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Correction of Mitochondrial Dysfunction in the Complex Rehabilitation of COVID-19 Patients

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Objective. To study the efficacy of courses of i.v., Cytoflavin in combination with the standard rehabilitation program for postcovid syndrome for correction of postcovid asthenia. **Materials and methods.** Follow-up investigations were carried out in 45 patients with postcovid syndrome at the second stage of rehabilitation. Patients were divided into two groups of comparable sex and age. The volume of lung damage was also similar in both groups, at 25–80%. The 24 patients making up the comparison group received standard postcovid rehabilitation: pulsed magnetotherapy, inhalation therapy, aeroionotherapy, infrared laser therapy, courses of aerobic training, rational psychotherapy, and successive drug therapy. The 21 patients of the study group additionally received intravenous Cytoflavin daily for 10 days. The dynamics of increases in scores on the Rehabilitation Routing Scale, the Hamilton Depression Rating Scale (HDRS), the Asthenic Status Scale, and the 6-minute walk test at admission and discharge were also monitored. **Results and conclusions.** Addition of courses of intravenous Cytoflavin to the complex rehabilitation program for postcovid syndrome significantly improved the general functional state of the body, decreased levels of depression and asthenization, and increased physical exercise tolerance.

Keywords: new coronavirus infection, COVID-19, rehabilitation, postcovid syndrome, postcovid asthenia, mitochondrial dysfunction.

The new coronavirus infection (COVID-19), due to SARS-CoV-2 and leading to the development of a planetwide pandemic in 2020, became one of the most serious outbreaks for the world community and healthcare systems in all countries seen from the historical perspective.

In the year following the onset of the pandemic, data from the site https://coronavirus-monitor.ru/ indicate that there were more than 111 million cases of infection and almost two and a half million deaths around the world directly linked with this infection.

The question of the physical and psychological rehabilitation of patients following the new coronavirus infection (COVID-19) and increases in their quality of life acquires ever more relevance.

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In Russia, as in the rest of the world, there is now extensive experience in the prevention, diagnosis, and treatment of COVID-19. The Russian Federation Ministry of Health has developed Temporary Methodological Guidelines (version 10 of February 8, 2021) for practical work [1]. In addition, the expert group of the Russian Rehabilitation Union has developed the temporary methodological guidelines "Medical rehabilitation for the new coronavirus infection (COVID-19)," version 2, July 31, 2020 [2]. In accordance with this latter document, practical work was undertaken to organize complex rehabilitation of COVID-19 patients.

In addition, the medical community is constantly seeking new approaches to increasing the efficacy of treatment and rehabilitation of the new coronavirus infection. One potential direction for these studies is correction of mitochondrial dysfunction.

It is now well known that the SARS-CoV-2 virus produces severe forms of illness in elderly people and patients with illnesses (metabolic syndrome, obesity, diabetes melli-

tus) [3]. The expert view is that this is linked with pre-existing age-dependent mitochondrial dysfunction, which plays a key role in the pathogenesis of these diseases [4, 5].

Recent studies have shown that SARS-CoV-2 virus can induce and significantly aggravate mitochondrial dysfunction, having complex pathological actions: direct damage to the mitochondrial inner membrane, impairment to the functioning of the respiratory chain enzymes, increases in the production of reactive oxygen species, with secondary damage to the mitochondrial membranes, hyperstimulation of the immune response leading on the one hand to cytokine storms and on the other to depletion of the pool of macroergic precursor compounds [6–10].

General weakness, decreased work capacity, and asthenia as a reflection of impairments to tissue respiration and oxidative phosphorylation in COVID-19 are encountered in more than 40% of cases, not infrequently dominating the clinical picture. Patients describe this state as "...complete lack of strength, energy, and the will to live..." Specialists term this state anergy, this designating a clinical syndrome developing presumptively as a result of a significant deficit of mitochondrial production of energy carriers.

A review by Wood et al. described a detailed analysis of the pathogenetic mechanisms by which mitochondrial dysfunction and its associated asthenic syndrome develop both in postcovid syndrome and in chronic fatigue syndrome due to viral infection of other etiologies [11]. These authors presented data indicating that complex impairments to the functions of internal and external respiration during the recovery period, along with deficit of ATP precursors, determine the severity of postcovid syndrome, which has a clinical picture reminiscent of that of chronic fatigue syndrome [11]. Mitochondrial dysfunction due to the specific actions of the virus on CNS neurons determine the development of cognitive impairments termed "brain fog" in the literature [12].

Many investigators have focused on studies of the correction of mitochondrial dysfunction due to SARS-CoV-2 [9, 10, 13]. Among the potential drugs with targeted influences on mitochondrial dysfunction is Cytoflavin [14–20]. This formulation is a complex of two metabolites – succinic acid, an endogenous intracellular metabolite of the Krebs cycle which carries out a universal energy-synthesizing function in cells, and inosine, an ATP precursor – and two vitamin coenzymes – riboflavin (vitamin B_2), a succinate dehydrogenase activator, and vitamin PP, an activator of nicotinamide-dependent Krebs cycle enzymes. The balanced composition of this formulation produces a whole series of metabolic effects: antihypoxic, antioxidant, antiasthenic, energizing, neuroprotective, and antiischemic.

Significant experience of the use of Cytoflavin in neurology, especially in ischemic brain damage [19, 20] has now accumulated. In acute cerebral ischemia, the main point of action of this formulation is the so-called penumbra zone or the ischemic penumbra, where a cascade of events unfolds, leading to acute ischemic mitochondrial dysfunction.

Considering the high efficacy of Cytoflavin in recovery from both acute and chronic mitochondrial dysfunction in the CNS, there are grounds for suggesting that the formulation may be effective in correcting the mitochondrial dysfunction developing in COVID-19.

The aim of the present work was to study the efficacy of courses of intravenous Cytoflavin combined with the standard program of rehabilitation for postcovid syndrome to correct asthenic syndrome, one of the mechanisms of which is mitochondrial dysfunction due to the SARS-CoV-2 virus.

Materials and Methods. Follow-up studies were run in 45 patients undergoing the second stage of medical rehabilitation at the Department of Rehabilitation, Nikolaevskaya Hospital, from June to October 2020.

The study group receiving additional Cytoflavin consisted of 21 patients (10 women and 11 men, mean age 56.0 ± ± 10.5 years). Cytoflavin was given by intravenous infusion of 10 ml of formulation in 100 ml of 0.9% sodium chloride solution at a rate of 3–4 ml/min, as courses of 10 daily infusions at the beginning of rehabilitation courses. The comparison group consisted of 24 patients receiving standard complex rehabilitation (12 women and 12 men, mean age 57.1 ± 11.0 years). The groups were comparable in terms of sex and age. The volumes of lung damage in patients of the two groups were comparable and were in the range 25–80%,

Rehabilitation courses lasted 21 ± 2 days. All patients received complex treatment based on temporary methodological guidelines [2], pulsed magnetotherapy, inhalation therapy, aeroionotherapy, infrared laser therapy courses of aerobic training taking account of physical exercise tolerance, rational psychotherapy in the form of medical psychology and psychotherapy sessions, along with successive medication therapy prescribed in the acute phase of the infective process – zinc formulations, omega-3 fatty acids, vitamins D and C, broncholytics, and mucolytics as indicated.

Assessment of patients' general functional state, emotional function, levels of asthenization, and physical exercise tolerance was conducted on admission and discharge using the following scales: the Rehabilitation Routing Scale (RRS), the Hamilton depression rating sale (HDRS), the Malkova Asthenic Status Scale (ASS), and the 6-minute walk test (WT).

The RRS is seen as the most convenient widely used tool in practical rehabilitation and is employed both for monitoring the efficacy of medical care and for routing streams of patients between different stages of medical rehabilitation. This test is clearly functional in nature, and the gradation of scores from 0 to 6 reflects the overall functional state of the body from normal to critically impaired viability. The HDRS allows determination of the presence and severity of emotional impairments in patients. The validated questionnaire covers all types of manifestation of depressive disorders: mood impairments, feelings of guilt, suicidal intent, sleep impairments, work capacity, lethargy, arousal, mental and somatic anxiety, autonomic gastrointestinal tract symp-

TABLE 1. Dynamics of Indicators of Functional State, the Emotional-Volitional Domain, Levels of Asthenia, and Physical Exercise Tolerance in Study Patients

Indicator	Study group, (n = 21)	Comparison group (n = 24)
RRS on admission, points	3.48 ± 0.75	3.54 ± 0.59
RRS on discharge, points	1.57 ± 0.60	2.04 ± 0.75*
Change in RRS, points	–1.90 ± 0.77	–1.50 ± 0.59*
HDRS on admission, points	17.7 ± 4.0	19.4 ± 1.8
HDRS on discharge, points	10.1 ± 3.3	14.0 ± 3.2**
Change in HDRS, points	–7.6 ± 3.9	–5.4 ± 2.1*
ASS on admission, points	104.4 ± 15.4	101.9 ± 8.0
ASS on discharge, points	70.3 ± 19.4	80.1 ± 7.3
Change in ASS, points	–34.0 ± 14.7	–21.8 ± 4.2**
WT on admission, points	222.0 ± 31.4	216.9 ± 19.6
WT on discharge, points	413.9 ± 32.8	364.0 ± 30.2**
Change in WT, points	191.9 ± 38.3	147.0 ± 20.6**

*$p < 0.05$; **$p < 0.005$.

toms, the general somatic features of depression, sexual disorders, unexplained weight loss, and insight into own condition. The ASS was developed by Malkova an adapted on the basis of Chertova's MMPI [21]. This method is intended for express diagnosis of the asthenic state. The WT is widely used in physical rehabilitation because of its simplicity and ability to provide an integral assessment of physical exercise tolerance in patients with cardiac and respiratory failure.

The study design was approved by the pharmacosurveillance ethics committee (Protocol No. 249, issue No. 3, September 3, 2020). All patients gave informed consent to take part in the study.

Data were analyzed using the computer programs Microsoft Excel 2010 (Microsoft, USA) and Statistica for Windows 10 (StatSoft, USA). The significance parameter was the Mann–Whitney test (U), $p < 0.05$.

Results. Study results are presented in Table 1.

It should be noted that the severity of impairments to patients' general functional state, level of asthenization, emotional status, and physical exercise tolerance on admission were comparable in the two groups. The test results show that all study indicators in the Cytoflavin group displayed better changes over time.

On average, assessments of patients' general functional state on admission using the RRS were comparable in the two groups, at around 3.5 points, which was apparent as a moderate restriction of movement ability, where normal physical activity produced weakness, fatigue, palpitations, and breathlessness. By discharge, the RRS score in the study group was significantly lower than in the comparison group. More than half the patients receiving Cytoflavin returned to their prior lifestyle by the end of rehabilitation courses and could maintain the former level of activity and social involvement, spending just as much time on daily tasks as before illness; they could also carry out physical exercise at a level above the normal without weakness, palpitations, or breathlessness. By the end of treatment, patients of the comparison group could not generally perform types of usual everyday activity, for example, drive vehicles, read, write, dance, work, etc. at the level they could prior to illness, though they could cope with them without assistance from others. Normal physical exercise in these patients did not induce marked fatigue, weakness, breathlessness, or palpitations, though these symptoms developed significantly more quickly on significant, accelerated, or prolonged effort.

At the beginning of treatment course, levels of depression in the two groups were consistent with mild and moderate depressive disorder, which was linked with the long period of social isolation and uncertainty in relation to the prognosis of disease. On discharge, this indicator in the comparison group decreased to a mild level of depression. The study group showed normalization of emotional state. Differences were mainly on subscales reflecting pathological changes to sleep and levels of general work capacity. Thus, these parameters recovered less well in the comparison group.

On admission, the levels of asthenization in the two groups were assessed as severe: total scores on the ASS averaged 101–104 points. By discharge, scores decreased in the comparison group to the level of moderate asthenia, while in the Cytoflavin group the level decreased to the mild. These differences mainly affected questions reflecting general tension and fatigue and the lack of complete recovery after normal physical exercise.

Physical exercise tolerance in both groups on admission was at the level of functional class 3. By the end of rehabilitation courses, this indicator in the Cytoflavin group

improved significantly as compared with the comparison group. Despite the fact that the outcome in both cases was increased exercise tolerance to functional class 2, the between-group difference was significant. Furthermore, the distance covered in 6 min in the study group almost reached boundary between functional groups 1 and 2, which in turn reflected a better result in terms of restoration of walking function in patients receiving intravenous metabolic support.

Conclusions. The results obtained here provide evidence that addition of courses of intravenous administration of the complex metabolic formulation Cytoflavin to the postcovid rehabilitation program significantly improved its results. Intravenous Cytoflavin infusions significantly increased rehabilitation potential, promoting recovery from depression and asthenization, also increasing physical exercise tolerance.

The main mechanisms of action of Cytoflavin can be regarded as making up for a deficiency of ATP precursors and correction of the mitochondrial dysfunction developing in coronavirus infection.

This allows Cytoflavin to be recommended as an element included in the basic complex rehabilitation scheme for COVID-19 patients with the aim of increasing the efficacy of the overall rehabilitation process by increasing its energy supply.

The authors declare no conflict of interest.

REFERENCES

1. Temporary Methodological Guidelines, *Prophylaxis, Diagnosis, and Treatment of the New Coronavirus Infection (COVID-19)*, Moscow, Vers. 10, Feb. 8, 2021.
2. Temporary Methodological Guidelines, *Medical Rehabilitation in the New Coronavirus Infection (COVID-19)*, Moscow, Vers. 2, July 31, 2020.
3. K. Holder and P. H. Reddy, "The COVID-19 effect on the immune system and mitochondrial dynamics in diabetes, obesity, and dementia," *Neuroscientist*, Online ahead of print, Sept. 26, 2020, https://doi.org/10.1177/1073858420960443.
4. D. Fernández-Ayala, P. Navas, and G. López-Lluch, "Age-related mitochondrial dysfunction as a key factor in COVID-19 disease," *Exp. Gerontol.*, **142**, 111147 (2020), https://doi.org/10.1016/j.exger.2020.111147.
5. A. Nunn, G. Guy, W. Brysch, et al., "SARS-CoV-2 and mitochondrial health: implications of lifestyle and ageing," *Immun. Ageing*, **17**, No. 1, 33 (2020), https://doi.org/10.1186/s12979-020-00204-x.
6. J. Burtscher, G. Cappellano, A. Omori, et al., "Mitochondria: In the cross fire of SARS-CoV-2 and immunity," *iScience*, **23**, No. 10, 101631 (2020), https://doi.org/10.1016/j.isci.2020.101631.
7. L. Gibellini, S. De Biasi, A. Paolini, et al., "Altered bioenergetics and mitochondrial dysfunction of monocytes in patients with COVID-19 pneumonia," *EMBO Mol. Med.*, **12**, No. 12, e13001 (2020), https://doi.org/10.15252/emmm.202013001.
8. S. Shenoy, "Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality," *Inflamm. Res.*, **69**, No. 11, 1077–1085 (2020), https://doi.org/10.1007/s00011-020-01389-z.
9. P. Gatti, H. S. Ilamathi, K. Todkar, and M. Germain, "Mitochondria targeted viral replication and survival strategies – Prospective on SARS-CoV-2," *Front. Pharmacol.*, **11**, 578599 (2020), https://pubmed.ncbi.nlm.nih.gov/32982760/#affiliation-2, https://doi.org/10.3389/fphar.2020.578599.
10. A. Gvozdjakova, F. Klauco, J. Kucharska, and Z. Sumbalova, "Is mitochondrial bioenergetics and coenzyme Q10 the target of a virus causing COVID-19?" *Bratisl. Lek. Listy*, **121**, No. 11, 775–778 (2020), https://doi.org/10.4149/BLL_2020_126.
11. E. Wood, K. Hall, and W. Tate, "Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/chronic fatigue syndrome: a possible approach to SARS-CoV-2 'long-haulers'?" *Chronic Dis. Transl. Med.*, Online ahead of print, Nov. 21, 2020, https://doi.org/10.1016/j.cdtm.2020.11.002.
12. G. Stefano, R. Ptacek, H. Ptackova, et al., "Selective neuronal mitochondrial targeting in SARS-CoV-2 infection affects cognitive processes to induce 'brain fog' and results in behavioral changes that favor viral survival," *Med. Sci. Monit.*, **27**, e930886 (2021), https://doi.org/10.12659/MSM.930886.
13. L. Ouyang and J. Gong, "Mitochondrial-targeted ubiquinone: A potential treatment for COVID-19," *Med. Hypotheses*, **144**, 110161 (2020), https://doi.org/10.1016/j.mehy.2020.110161.
14. V. V. Afanas'ev, *Cytoflavin in Intensive Care. A Manual for Doctors*, St. Petersburg (2005).
15. V. V. Bul'on, I. V. Zarubina, A. L. Kovalenko, et al., "The cerebroprotective effect of Cytoflavin in closed traumatic brain injury," *Eksperim. Klin. Farmakol.*, **6**, 46–48 (2003).
16. P. R. Kamchatnov, *Chronic Disorders of the Cerebral Circulation, the Possibilities of Metabolic Therapy. A Manual*, Moscow (2008).
17. E. G. Klocheva, M. V. Aleksandrov, and E. B. Fomina, "The use of Cytoflavin in patients with cerebral hypoxia of ischemic origin," *Vestn. St. Peterb. Gos. Med. Akad. Mechnikova*, No. 1–2, 24–30 (2002).
18. A. I. Fedin, S. A. Rumyantseva, O. R. Kuznetsov, et al., *Antioxidant and Energy-Protective Therapy of Ischemic Stroke. Methodological Guidelines*, Moscow (2004).
19. A. I. Fedin, S. A. Rumyantseva, and M. A. Piradov, et al., "Efficacy of the neurometabolic protector Cytoflavin in cerebral infarct," *Vestn. St. Peterb. Gos. Med. Akad. Mechnikova*, No. 1, 13–19 (2005).
20. A. I. Fedin, S. A. Rumyantseva, M. A. Piradov, et al., "Clinical efficacy of Cytoflavin in patients with chronic cerebral ischemia (a multicenter placebo-controlled randomized trial)," *Vrach*, **13**, 52–58 (2006).
21. V. V. Zakharov and T. G. Voznesenskaya, *Neuropsychiatric Disorders. Diagnostic Tests*, N. N. Yakhno (ed.), MED Press-Inform, Moscow (2016).