საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 16, №4, 2022
BULLETIN OF THE GEORGIAN NATIONAL ACADEMY OF SCIENCES, vol. 16, no. 4, 2022

Medical Science

COVID-19 Neuromuscular Comorbidity

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The outbreak of the novel and highly infectious COVID-19 has resulted in hundreds of millions of infections and millions of deaths globally. Infected individuals experience upper and lower respiratory complications that range in severity and may lead to wide-spread inflammation and generalized hypoxia or hypoxemia that impacts multiple organ systems, including the central and peripheral nervous systems. According to the data available today, the neurological symptoms associated with COVID-19 infection are described in detail. Based on these studies, it can be assumed that SARS-CoV-2 may be neurotropic and / or contribute to or create conditions conducive to direct or indirect damage to the nervous system. The aim of the study was to identify complications of COVID-19 infection in patients with neuromuscular diseases (myasthenia gravis, chronic polyneuropathy, myopathy). 20 patients with generalized form of myasthenia gravis, 8 patients with chronic polyneuropathy and 5 patients with progressive muscular dystrophy infected with SARS-CoV-2 were examined. There were 15 women and 5 men among patients with myasthenia, age - 50-69 years, among patients with chronic polyneuropathy – 3 women, 5 men, age 25-74 years; There were 3 women and 2 men, aged 36-73 years, among patients with progressive muscular dystrophy. Patients were examined within a time interval of 3 weeks to 2 months after confirmed COVID-19 infection. All of them underwent computed tomography of the chest, clinical electroneuromyography study, titers of antibodies against acetylcholine receptors, titin and MUSK were determined in patients with myasthenia gravis. In patients with myopathy, the level of creatine phosphokinase (CPK), LIA-ANA test, general blood analysis, C-reactive protein was determined. Myopathy was confirmed by genetic diagnosis. Based on the results obtained, it can be assumed that not only comorbid pathology occurs as a result of infection with COVID-19, but the COVID-19 virus can also be considered as a modifying factor in the course of the disease. *© 2022 Bull. Georg. Natl. Acad. Sci.*

COVID-19, comorbidity, modifying role

It is known that the world is currently fighting a pandemic caused by the new COVID-19, which is characterized by frequent unsafe solutions and lethality. Lethality is not only related to respiratory failure and hypoxia caused by impaired gas metabolism in the lung alveoli. Many organs and systems are damaged, their function and structure are disrupted. The central and peripheral nervous system is also involved in the pathological process. A viral agent penetrating the CNS through the hematoencephalic barrier changes the state of T- and B-cell immunity. Because the change in immunity is varied, the cellular responses can be asymptomatic as well as with a variety of sym-

ptoms: mild cold, respiratory distress syndrome, meningitis, encephalitis, encephalopathy, cranial and other peripheral nerve lesions, muscle damage, and rhabdomyolysis.

There is no longer any doubt today that COVID-19 is a multisystem disease that can damage any organ, ranging from the lungs to cognitive dysfunction. Complications from the nervous, cardiovascular, respiratory and digestive systems are considered to be particularly dangerous symptoms. In addition, underlying chronic diseases are exacerbates [1,2].

Early reports from Wuhan already indicated the neuroinvasive potential of SARS-CoV-2 (headache, dizziness, anosmia and/or ageusia), followed by symptoms of central and peripheral nervous system damage [1,2].

Based on the data available today, it can be assumed that SARS-CoV-2 may be neurotropic and/or contribute to the creation of conditions conducive to direct or indirect damage to the nervous system.

Purpose. The aim of the work was to study comorbidity in patients with neuromuscular diseases (myasthenia, chronic polyneuropathy, myopathy) infected with SARS-CoV-2 and to reveal the modifying role of SARS-CoV-2 virus on the course of background diseases.

Material and Methods

20 patients with generalized myasthenia gravis, 8 patients with chronic polyneuropathy and 5 patients with progressive muscular dystrophy infected with COVID-19 were included in the study. Among the patients with myasthenia gravis there were 15 women and 5 men, aged 50-69 years. Among the 8 chronic polyneuropathy patients transferred to COVID-19, there were 3 women, 5 men, their age varied from 25-74 years. Among the patients with muscular dystrophy there were 3 women and 2 men, the age ranged from 36 to 73 years. All patients had confirmed COVID-19 infection and were examined within a time interval from 3 weeks to 2 months after infection. They underwent computed tomography of the chest, clinical-electroneuromyography examination (ENMG), titers of antibodies to AChE, MuSk, Titin, LIA-ANA profile were determined, blood tests were performed, creatine phosphokinase (CPK) and C-reactive proteins were determined in the blood. Progressive muscular dystrophy was confirmed by genetic analysis.

Results

According to our material, 27 out of 72 patients with myasthenia gravis who were on hormone therapy and/or anticholinesterase treatment were infected with COVID-19 infection, and 7 (25.9%) of the infected patients had a fatal outcome. The condition of 15 of the remaining 20 patients with myasthenia gravis worsened, mainly with respiratory symptoms, ENMG study showed a deepening of the M response, 1 patient was diagnosed with Lambert-Eaton syndrome, and 3 with motor-sensory polyneuropathy with predominant damage to sensory fibers; The condition of 5 patients did not change and the infection was asymptomatic.

It is probably accepted, that the data in the medical literature about the manifestation of myasthenia gravis after the infection with COVID-19 should be considered as a subclinical or minimally symptomatic process that was provoked by the infection [3,4]. Since infection is known to trigger myasthenia gravis, it is also possible that COVID -19 infected myasthenia gravis patients are treated with medications that cause myasthenia gravis. In particular, most patients with myasthenia gravis are on immunosuppressive therapy. At the beginning of the pandemic, azithromycin and hydroxychloroquine were actively used. Later studies showed that 40% of myasthenia gravis patients infected with COVID-19 worsened with this anti-covid therapy [5-7]. Overall, 24% of patients with myasthenia gravis were fatal, and

43% partially improved and were discharged from the hospital [5-7].

According to American authors, 0.94% of myasthenia patients were diagnosed with COVID-19 infection; according to French authors, this rate is 0.96% [4-7]; according to these data, 27-69% of myasthenia patients were hospitalized, 10-26% required intensive therapy, the lethality is 7 -24%.

These data are not accurate, as well as the data on the need for intensive care and lethality in general, since asymptomatic and mild (5-32%) infections may not be diagnosed and registered. There are data according to which patients with myasthenia gravis have a higher risk of hospitalization, admission to intensive care, intubation, and mortality, compared to the general population [5-7]. Alternatively, some studies show no difference.

Complications are mainly seen in MGFA classification stage 4 and in seropositive patients, isolated cases are manifested in MuSK positive patients. Complications are mainly associated with respiratory manifestations.

According to our material, 66.7% of patients with chronic inflammatory demyelinating polyneuropathy (8 out of 12 patients) were infected with COVID-19. No lethal outcome was observed, but the course of the disease worsened in 50% of infected patients (4 patients). Among them, electrophysiological markers typical for polymyositis were detected in one patient. Clinically, this patient had more proximal muscle weakness, and proximal muscle pain was also present. CPK and C-reactive protein levels were elevated, which was not observed before the infection with COVID-19. In 2 cases, neuromuscular weakness was detected in patients who did not have symptoms of pathological fatigue before COVID-19 infection. The reason for the visit was post-COVID numbness in the limbs, which was considered an exacerbation of chronic polyneuropathy. Initial strength deficit in proximal muscles was not detected during examination, but pathological fatigue appeared after loading. Neuromuscular transmission testing in these patients revealed a decrement of the M response pathognomonic for damage to neuromuscular transmission with worsening sensory neuropathy.

40% of patients with peripheral neuropathy detected after COVID-19 infection had n. phrenicus demyelination and axonopathy. 20% of patients with n. phrenicus injury had respiratory symptoms against the background of non-gross lung damage (4-5point), therefore, the respiratory symptoms were caused by n. phrenicus damage. Thus, n. phrenicus can be considered as one of the important links of the respiratory system.

According to various sources, peripheral nerve damage during the infection with COVID-19 was completely detected in 1.3 to 9.5% (average – 3.3%), of which Guillain-Barre syndrome accounted for 18.9%, out of which 70.7% had the classical phenotype; Miller-Fisher form was observed in 10.9% and cranial nerve damage – in 16.3%, facial nerve damage prevailed. Exacerbation of chronic inflammatory demyelinating polyneuropathies occurs in 5 to 16% of cases during COVID-19 infection [8-10].

Among the complications of COVID-19, Guillain-Barre syndrome and neuromyopathies of critical states occupy an important place. Guillain-Barre syndrome is more common in the elderly. In young people, it is milder and lethality is practically not described [8-10].

Currently, studies are underway in the medical literature to determine the relationship between this two nosology's in cases of Guillain-Barré syndrome in patients with COVID-19. According to some data, the incidence of Guillain-Barré during the pandemic was 2.6 times higher than in the non-pandemic period [8,9]. According to other works, the number of patients hospitalized due to Guillain-Barre syndrome during the pandemic has not increased compared to the period before the pandemic.

Just as during Guillain-Barré syndrome developed against the background of C.jejuni, sialic acid in the host cell binds to the ganglioside of the host cell, so the spike protein of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor. Cross-reactivity between epitopes of the complex, namely the viral spike protein and host cell gangliosides, is also expected, although convincing evidence has not yet been obtained.

Guillain-Barré syndrome predominated in men. The disease was mainly manifested at the age of 50 to 75 years, the average age is 58 years. Motor paresis prevailed over sensory, lower limb damage over upper limb. These data practically do not differ from the data in the population [9,10].

The need for intensive care was observed in about 40% of patients. Mechanical ventilation – in 21.7%, in the general population this figure is equal to 25%. Autonomic dysfunction during Guillain-Barre was seen in 19.4%, but these data are highly variable. Among those infected with COVID-19, the bad outcome of Guillain-Barré syndrome was observed in 40 to 50% of cases, in the general population this figure is 20%, in case of COVID-19, lethality is in 6.5%, in non-COVID-19 population – 4-7%.

Acute inflammatory demyelinating polyneuropathies with axon damage were most often observed, unlike non-COVID-19 forms where the axon is less frequently damaged, and the rate of F wave blocking was also high compared to non-COVID-19 forms.

Laboratory testing showed albumin-cytological dissociation in CSF fluid. Only in one case was positivity for SARS-CoV-2 genome detected in CSF fluid [9,10].

MRI did not reveal any specific changes in the peripheral nervous system for COVID-19.

The etiological association between cranial neuropathy and COVID-19 is also unclear. Damage to the sense of smell, face, vision, trigeminal nerves and hearing loss are revealed. Just as anosmia, ageusia, and trigeminal nerve terminals can be viewed as gateways for the virus to spread through the nervous system via retrograde axonal transmigration, so the lower cranial nerves can be viewed as a pathway to the brainstem and subsequent hypoxia [10].

According to our material, 5 patients with progressive muscular dystrophy were diagnosed with COVID-19 and had pain in their limbs both during and after the COVID-19 infection. Out of 5 patients with progressive dystrophy, 2 were diagnosed with sensory-motor polyneuropathy, which was not present before the COVID-19 infection, and in 2 patients, the degree of muscle damage increased electrophysiologically, and in 1 patient, ENMG changes characteristic of polymyositis were detected.

Early in the pandemic, it became clear that skeletal muscle damage was observed during the infection. Myalgia and weakness were observed in 11-70%, increased creatine phosphokinase level in 9-33%. There is an active search in the literature regarding the pathomechanisms of the development of COVID-19 -related myopathies, rhabdomyolysis, myositis and critical state myopathies. About 30 papers have been published indicating rhabdomyolysis in COVID-19 patients, which occurs in 1.1% of hospitalized patients. Rhabdomyolysis can be caused by electrolyte imbalance, ischemia, prolonged immobilization, drug-induced myotoxicity. Immune-mediated damage to myocytes caused by viruses is allowed to be one of the possible mechanisms and is the subject of further research [11].

Myositis, dermatomyositis with high creatine phosphokinase and bilateral swelling of the thigh muscles on MRI, perivascular inflammation, endomysial spread and abnormal sarcolemmal and sarcoplasmic expression of major histocompatibility antigen (MHC-1) were seen on biopsy.

It is not clear why SARS-CoV-2 damages muscles is not clear. The ACE2 receptor through which SARS-CoV-2 infects the host cell is also expressed in skeletal muscles, including the

diaphragm, leading to direct infection of the muscle. Autopsy showed muscle inflammatory cell infiltration, necrotic muscle fibers, MHC-1 expression in muscle fibers, MxA (myxovirus resistance protein) expression in capillaries, but immunohistochemically there is no evidence of direct virus invasion.

Finally, weakness requiring intensive care including critical polyneuropathies is not specific to COVID-19 but is noteworthy. Compressive neuropathies were common among critical neuropathies, ulnar, radial, medial, and sciatic nerves were often damaged. Risk factors are long-term immobilization, sepsis, systemic inflammatory reaction syndrome, comorbid diseases, age, multiorgan failure that can be aggravated by COVID-19 infection. Complications from intensive care are expected when critically ill patients have diffuse weakness and/or difficulty weaning from mechanical ventilation [11,12].

In surviving patients, improvement in strength took several weeks to several months. Post-COVID-19 critical myopathies and polyneuropathies are virtually identical to post-infection critical myopathies and polyneuropathies. There are some data on type 2 muscle fiber atrophy in patients who have died from COVID-19.

SARS-CoV-2 is an epochal challenge and may become a companion to humanity. It is expected to be eradicated, but most likely it remains a constant companion of humanity, changes the planetary health of the population, modifies the immune system, changes the parameters of human health, new biological changes appear that determine the length of life, changes the biological age of a person.

According to some data, it accelerates the process of premature aging of people, thus explaining the high rate of lethality in the elderly.

According to Lippi and co-authors, SARS-CoV-2 affects proteostasis, causes neurodegeneration and accelerates the aging process of the brain, although this statement is controversial, since a number of researchers point to the reversible nature of the aging-like processes of COVID-19. A person can recover and return to their biological age [12]. Everything needs more evidence.

Conclusion

According to the obtained results, it can be assumed that as a result of COVID-19 infection, not only comorbid pathologies appear, but the COVID-19 virus can be considered as a modifying factor in the course of the disease.

სამედიცინო მეცნიერება

COVID-19-ის ნერვკუნთოვანი კომორბიდიზმი

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ნაშრომის მიზანს შეადგენდა კომორბიდიზმის შესწავლა SARS-CoV-2 -ით დაინფიცირებული ნერვკუნთოვანი დაავადებების (მიასთენია, ქრონიკული პოლინეიროპათია, მიოპათია) მქონე პაციენტებში და ფონური დაავადებების მიმდინარეობაზე SARS-CoV-2 ვირუსის მამოდიფიცირებელი როლის გამოვლენა. გამოკვლეული იყო SARS-CoV-2-ით ინფიცირებული მიასთენიის გენერალიზებული ფორმით დაავადებული 20, ქრონიკული პოლინეიროპათიით – 8 და პროგრესული კუნთოვანი დისტროფიით 5 პაციენტი. მიასთენიით დაავადებულთა შორის იყო 15 ქალი და 5 მამაკაცი, ასაკი – 50-69 წელი, ქრონიკული პოლინეიროპათიით დაავადებულებში ქალი – 3, მამაკაცი – 5, ასაკი 25-74 წელი; კუნთთა პროგრესული დისტროფიით დაავადებულებში იყო 3 ქალი და 2 მამაკაცი, ასაკი 36-73 წელი. პაციენტები გამოკვლეულები იყვნენ დადასტურებული კოვიდ ინფექციის შემდეგ 3 კვირიდან 2 თვემდე დროის ინტერვალში. ყველას ჩაუტარდა გულმკერდის კომპიუტერული ტომოგრაფიული გამოკლვევა, კლინიკურ ელექტრონეირომიოგრაფიული კვლევა; მიასთენიით დაავადებულებში განსაზღვრული იყო ანტისხეულების ტიტრი აცეტილქოლინორეცეპტორების, ტიტინისა და MUSK-ის მიმართ. მიოპათიის მქონე პაციენტებში განისაზვრა კრეატინფოსფოკინაზის დონე (კფკ), LIA-ANA-ს ტესტი, სისხლის საერთო ანალიზი, C- რეაქტიული ცილა; მიოპათია დადასტურებული იყო გენეტიკური დიაგნოსტიკით. მიასთენიის გენერალიზებული ფორმით დაავადებული 27 პაციენტიდან ლეტალობა დაფიქსირდა 7 პაციენტში, დანარჩენი 20 პაციენტიდან 15-ის მდგომარეობა გამწვავდა რესპირატორული სიმპტომატიკით, გაიზარდა M პასუხის დეკრემენტი, ერთ პაციენტს გამოუვლინდა ლამბერტ-იტონის სინდრომი, 3-ს მოტორულ-სენსორული პოლინეიროპათია. კოვიდ-19 ინფექციით დაინფიცირებული 8 ქრონიკული პოლინეიროპათიის მქონე პაციენტიდან დაავადება გაუმწვავდა – 4 (50%), აქედან ერთს დაუფიქსირდა პოლიმიოზიტისათვის სახასიათო კლინიკურ-ელექტრომიოგრაფიული და ბიოლოგიური მარკერები, კერძოდ მომატებული კრეატინფოსფოკინაზა (კფკ), C რეაქტიული ცილის მაჩვენებელი, რომელიც არ უფიქსირდებოდა ინფექციამდე, პოლიმიოზიტი დადასტურდა LIA-ANA-ს მეთოდით გამოვლენილი აუტოანტისხეულებით. პაციენტთა 40%-ს გამოუვლინდა n. phrenicus-ის როგორც აქსონოპათია, ასევე დემიელინიზაცია. ამ პაციენტებში რესპირატორული სიმპტომატიკა გამოვლინდა ფილტვების არაუხეში დაზიანების ფონზე (4-5ქულა). კუნთთა პროგრესული დისტროფიით დაავადებული 5 პაციენტიდან, 2-ს გამოუვლინდა სენსორულ-მოტორული პოლინეიროპათია, რომელიც ინფექციამდე არ აღინიშნებოდა. ერთ პაციენტში გამოვლინდა პოლიმიოზიტისათვის სახასიათო ელექტრონეირომიოგრაფიული ცვლილებები, დადებითი LIA-ANA ტესტით. მიღებული შედეგების მიხედვით დასაშვებია, რომ კოვიდ-19 ინფექცია

განიხილებოდეს არა მარტო, როგორც ფონური დაავადებების ფონზე განვითარებული კომორბიდული პროცესი, რომელიც ართულებს ძირითადი დაავადების მიმდინარეობას, არამედ კოვიდ-ვირუსი შეიძლება წარმოჩინდეს დაავადების მიმდინარეობის მამოდიფიცირებელ ფაქტორადაც.

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Received October,2022