, most of them with negative prognostic impact associated with COVID-19 infection (hypertension, metabolic disorders, hematological diseases).

The neurological manifestations recorded up to 1 years after SARS-CoV-2 infection in the patients surveyed were varied: paresthesia, nonspecific myalgias or fibromyalgia, headache or migraine, various neuralgias (trigeminal, facial), confusional syndromes or new or aggravated cognitive disorders in patients with previous cognitive impairment (with MMSE score 18-20). However, the most frequent neurological disorder was chronic fatigue syndrome reported in all age groups (41.67% of cases) (fig. 2).

The 55 patients with chronic fatigue syndrome were subsequently analyzed to establish correlations between demographic and biological parameters with the degree of neurocognitive impairment (SCGI Scale) (tab. I, fig. 3).

The data obtained revealed a significant correlation between the severity of cognitive impairment (SCGI score between 27-30) and the patient's age ($p<0,0001$). A weaker, but clinically significant correlation was also obtained for serum vitamin D values ($p=0.015$), as well as for vitamin B_{12} ($p=0.006$). Patients' gender was not correlated with neurological manifestations in our analysis ($p=0.589$).

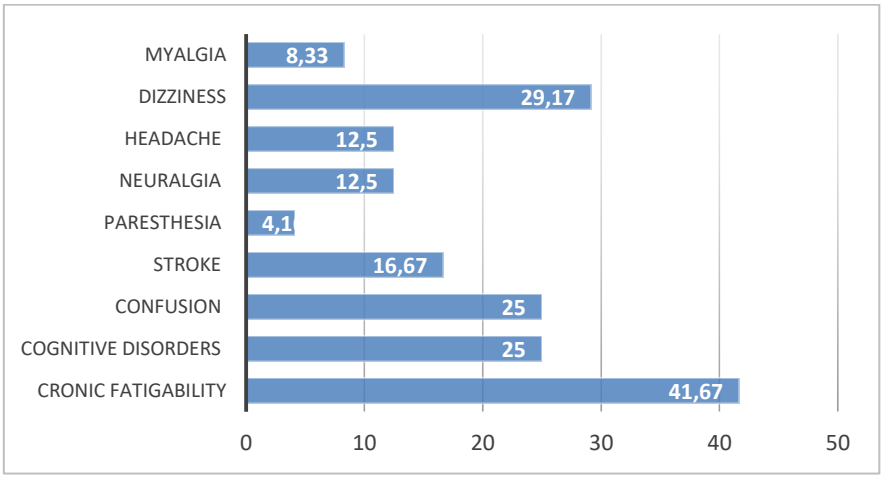

Fig. 2. Neurological manifestations associated with Long - COVID (% cases)

TABLE I.

Correlation between various parameters and SCGI score (Pearson test)

Variable	Pearson's r	p - value	CI95%
Age	-0,683	<0,0001	[-0,803; -0,510]
Gender	-0,182	0,589	[-0,195; 0,333]
IL-6	0,074	0,467	[-0,170; 0,356]
LDH	0,100	0,502	[-0,349; 0,177]
D-dimer	0,019	0,891	[-0,248; 0,283]
Ferritin	0,027	0,844	[-0,240; 0,290]
Vit D level	0,327	0,015	[0,068; 0,545]
Vitamin B12	-0,369	0,006	[-0,578; -0,115]
Folic acid	-0,156	0,254	[-0,405; 0,114]

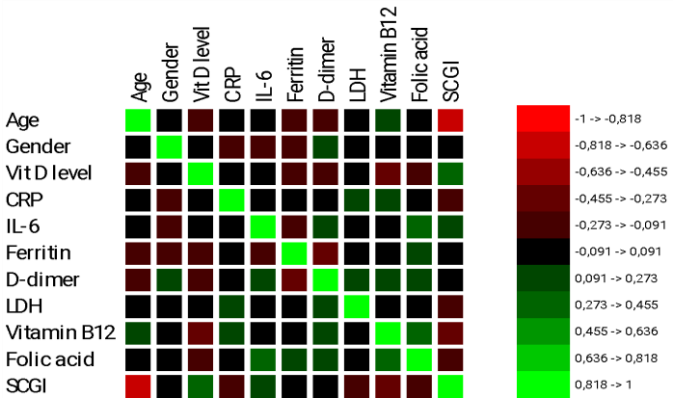

Fig. 3. Correlation map (Pearson test) between SCGI and various parameters

DISCUSSION

The SARS-CoV-2 virus is responsible for a multisystem infection, and neurological manifestations are common in the acute phase of infection. Multiple clinical studies, as well as real-world clinical experience, have shown that symptoms such as headaches, anosmia, ageusia, paresthesia, and myalgias are significant in COVID-19. A retrospective analysis of patients admitted to the "Sf. Parascheva" Infectious Diseases Hospital in Iasi between 2020 and 2022 showed that the most common symptoms were fatigue (85% cases), headache (51.25% cases), myalgia (41.25% cases) (7). To date, various hypotheses have been proposed regarding the pathophysiological mechanisms of neurological disorders in COVID-19, including direct invasion of the central nervous system, disruption of the blood-brain barrier, or dysregulation of the gut–brain axis (5).

On the other hand, the SARS-CoV-2 virus can trigger a "cytokine storm," characterized by the excessive release of proinflammatory cytokines (TNF-alpha, IL-6, IL-1, etc.), with significant changes in the immune system that ultimately lead to a systemic hyperinflammation syndrome (8). This mechanism can also induce neuroinflammation, which is responsible for both acute symptoms and long-term neurological changes (5, 8, 17).

Analysis of a cohort of over 150,000 patients in the USA identified the following neurological complications of SARS-CoV-2 infection, classified as Long-COVID syndrome: cerebrovascular diseases, cognitive and memory disorders, peripheral nerve disorders, migraine, extrapyramidal and motor disorders psychiatric disorders, and other complications (dizziness, drowsiness, Guillain–Barré syndrome, encephalitis, transverse myelitis, encephalopathy) (9-11). Our data are in line with extensive studies published by other authors. The most common neurological manifestations were chronic fatigue syndrome (over 40% of cases), followed by cognitive deficit with new onset or worsening of a pre-existing cognitive deficit.

Chronic fatigue syndrome defined as Myalgic Encephalomyelitis is a complex condition, characterized by significant asthenia, reduced exercise capacity, cognitive disorders (including "brain fog"), sleep disorders, myalgia or other forms of pain, vegetative syndrome (12). The etiology is not completely known, but a prevalence of up to 11% has been identified in severe infections (Epstein Barr virus (EBV), Ross River virus, Giardia lamblia, parvovirus B19, and Q fever infections) (13).

In an extensive analysis of 41,802 women in the US, chronic fatigue syndrome was identified in only 102 women. Risk and predisposing factors for Myalgic Encephalomyelitis or severe fatigue were advanced age, higher BMI in adulthood, hormone therapy, alcohol intake (14). In our study, patients' age, as well as serum levels of vitamin D and vitamin B_{12}, were significantly correlated with the occurrence of chronic fatigue.

The protective role of vitamin D in infectious pathology has been intensively studied and is well defined. In addition to its direct involvement in calcium metabolism and the maintenance of bone health, vitamin D exerts numerous effects, including anti-inflammatory, immunomodulato-

ry, and even antibacterial or antiviral properties (15). Increasing amounts of data are available regarding the relationship between vitamin D and cognitive function. Vitamin D receptors have been identified in the nervous system (neurons and glial cells). Vitamin D has been found to impact numerous brain processes, including cell differentiation, neurotrophic factor production and release, neurotransmitter synthesis, intracellular calcium homeostasis, prevention of oxidative damage, neuronal structure and metabolism, and ultimately, cognitive functioning (16). Hypovitaminosis D has been associated with the onset of neurodegenerative diseases, schizophrenia (18). Clinical data support this benefit of vitamin D for the treatment of several neurocognitive disorders, including those associated with chronic fatigability.

The small sample size evaluated is the main limitation of the current analysis. However, this is an interim analysis of patients monitored up to three years and the final conclusions will be disseminated.

CONCLUSIONS

Chronic fatigability is a common neurological complication of COVID-19 infection. Older people, those with low vitamin D and vitamin B_{12} levels, have higher risk of developing this syndrome.

The COVID-19 infected patients need multiple investigations and a multidisciplinary approach to prevent these long-term complications.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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