

Postcovid-19 Asthenic Syndrome

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Objective. To study the characteristics of asthenic syndrome and the potential for treating it in the postcovid period. **Materials and methods.** A continuous sampling method was used to select 129 patients (mean age 49.8 ± 8.9 years) after COVID-19. Study patients were selected at the clinical out-patient and polyclinic facilities in Samara in the period July–August, 2020. All patients signed informed consent. The envelope method was used to randomize patients into two groups: the study group ($n = 64$) received ethylmethylhydroxypyridine succinate (Neurox) 1 tablet (125 mg) three times daily for four weeks; medications in the reference group ($n = 65$) did not include any substances of the pharmacological antihypoxant/antioxidant/nootrope groups. Three visits (V) were made: the first (V_1) was before inclusion in the study; the second (V_2) was at 14 days; the third (V_3) was on day 28 from treatment initiation. The dynamics of overall status (weakness, fatigue, concentration of attention, vertigo, headache, sleep impairment) were evaluated on a visual analog scale (VAS); the subjective perception of the severity of asthenia (tiredness, physical and mental fatigue, decreased motivation and activity) was evaluated using the Multidimensional Fatigue Inventory, MFI-20); cognitive functions were assessed using the Mini Mental State Examination (MMSA); and autonomic tone was assessed using the Kérdö index. **Results.** At the end of the study (V_3), statistically significant changes in measures (VAS, MFI-20) were seen only in patients of the study group; the Kérdö Index showed no statistically significant differences. Analysis of MMSE data revealed a decline in cognitive functions in both groups, which may be linked with pseudocognitive deficit due to asthenia. **Conclusions.** Our studies yielded evidence of a high incidence of asthenic syndrome after COVID-19. Neurox decreased the severity and extent of the symptoms of asthenia.

Keywords: COVID-19, postcovid period, asthenia, asthenic syndrome, Neurox.

The appearance of the new coronavirus (SARS-CoV-2), which causes coronavirus disease (COVID-19) led to a worldwide pandemic with powerful negative social and economic consequences [1–3]. The world scientific community carried out unprecedentedly rapid large-scale studies to understand the molecular basis of the infection and the evolution of SARS-CoV-2, to develop vaccines and effective therapeutics, and to introduce preventive and monitoring strategies [4–7]. These studies continue and, furthermore, attract the attention of both scientists and clinicians.

Despite the fact that the main clinical manifestations of COVID-19 are now known, there are still many ques-

tions relating to their severity, the prognosis of infection outcomes, and the main sequelae arising in patients after suffering from the infection. Time and clinical observations are needed for evaluation of the severity of the effects of the disease on subsequent health status, though it is already apparent that most patients, both in the acute period of disease and after recovery, have symptoms of asthenic syndrome. Thus, severe general weakness at disease onset and at each of its stages is, along with temperature, a pathognomonic sign in most patients.

It should not be forgotten that asthenic syndrome is encountered quite often in the practice of any physician, including patients after acute inflammatory diseases. The term “asthenic syndrome” (AS) itself in the scientific literature has different connotations. In translation from the Greek, “asthenia” means the absence of strength [8] and asthenic syndrome in many non-Russian sources is associated with

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chronic fatigue syndrome (CFS). However, many publications indicate that AS is rather wider in its etiopathogenetic and clinical characteristics than chronic fatigue syndrome, including in patients who have had acute viral infections [9–11]. AS can be different in different nosological manifestations, with dominance of different symptoms. Thus, post-stroke patients or those with chronic cerebral ischemia typically complain of decreased motivation and work capacity on the background of cognitive signs in the form of memory impairments, particularly short-term, along with elements of indifference to themselves and others [12]. Various infectious diseases and viral infections are known to lead to the development of asthenic syndrome [13, 14]. In many cases, the leading signs of asthenic syndrome are irritability, emotional lability, and anxiety, which can be combined with autonomic manifestations in the form of increased palpitations, sweating, and impaired intestinal function.

Postcovid asthenia has a number of characteristics to which clinicians' attention should be drawn. The number of publications on this theme is currently limited, though some reports have articulated the problems of asthenic syndrome and the management of patients who have had COVID-19 [15, 16].

SARS-CoV-2 is known to be able to cross the blood–brain barrier to cause damage in the central nervous system (CNS). Preliminary studies have shown that COVID-19 is associated with multiple neurological symptoms (hypoesthesia, hyposmia, acute polyneuropathy, headaches) and CNS-associated disorders, including encephalopathy, encephalitis, acute cerebrovascular diseases, etc. [17]. The authors of published studies have identified the development of neurological symptoms, including psychosis, in a number of patients with COVID-19, which is evidence of the possible occurrence of changes in the psychoemotional domain in patients [18]. However, the clinical features, pathogenetic mechanisms of CNS damage, and therapeutic possibilities remain incompletely characterized. The mechanisms of indirect neuron damage due to the hypoxia arising in most patients during the acute phase of COVID-19 continue to be assessed. In hypoxia, cells undergo activation of the processes leading to the accumulation of toxic metabolites in conditions of mitochondrial damage, which is simultaneously accompanied by microvascular impairments with formation of areas of cerebral ischemia [19]. In cytokine storms and multiorgan failure, the extent of CNS damage is linked with the rapid development of cerebral edema and lethal outcomes [20].

However, CNS damage persists in the long term following the recovery period, though this may be linked with the immunologically mediated responses of glial cells, which can secrete inflammatory factors including IL-6, -12, and -15, and TNF- α for long periods [21]. During the early recovery period after COVID-19, there is an elevated risk of developing persistent asthenia with the main manifestations of rapid physical and mental weakness, headaches, sleep im-

pairments and emotional and autonomic lability, including changes in the cardiovascular system (CVS), with significant daily variation in arterial blood pressure (BP) and heart rate (HR).

The aim of this study was to investigate the features of asthenic syndrome and the potential for its pharmacological therapy in patients after COVID-19.

Materials and Methods. Study patients were selected at clinical out-patients and polyclinic institutions in Samara in the period July–August 2020. Continuous selection was used to recruit 129 patients aged 49.8 ± 8.9 years with COVID-19.

Inclusion criteria. Time from onset of illness no greater than 23 ± 5.5 days; diagnosis of COVID-19 with approved laboratory confirmation by polymerase chain reaction using biological material; voluntary informed consent to take part in the study.

Data were acquired by specially trained staff and physicians at centers taking part in the study to record the main clinical and demographic parameters. After giving signed voluntary informed consent, recruited patients were randomized to two groups by the envelope method. Patients of the study group ($n = 64$) were prescribed ethylmethylidihydroxypyridine succinate (Neurox) at a dose of 1 tablet (125 mg) three times daily for four weeks. Patients of the reference group ($n = 65$) did not receive medications of the antihypoxant/antioxidant/nootrope groups. Three visits (V) were made: the first visit (V₁) at recruitment, the second (V₂) at 14 days, and the third (V₃) on day 28 from treatment initiation.

Clinical and demographic data, including sex, age, body mass index (BMI), diastolic arterial blood pressure (DBP), systolic blood pressure (SBP), information on smoking, and data on concomitant diseases were noted on electronic individual record cards for each patient at V₁.

The dynamics of patients' status were assessed at each visit using a visual analog scale (VAS) on a centimeter scale for assessment of complaints (total weakness, fatigue, decreased concentration of attention, nonsystemic vertigo, headache, sleep impairment), the Multidimensional Fatigue Inventory [22], which provides quantitative assessment of subjective perceptions of the overall severity of asthenia (an integral parameter), and the extent of general tiredness, physical and mental fatigue, and reductions in motivation and activity.

The MFI-20 scale consists of 20 statements, the response to each being evaluated on a scale of 0 to 5. Points were assessed on five subscales: total asthenia, physical asthenia, decreased activity, low motivation, and mental asthenia. At a total of >12 points on at least one subscale and a total score of >60 points, asthenia was regarded as significant. Physical and mental fatigue were assessed on the Fatigue Score (in points); the severity of asthenia was evaluated on the Fatigue Severity Scale (in points), and the extent of autonomic lability was evaluated using the Kérdö index [23]. The Kérdö index was taken as an integral indicator allow-

TABLE 1. The Main Complaints of COVID-19 Patients

Complaints	Study group, <i>n</i> = 64 (<i>n</i> /%)	Reference group, <i>n</i> = 65 (<i>n</i> /%)	<i>p</i>
General weakness	64/100	65/100	1.000
Fatigue	57/89.1	56/86.2	0.643
Tiredness on physical and mental loading	52/81.3	53/81.5	0.999
Decreased memory	39/60.9	38/58.5	0.833
Decreased concentration of attention	51/79.7	52/80.0	0.981
Sleep disorders	39/60.9	41/63.1	0.729
Headaches	38/59.4	38/58.5	0.755
Vertigo	10/15.6	10/15.4	1.000

p identifies significant differences in values between patients in the groups studied.

ing individual parameters characterizing autonomic tone to be assessed. The Kérdö index was computed as $(1-DBP/Pulse) \cdot 100\%$, where DBP is the numerical value of diastolic blood pressure (mmHg) and Pulse is the numerical value of HR (bpm,) with subsequent interpretation of results as follows: values of the index of >0 indicate predominance of sympathetic (excitatory) influences in autonomic nervous system activity, values of <0 indicate predominance of parasympathetic (inhibitory) influences, while 0 corresponds to data mainly indicating functional equilibrium (normalized values from -10% to 10%). The mean Kérdö index was computed from the results of three measurements on V_1 and V_3 . Cognitive functions were assessed using the Mini Mental Scale Examination (MMSE) [24]. The maximum MMSE score is 30 points, which corresponds to complete retention of cognitive functions.

Data were processed using standard software Microsoft Excel and statistics package Statistica for Windows v. 6.0. Normally distributed quantitative properties were described in terms of the mean and the mean square deviation ($M \pm SD$). Analysis was based on descriptive statistics using Student’s parametric *t* test. Parameters with nonnormal distributions were described in terms of the mean and the upper (25th) and lower (75th) quartiles – $Me(Q25; Q75)$. Independent groups were compared by one-way analysis of variance (ANOVA) and studies of interactions between quantitative values used the Spearman rank correlation coefficient (*r*). Differences between study parameters were taken as statistically significant at $p < 0.05$. The main characteristics of diagnostic methods were computed in compliance with the CONSORT requirements (CONSORT group, 1996).

Studies were carried out in compliance with good clinical practice and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Samara State Medical University.

Results. At recruitment into the study, patients in both groups presented complaints of general weakness, significant fatigue, tiredness on physical and mental loading, de-

creased memory and concentration of attention, sleep disorders, headaches, and vertigo. The frequencies of individual complaints are shown in Table 1. Attention is drawn to the high frequency of complaints of fatigue, weakness, and sleep impairments.

Neurological examination showed that 12 patients (18.8%) in group 1 and 11 (17.0%) in group 2 ($p = 0.978$) showed disseminated microfocal neurological symptomatology in the form of mild diffuse changes in muscle tone and minor asymmetry of reflexes. Neuropsychological testing before treatment showed reductions in short-term memory, difficulty recalling unrelated elements, significant increases in task performance time, exhaustion, and lability of active attention in patients of both groups. Assessment of the dynamics of the main complaints on the VAS at all visits showed that treatment in patients of the study group produced statistically significant decreases in the severity of general weakness, tiredness, decreased memory, and insomnia as compared with patients not treated with Neurox (Table 2).

Analysis of MMSE data revealed decreased cognitive capacities in both groups. Thus, MMSE scores before treatment were 24.61 ± 1.5 points in the study group and 24.88 ± 0.75 points in the reference group ($p = 0.754$). The quite young age of patients should be noted; most had no history of chronic cerebral ischemia. In each patient, the MMSE test was performed twice, with a 30-min interval, in a calm setting, and the results demonstrated the presence of cognitive disorders. In our view, this phenomenon, i.e., low MMSE scores in patients whose age is not associated with any significant cognitive disorders, is linked with pseudocognitive deficits on the background of severe asthenic syndrome.

The study results indicated that at the moment of recruitment, all patients had significant autonomic lability (Table 3). The Kérdö index showed a predominance of excitatory autonomic reactions, such that there were no statistically significant differences in this parameter at the moment patients of both groups were recruited ($p = 0.634$);

TABLE 2. Dynamics of Changes in the Severity of Complaints ($M \pm SD$), VAS Scores

Complaints	Study group ($n = 64$)			Reference group ($n = 65$)		
	visit 1	visit 2	visit 3	visit 1	visit 2	visit 3
General weakness	8.4 ± 2.5	5.5 ± 1.7*	3.9 ± 1.2*	8.2 ± 2.7	6.9 ± 2.0	5.1 ± 1.4
Fatigue	7.3 ± 1.9	5.1 ± 1.5	3.1 ± 1.0*	7.0 ± 1.5	6.0 ± 1.3	5.5 ± 1.8
Decreased memory and concentration of attention	5.9 ± 2.2	4.2 ± 2.3*	3.5 ± 0.5*	6.0 ± 2.5	5.5 ± 0.7	5.0 ± 0.5
Sleep disorders	5.0 ± 1.7	4.5 ± 1.5	3.3 ± 0.5*	5.0 ± 1.2	4.8 ± 1.0	4.5 ± 1.0
Nonsystemic vertigo	3.2 ± 2.5	2.8 ± 0.5	2.9 ± 0.8*	3.0 ± 1.9	2.5 ± 0.4	2.2 ± 1.0
Headache	5.8 ± 2.5	4.5 ± 1.0*	3.1 ± 1.5*	5.5 ± 2.9	5.0 ± 1.3	4.5 ± 1.0

Here and in Table 3 – quantitative values are given as mean ± standard deviation ($M \pm SD$); *significance of differences in values between patients in the groups studied ($p < 0.05$).

TABLE 3. Results of Testing for Asthenic Syndrome

Scale	Study group ($n = 64$)			Reference group ($n = 65$)		
	visit 1	visit 2	visit 3	visit 1	visit 2	visit 3
Integrative parameter, MFI-20, points	70.85 ± 10.1	56.21 ± 13.2*	49.03 ± 10.1*	69.99 ± 11.5	65.42 ± 11.09	56.18 ± 11.25
Fatigue Score, points	15.32 ± 5.1	11.17 ± 5.03*	9.18 ± 4.05*	15.00 ± 6.28	14.07 ± 6.23	12.17 ± 4.23
Fatigue Severity Scale, points	46.99 ± 13.5	41.28 ± 10.3*	38.33 ± 9.15*	48.32 ± 12.03	46.18 ± 10.75	42.11 ± 10.22

the Kérdő index in the study group was $19.5 \pm 5.5\%$ while that in the reference group was $20.5 \pm 5.0\%$. However, at V_3 there were statistically significant differences between groups, with some predominance of functional equilibrium in patients of the study group and retention of a high level of excitatory influences in the control group. At the end of the study, the Kérdő index in patients of the study group was $10.5 \pm 4.5\%$, while that in the reference group was $18.9 \pm 3.5\%$, which is evidence of a higher level of compensation of autonomic process in the study group. In the study group at V_3 , the threshold of excitation of the autonomic nervous system remained high in 83.1% of patients. Test results from patients for detection of the main signs of asthenic syndrome on the Fatigue Score and Fatigue Severity Scale are shown in Table 3.

Discussion and Conclusions. Asthenic syndrome in patients in the study consisted primarily of a set of nonspecific and subjective complaints arising in interaction with COVID-19 infection and having significant influences on patients' quality of life, decreasing their work, social, and daily activities. Lack of strength and general weakness were the main complaints of all patients with COVID-19. This provides grounds for suggesting that the development of asthenia from the earliest days of illness and its long-term retention are among the pathognomonic signs of this infection.

Published studies have addressed the questions of using medications influencing patients' cognitive potential and increasing adaptive capacities of patients with asthenia [25], though separate study of postcovid syndrome is required

with assessment of the potential for pharmacological correction. Thus, use of Neurox was shown to be accompanied not only by decreases in the main symptoms of AS, but also by stabilization of autonomic status, which is a more important point. It is these autonomic changes which largely determine the development of adverse vascular reactions in patients with COVID-19 and its associated BP instability, along with heart rate impairments. In many cases, it can be said that the cytokine storm of the acute phase is replaced by an autonomic storm in the period following viral infection. Postcovid asthenia undoubtedly involves significantly more manifestations than simply asthenic syndrome. The main nucleus consists of general weakness, fatigue not passing after rest, and decreases in work capacity combined with cognitive and clinically marked psychoautonomic disorders.

Treatment led to a statistically significant ($p < 0.05$) decrease in the extent of complaints of general weakness, headache, and degradation of memory and concentration of attention in patients of the study group, which was particularly apparent at V_3 . On the background of use of Neurox there was a statistically significant reduction in the severity and extent of asthenic syndrome, as well as general fatigue and somatoautonomic manifestations. As further information on the pathophysiological mechanisms of organ and tissue damage by SARS-CoV-2 virus accumulates, existing treatment methods may be reconsidered or supplemented [26]. However, in conditions of real clinical practice, it is currently extremely important to initiate treatment promptly to correct the signs of postcovid asthenic syndrome.

The data obtained here provide evidence of a high incidence of asthenic syndrome in patients with COVID-19, who are characterized by a greater extent of significant weakness, decreased work capacity, and high variability in autonomic reactions. Use of Neurox for one month was associated with a statistically significant improvement in patients' condition in the form of reductions in general weakness, decreased headaches, improved cognitive functions, and, of particular importance, stabilization of autonomic status.

The authors have no conflicts of interest to declare.

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