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PATHOGENETIC ASPECTS OF NEUROLOGICAL COMPLICATIONS OF POST-COVID SYNDROME

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Abstract
The emergence of a new coronavirus infection COVID-19, caused by the SARS-Cov-2 virus, has stimulated active scientific study of both this infection and many of the problems associated with it. In the first months of the existence of COVID-19, attention was paid almost exclusively to severe complications of a pulmonary nature, pathogenetic features of immunological reactions. However, already in the first publications describing the clinical course of the disease, there were reports of frequent damage to other organs and systems, among which it is necessary to single out damage associated with the pathology of the nervous system - from strokes to necrotizing encephalopathy and Guillain- Barré syndrome .

Keywords: COVID-19, post-covid complications, post-covid syndrome

A few months after the onset of the COVID-19 outbreak, descriptions of delayed disorders appeared, which have several names: prolonged covid , post-covid conditions, post-covid syndrome . This heterogeneous group of conditions has received its "place" in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [3] with the code i09.9 - Condition after COVID-19. However, there is no generally accepted clinical picture and unambiguous understanding of the ongoing processes leading to the development of symptoms. The epidemiology of this syndrome is also unclear, which is due, among other things, to various interpretations of the syndrome. According to [4], out of 47,780 patients with the acute phase of COVID-19 discharged from hospitals in the UK up to August 2020, over the next 140 days, almost a third of persons were rehospitalized (14,060), and more than 1 in 10 (5875) died, which is 4 and 8 times more likely than in the matched control group, respectively.
In this regard, the aim of the work is to describe the symptoms of post-COVID syndrome with the formation of an “image of the disease” and to evaluate the possible pathogenetic mechanisms for the development of this condition.

Tasks :

1. Assess the symptoms of the disease and quantify them.
2. To develop and scientifically substantiate the scheme of the pathogenesis of the development of symptoms of post-COVID syndrome.
3. Present the clinical classification of post-COVID syndrome.

Materials and Methods

To form the “image of the disease” at the first stage, the Moscow City Scientific Society of Therapists (MGNOT) in July-September 2020 analyzed the messages of patients in social networks, first of all, “ Atypical coronavirus ." This Russian-speaking group includes more than 40 thousand users. Based on the results of a qualitative analysis of the complaints made, an initial questionnaire was formed, its automated version was created, a link to which was sent by the group administrators to about 20 thousand addressees - group members by e-mail. The developed questionnaire had 38 questions, including the most common complaints among patients. The respondent had to indicate the presence of one or another symptom from the proposed choice. In addition, an additional field was included for free-writing symptoms that were not mentioned. in the questionnaire . It was not possible to statistically process the manually entered symptom information.

At the second stage, 1,400 responses from respondents were accepted for analysis and statistical processing of the information received was carried out. The frequency of response to the question was assessed and matrices were developed according to the frequency of occurrence of symptoms. At the third stage in February-March 2021, the second updated questionnaire was compiled on the symptom checker platform MBAB [5], and the participants of the above group 2 are invited to its passage. Symptomchecker allows you to answer "yes" or "no" to closed questions of the system, has extensions to clarify the situation by the type of "decision tree". In addition, for a number of questions, scales were made to evaluate certain symptoms in a gradation from 0 (no symptom) to 10 (maximum symptom severity). According to the unique 1P addresses, it was established that among those who were surveyed with the help of a symptom checker , there were no persons who underwent the initial survey.

Results and Discussion

A survey of 1,400 patients with postocular syndrome on social networks showed that 76% of respondents underwent an immunological examination for COVID-19 (PCR or the presence of antibodies), and 24% did not pass the tests. In 51.4% of respondents , the diagnosis of coronavirus infection was previously confirmed by laboratory tests,

24.6% had a negative laboratory test result. There were no significant differences in the frequency of symptoms between patients with confirmed COVID-19 infection and those without it.

The duration of the post-COVID state was less than 1 month in 22.7%, 1–2 months in 19.5%, 2–3 months in 13.5%, and more than 3 months in 44.3% of respondents. In 74.1%, the undulating nature of the course of the disease was noted, in 25.9%, the signs of the disease were permanent.

The most common symptom was weakness (80%). At the same time, 58.6% of respondents could not perform their usual physical activity.

50.8% had a periodic increase in body temperature, 47.1% had chills or chills, 44.9% had night sweats or daytime sweats. An association between chills, sweating, and fever could not be established.

Neurological symptoms were noted in almost all respondents: 50.8% had insomnia , drowsiness, disruption of day and night, 18.4% had unusual and vivid dreams, 45.2% had signs of depression, and 43.6% had headache.

47.1% of respondents had a feeling of congestion in the chest and lack of air. 43.0% had pain in the region of the heart of a non-angina pectoris, 41.5% had tachycardia attacks, 30.4% noted an increase in blood pressure (BP), and 14.9% had a decrease in blood pressure (these symptoms were regarded by us as a violation of the nervous regulation of blood pressure).

A large number of patients had signs of skin vasculitis and damage to the venous system: more than a third (35.1%) complained of hair loss, 19.6% had skin rashes, 18.2% had "knots" on the veins, soreness of the veins . A frequent "skin" manifestation of the disease was the presence of goosebumps, a burning sensation of the skin (32.9%).

28.1% of respondents had visual impairment, 13.6% had hearing impairment, 17.9% had gait disturbance, and 25.4% had diarrhea.

Other symptoms were less common (less than 10%) or we could not estimate their frequency: panic attacks, convulsions, polyneuropathy , sensation of vibration in the head and chest (some figuratively called this sensation of a transformer), difficulty concentrating, absent-mindedness, forgetfulness, the appearance of "fog in the head", gynecomastia, menstrual disorders, libido and other sexual functions, dizziness, tinnitus and ringing in the ears, bruising, nasal bleeding, emotional lability, pathophagy and pathosmia (lack of smell or haunting odors, aversion to meat , chocolate, alcohol), toothache, dental problems (some have cystic changes in the bones of the jaw), allergic reactions, edema, lymphostasis , lymphadenopathy . The results of this work have been partially published [7].

At the third stage, in the process of creating a symptom checker on the MeDiCase platform , taking into account the first version of the questionnaire and the emergence of clinical experience of remote work with patients with post-COVID syndrome, the questionnaire was significantly revised, new questions and clarifications on symptoms were added to it. The total number of questions was 137, of which there were 36 basic (mandatory for all) questions and 101 additional questions 2 and 3. The questionnaire included symptoms that are common in this pathology or of a specific nature, which was evaluated empirically.

After the creation of the automated questionnaire, invitations to take the survey were placed several times in the above group. As a result, 327 respondents took part in the second survey, 194 questionnaires were processed. The culling was associated with a negative answer to the distractor question "Did you answer the questions truthfully?" According to the results of this survey, the duration of the disease was 1–3 months after acute covid in 44.3%, 3–5 months in 29.4%, and more than 5 months in 26.3% of respondents. Women clearly predominated over men - 78.9%, under the age of 18 there were 3.6%, in the age group 18-55 - 82%, and over 55 years - 14.4%. Acute COVID -19 was confirmed by a doctor in 62.9%, 82% were tested for covid , the diagnosis was confirmed immunologically in 87.4% of them (in 71.7% of the total sample).

The frequency of symptoms was as follows (grouped in descending order):

— weakness, fatigue had 84.5%;

- insomnia, daytime sleepiness - 77.3%. This symptom turned out to be quite painful, the vast majority have its various manifestations: 71.3% do not fall asleep well, 70% have superficial sleep, 78% often wake up at the beginning (it should be especially noted that many indicated the time of waking up at 4 am), 80% wake up sleepy , broken, daytime sleepiness is noted in 72%;
- various manifestations of depression were noted by 68.6%, the same number of anxiety, while the feeling of guilt was in 50.5%, depressing thoughts about past mistakes - in 51.5% and suicidal thoughts - in 35.5% of the total sample;
- pain in muscles, bones and joints - 63.9%;
- palpitations, cardiac arrhythmias - 63.4%;
- impossibility to perform normal loads - 60.3%;
- violation of the regulation of blood pressure was noted in 55.2%, an increase in blood pressure - in 76.6% and a decrease in blood pressure - in 37.4%; it should be noted that a small part of the respondents were concerned about both the increase in blood pressure and its decrease;

- dizziness - 52.6% (attacks of sudden dizziness - in 67.6% and accompanied by gait disorders - in 58.8%);
— chilling was noted by 51.5%; this symptom does not correlate with fever and is an independent symptom of the disease: 34% had elevated body temperature, 34% had low body temperature, and 32% had normal body temperature;
- violation of the regulation of body temperature was noted by 47.9%: of these, 55.9% of respondents noted an increase in temperature, and subfib -
fever was in 90.4% (up to 37 °C - 42.3%, up to 37.5°C 48.1%), febrile in 8.6% (up to 38.5°C in 8% and over 38 °C at 3.8%); at the same time, a decrease in body temperature was noted by 47.3%, of which up to 36°C - in 52.3%, below 36°C - in 47.7% of respondents;
- Sweating at night or during the day disturbed 46.9% of the respondents, it was not possible to establish a correlation with hyperthermia: of those who noted sweating, the temperature was increased in 35.2%, decreased - in 16.5 and 48.4% had a normal temperature;
- Headache, which had not previously been noted in 43.8%, and in 24.7% it was constant, and in 71.8% it was paroxysmal in nature (the rest did not give an answer about the nature of the pain; it should be noted that the respondent could indicate both characteristics at the same time);
- hair loss - 41.2%;
- visual impairment - 40.7%. Patients describe this condition in different ways: 84.8% as a violation of focus (which may reflect dysfunction of the oculomotor nerves), subjective decrease in visual acuity - 83.5%, flickering before the eyes - 44.3%;
43.3% had pain in the region of the heart. This symptom is very exciting for patients and they give colorful descriptions of it, the frequency of which significantly exceeds that in the population: unbearable pain behind the sternum - in 10.3%, pierces from front to back in 25.9%, accompanied by cold sweat, weakness, interruptions, shortness of breath in 62.1%. Such characteristics require the assumption of an acute coronary syndrome, however, it is obvious that this disease does not exist, the respondents coexist with this symptomatology for a long time, many performed ECG and echocardiography without detecting pathology, which indicates the pseudocoronarogenic nature of this cardialgia ;
- tinnitus, hearing impairment had 40.7%;
- weight loss - 40.7% (up to 5 kg - 58.2%, within 5-10 kg - 34.2%, and more than 10 kg - 7.6% of respondents);
- unusual vivid dreams appeared in 37.6%;
- goosebumps were noted by 37.1%, burning, skin tightening - by 35.1%;

- congestion in the chest, breathing problems were in 36.6%. Most often, it is not about shortness of breath, but about the inability to take a deep breath;
- rashes on the skin were noticed by 25.3% (of which such rashes had previously occurred in 28.6%, they first appeared in 71.4%);
— loss of appetite — in 28.4%;
- violation of sexual functions: menstrual cycle - in 27.7% of women, and potency, libido - in 7.2% of men;
- frequent urination was observed in 24.2%;
— gait disturbance — 24.2%;
- loose stools - 22.7%;
- knots on the veins resembling aneurysms, soreness of the veins, an altered venous pattern were noted by 22.7%. This is a somewhat unusual feature, which has not previously been given sufficient attention. Venous mesh on the legs was noted by 75% of the respondents of this subgroup, soreness, burning along the veins - 50%, knots or swelling on the veins - 50% (the latter are clearly visible in the photographs sent to us);
— 18.6% of respondents had enlarged and sore lymph nodes, which may indicate immune processes, of which 77.8% had enlarged lymph nodes in the submandibular region on the neck, 30.6% in the axillary region, and 30.6% in the inguinal region. 19.4%; about a quarter of respondents have enlarged lymph nodes in different regions. So, the symptoms and manifestations of the post-covid syndrome - the "image of the disease" - are diverse and affect almost all organs and organ systems. At the same time , it is obvious that they are not a manifestation of intoxication, tissue breakdown: most likely they reflect an actively ongoing inflammatory process. We are well aware of systemic inflammatory, aseptic, chronic processes, which are combined into a group of rheumatic diseases. However, the existing symptoms do not fit into the picture of any known nosological form. Thus, we can most likely talk about a relatively new post-infectious pathology, which, however, was previously known for many infectious diseases, such as chikungunya , Ebola , borreliosis , etc. [8, 9].
When analyzing the symptoms described above, it is noteworthy that a significant number of them are associated with one or another pathology of the nervous system (central, peripheral, sympathetic and parasympathetic, metasympathetic). These symptoms can be attributed to 17 of the 29 signs listed above. 4 signs are definitely not related to nervous regulation (enlarged lymph nodes, aneurysmal and other changes in veins, skin rashes and hair loss). However, the remaining 8 signs (diarrhea, urination disorders, sexual dysfunction, weight loss, cardialgia , cardiac arrhythmias, myalgia and arthralgia) may also be neurogenic in nature. Just these functions are

regulated by the sympathetic, parasympathetic and metasympathetic divisions of the nervous system.

the question arises : what is the mechanism of damage to the nervous system? It is known that the tropism of the SARS - Cov -2 virus to the nervous tissue is low: its penetration into the nerve endings on the nasal mucosa is discussed, this sometimes explains anosmia and adhesion , migration along the "olfactory tract" or through the vagus or trigeminal pathways [10], but the final and there is no conclusive evidence for this. The SARS - Cov -2 protein was found on histochemical examination in the endothelium of cerebral vessels, but not in neurons or glia [11]. The authors note that the presence of SARS - Cov -2 in the central nervous system (CNS) leads to a local CNS response mediated by HlNGO+ microglia as effectors of the myeloid- induced inflammatory response . The authors correctly write that since they were able to detect SARS - Cov -2 RNA in areas of the brain, such as the cerebellum, which is not directly connected by any "paths" to the olfactory nasal mucosa, there may be other mechanisms for the virus to enter the CNS, possibly , in addition to or in combination with axonal transport. For example, migration of SARS - Cov- carrying leukocytes across the blood-brain barrier or viral entry along the CNS endothelium cannot be ruled out. In confirmation , immunoreactivity to the SARS - Cov protein was found in cerebral and leptomeningeal endothelial cells.

Histopathological analysis of brain tissue showed microglial nodules and neuronal phagocytosis (neuronophagy) in the brainstem and less commonly in the cortex and limbic structures associated with lymphocytic infiltration, and no correlation between histopathological findings and levels of viral messenger RNA in the same brain [10]. Brainstem damage may explain persistent autonomic abnormalities and anxiety (panic attacks). In the damage to brain structures, inflammatory reactions characteristic of SARS - Cov -2 invasion may play a role. It is inflammation that plays a key role in the acute period of the disease in the development of complications, triggering intravascular coagulation of blood, having a direct negative impact on many functions, including brain tissue. The entry of the virus into the endothelial cells of the vascular network of the brain activates neutrophils, macrophages, thrombin, promotes microthrombosis and impaired vascular permeability. Tumor necrosis factor (TNF-a), cytokines can pass through the blood-brain barrier due to its increased permeability. Cytokines activate microglia and astrocytes . Macro- and especially micro-hypoxic ischemic damage and infarcts in the brain tissue mediate the pathological " synaptic pruning" of microglia (cells of a macrophage nature) - a decrease in the number of synaptic connections . Microglia secrete specific inflammatory mediators, including quinolinic acid, which leads to an increase in

glutamate levels and an upregulation of NMDA receptors, which can cause mnestic disorders - learning, memory, neuroplasticity , as well as cause hallucinations and nightmares, disrupt sleep.

If for the acute period of the disease all the above arguments and findings look convincing enough, then there is no such information for the post-COVID syndrome. Moreover, no and signs of viral infection. Therefore, recognizing damage to the brain tissue, it is necessary to look for other, non-infectious causes of damage to it. Such a cause, most likely, is immune chronic inflammation involving microvessels, which can be called immunothrombosis , thrombovasculitis , endotheliopathy . A key role in the development of the process is played by the appearance of various antibodies that form immune complexes or have a direct damaging effect on the structures of the nervous tissue. Among the known ones are antiphospholipid antibodies, antibodies to antimyelin-oligodendrocyte glycoprotein [12].

An additional factor that allows us to talk about immunothrombosis are numerous other conditions - various skin vasculitis , visible damage to venous vessels, the appearance of degenerative changes in the nails (transverse striation , Bo lines) [13], Kawasaki-like syndrome with damage to the vasa vasorum , etc.

Thus, we propose the following definition of " post-covid syndrome": a clinical condition that occurs several weeks after an episode of acute COVID-19 infection, ending in clinical recovery and characterized by non-specific neurological symptoms associated with meningoencephalitis , cutaneous vasculitis , sometimes mental abnormalities and dysfunction individual organs and systems.

ICD-10 is not a clinical classification and serves the purpose of statistical analysis of diseases and causes of death. Direct use of ICD-10 in clinical practice is not provided. It should be noted that this classification is changing rapidly, so that what was true until recently may already be canceled or replaced. As of January 2021, ICD-10 has several codes related to post-COVID syndrome: COVID-19, confirmed or probable, which has affected a person's health, but the person is no longer sick with COVID-19; U09.9 Condition after COVID-19. This optional code allows you to establish an association with COVID-19. It should not be used in cases where there are still signs of acute COVID-19 infection; U10.9 Multisystem inflammatory syndrome associated with COVID-19, unspecified.

Temporally related to COVID-19 :

- Cytokine storm;
- Kawasaki syndrome;
- multisystem inflammatory syndrome in children (Multisystem Inflammatory Syndrome in children , MIS-C);

Pediatric inflammatory multisystem syndrome (Pediatric Inflammatory Multisystem Syndrome , PIMS);
- excluded: mucocutaneous lymphonodular syndrome [Kawasaki] (M30.3).
U12.9 Adverse effects of therapeutic use of COVID-19 vaccine, unspecified. This code should be used as an external cause code (i.e. as a subcategory under (Y59) Other and unspecified vaccines and biological substances). In addition, a code from another chapter of the classification indicating the nature of the adverse effect should be used. Proper administration of the COVID-19 vaccine in prophylactic therapeutic applications as the cause of any adverse effect.

Conclusion

Creating an "image of the disease" using automated survey systems allows us to express and substantiate a hypothesis about the relationship between the main symptoms of post-COVID syndrome and the development of meningoencephalitis , caused, in turn, by thrombovasculitis . To confirm this hypothesis, scientific research should be directed towards studying the morphology of the nervous tissue, including using immunohistochemical methods , assessing the immunological status and processes of intravascular blood coagulation. An important limitation of our study should be recognized as the formation of a sample exclusively from individuals - users of social networks on the Internet. Patients with limited use of the Internet were not included in the sample of this study: they, quite naturally, may constitute a cohort of patients with other , more severe post- COVID complications described in [4]. For such patients, a separate facet is allocated in the proposed classification .

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