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Diagnostic and pharmacological correction of cardiovascular system changes in children, adolescents, and young adults with long COVID: comparative randomized clinical trial in parallel groups

L.A. Balykova[1], M.V. Shirmankina[1], A.V. Krasnopolskaya[1], A.A. Stradina[2], S.A. Ivyansky[1], T.M. Duvayarova[1], D.S. Rodionov[1]

[1] National Research Ogarev Mordovia State University,
68 Bolshevistskaya Str., Saransk, Russia, 430005
[2] Children's Polyclinic No. 4,
92 Volgogradskaya str., Saransk, Russia, 430009

E-mail: larisabalykova@yandex.ru

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The aim. To evaluate the effectiveness of L-carnitine in the complex correction of cardiovascular and autonomic manifestations of long COVID in children, adolescents, and young adults.

Materials and methods. Within the framework of an open, simple, randomized, parallel-group comparative clinical study, the effectiveness of L-carnitine at a dose of 50–75 mg/kg per day in 2 doses for 6 weeks in addition to standard therapy in children and adolescents aged 10 to 17 years, as well as young people aged 18–25 years with long COVID (n = 45) was studied in comparison with the standard therapy (n = 45) using clinical and anamnestic, electrophysiological, echocardiographic and other methods. The statistical processing of the results was carried out by the variational method, and correlation and regression analysis using Student's t-test for dependent samples, as well as the McNemar chi-square test.

Results. The most frequent clinical manifestations of long COVID were: high fatigue, headaches and muscle weakness — in 66.7–100%. After 6 weeks of treatment, the absence of complaints and normalization of objective status were noted in 93.3% of patients in the main group and 66.7% in the comparison group ($p < 0.05$). Repolarization abnormalities and rhythm disturbances, initially registered in 43.3% of patients, were not observed after 6 weeks of therapy in the main group, while they persisted in more than 50% in the comparison group. By the 6 weeks of treatment, there were no changes in Echo in the main group, while in the comparison group (slight dilatation of the left ventricle) persisted in 9 out of 12 patients. In the main group, according to Holter monitoring, restoration of heart rate, normalization of its autonomic regulation, reduction in the representation of bradyarrhythmias and "density" of extrasystoles were achieved.

Conclusion. The effectiveness of L-carnitine for the correction of the frequency and severity of autonomic and cardiac disorders in the subjects with long COVID has been shown.

Keywords: L-carnitine; long COVID; cardiovascular system; children; adolescents; young adults

List of abbreviations: HR — heart rate; LA — left atrium; LVEDD — left ventricular end-diastolic diametr; LV — left ventricle; LVEF — left ventricular ejection fraction; DMSVS — Paediatric multisystem inflammatory syndrome; CVS — cardiovascular system; BP — blood pressure; HM — Holter monitor; AEs — adverse effects; SAEs — serious adverse effects; HR — heart rate; AST — active stand test; HRV — heart rate variability.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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Возможности диагностики и фармакологической коррекции изменений сердечно-сосудистой системы у детей, подростков и лиц молодого возраста с постковидным синдромом: сравнительное параллельное рандомизированное клиническое исследование

Л.А. Балыкова[1], М.В. Ширманкина[1], А.В. Краснопольская[1], А.А. Страдина[2], С.А. Ивянский[1], Т.М. Дуваярова[1], Д.С. Родионов[1]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Национальный исследовательский Мордовский государственный университет им. Н.П. Огарёва», Россия, 430000, г. Саранск, ул. Большевистская, д. 68

[2] Государственное бюджетное учреждение здравоохранения Республики Мордовия «Детская поликлиника № 4»,
Россия, 430009, г. Саранск, ул. Волгоградская, д. 92

E-mail: larisabalykova@yandex.ru

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Цель. Оценка эффективности препарата L-карнитина в комплексной коррекции кардиоваскулярных и вегетативных проявлений постковидного синдрома ПКС у детей, подростков и лиц молодого возраста.

Материалы и методы. В рамках открытого простого рандомизированного сравнительного клинического исследования в параллельных группах изучена эффективность L-карнитина в дозе 50–75 мг/кг в сутки в 2 приёма в течение 6 нед в добавлении к стандартной терапии у детей и подростков в возрасте от 10 до 17 лет, а также молодых людей 18–25 лет с ПКС (*n*=45) в сравнении со стандартной терапией (*n*=45) с использованием клинико-анамнестических, электрофизиологических, эхокардиографических методов. Статистическая обработка результатов была проведена методом вариационного и корреляционно-регрессионного анализа с использованием критерия Стьюдента для зависимых выборок, а также хи-квадрата МакНемара.

Результаты. Наиболее частыми клиническими проявлениями ПКС были повышенная утомляемость, головные боли и мышечная слабость — у 66,7–100%. Через 6 нед лечения отсутствие жалоб и нормализация объективного статуса отмечались у 93,3% пациентов основной группы и 66,7% в группе сравнения (p <0,05). Аномалии реполяризации и нарушения ритма, зарегистрированные исходно у 43,3% пациентов, через 6 нед терапии в основной группе не отмечались, а в группе сравнения сохранялись более, чем в 50%. К 6 нед лечения в основной группе изменения ЭхоКГ отсутствовали, тогда как в группе сравнения (незначительная дилатация левого желудочка) сохранялись у 9 из 12 пациентов. В основной группе по данным холтеровского мониторирования достигнуто восстановление частоты ритма, нормализация его вегетативной регуляции, сокращение количества брадиартимий и «плотности» экстрасистолии.

Заключение. Показана эффективность L-карнитина для коррекции частоты и выраженности вегетативных и кардиальных нарушений у исследуемых с ПКС.

Ключевые слова: L-карнитин; постковидный синдром; сердечно-сосудистая система; дети; подростки; лица молодого возраста

Список сокращений: ЧСС — частота сердечных сокращений; ЛП — левое предсердие; КДР ЛЖ — конечный диастолический размер левого желудочка; ПКС — постковидный синдром; ЛЖ — левый желудочек; ФВЛЖ — фракция выброса левого желудочка; ДМСВС — детский мультисистемный воспалительный синдром; ССС — сердечно-сосудистая система; АД — артериальное давление; ХМ — холтеровское мониторирование; НЯ — нежелательные явления; СНЯ — серьёзные нежелательные явления; ЧСС — частота сердечных сокращений; АОП — активная ортостатическая проба; ВСР — вариабельность ритма сердца.

INTRODUCTION

Despite the relatively low incidence and predominance of mild forms of the new coronavirus infection among children and adolescents, the consequences of the pandemic for children's health have yet to be assessed [1]. At the beginning of the pandemic more attention was paid to the acute period of COVID-19, then at the moment the vector of interest has shifted towards the subacute and chronic phases of the coronavirus infection — the so-called "long COVID", in which, according to the recommendations of the National Institute for Health and Care Excellence (NICE) of Great Britain, persistent symptomatic (ongoing) COVID (4–12 weeks from the onset of the disease) and post-COVID syndrome (after 12 weeks)[1] are

[1] COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (NICE). – 2024. Available from: https://pubmed.ncbi.nlm.nih.gov/33555768/

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distinguished. A special form of long-term COVID-19 in pediatric practice is the multisystem inflammatory syndrome in children (MIS-C), characterized by the development of a systemic inflammatory response with multi-organ lesions 2–6 weeks after the disease [2].

The prevalence of long-term consequences of COVID-19 varies widely — from 1.6 to 70.0% due to the lack of unified approaches to classification and diagnosis[2] [3]. The frequency of post-COVID syndrome (PCS) in the pediatric population, according to a meta-analysis by Jiang et al., was 16.2% [4]. The clinical manifestations of PCS have much in common in children and adults, with a predominance of asthenic syndrome and other disorders of the nervous system, changes in the gastrointestinal tract (GIT), bronchopulmonary and cardiovascular disorders. Symptoms of post-COVID asthenia in children and adolescents are manifested by cognitive and psychological disorders: in a third, the quality of life decreases, and more than half cannot attend school for a full school day or participate in extracurricular activities [5].

Some patients with PCS have involvement of the cardiovascular system (CVS) with blood pressure (BP) instability, heart rhythm and conduction disorders, valvular dysfunction, pericardial effusion, etc. [6]. Abnormal results of cardiac MRI an average of 2.5 months after COVID-19 infection were observed in 78% of convalescents: late gadolinium enhancement, pericardial enhancement, lower left ventricular ejection fraction (LVEF), higher left ventricular (LV) volumes, higher LV myocardial mass in combination with elevated troponin levels and active lymphocytic inflammation according to endomyocardial biopsy in severe cases [7]. Therefore, cardiac symptoms in patients who have had a coronavirus infection require the exclusion of classical myopericarditis, including coronary arteritis, endocarditis, myocardial infarction, rhythm and conduction disorders, pulmonary embolism, etc. [8, 9], and only then persistent symptoms can be considered as manifestations of PCS.

Unified approaches to the diagnosis and treatment of post-COVID disorders have not been defined [10, 11]. It can be partly explained by the complex and multicomponent nature of the pathogenesis of PCS and its cardiac manifestations, which are based on increased thrombosis, mainly in the vessels of the microcirculatory bed with the development of local ischemia, endothelial dysfunction, oxidative stress, mitochondrial dysfunction, viral persistence[3] [5]. L-carnitine has shown its effectiveness in leveling the manifestations of asthenic syndrome in various diseases [12]. In addition, it has a cardioprotective effect, reduces the severity of autonomic disorders, and corrects endothelial dysfunction [13–15], which determined the choice of L-carnitine as a drug for the complex therapy of PCS in children and adolescents.

THE AIM. To evaluate the effectiveness of L-carnitine in the complex correction of vegetative and cardiovascular manifestations of post-COVID syndrome in children, adolescents, and young adults.

MATERIALS AND METHODS

Study design

An open (unblinded) controlled, comparative randomized clinical trial in parallel groups included 90 individuals who had a new coronavirus infection 12 or more weeks ago, with clinical manifestations of PCS, and 30 practically healthy individuals who made up the control group.

Patients with post-COVID syndrome (30 children — 10–14 years old, 30 adolescents — 15–17 years old and 30 young people — 18–25 years old) were randomized according to age into two groups in a 1:1 ratio: the main group (n = 45), whose treatment plan, in addition to standard therapy, included L-carnitine (PIC-Pharma LLC, Russia) at a dose of 50–75 mg/kg per day in 2 doses, selected on the basis of previous studies [16, 17] for 6 weeks, and the comparison group (n = 45), whose patients received standard therapy — group or individual psychotherapy, massage, therapeutic exercises. The obtained results were compared with the corresponding indicators of individuals in the control group (n = 30), similar to the study subjects in terms of gender and age.

Study setting and duration

The work was performed on the clinical bases of Pediatrics of the Children's Polyclinic No. 4 (Saransk, Russia) and the Center for Medicine "MEDiZ" of the National Research Ogarev Mordovia State University (Saransk, Russia). The study was conducted from February 2022 to May 2024; the duration of the intervention was 6 weeks.

Randomization

All patients included in the study were divided into groups using simple randomization (the "heads" and "tails" method).

Eligibility criteria

Inclusion criteria for the study group: children and adolescents aged 10 to 17 years 11 months and 29 days, as well as young people 18–25 years of male and female sex with a history of 4 or more weeks ago and laboratory-confirmed new coronavirus

[2] Ibid.
[3] Ibid.

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infection; PCS diagnosed by a pediatrician or therapist in children, adolescents and young adults according to the Methodological Recommendations “Features of the course of Long-COVID infection. Therapeutic and rehabilitation measures” [2]; manifestations of PCS from 2 or more organs and systems, including the CVS and nervous system, in the form of objective changes and/or pathological results of laboratory and instrumental methods of examination; written informed consent of parents (legal representatives) of a child under 14 years of age and/or an adolescent 15–17 years of age or a patient 18–25 years of age to participate in the study.

Exclusion criteria for patients in the study: children under 10 years of age; pregnant women; children with previously established chronic diseases of the CVS, respiratory, central nervous, endocrine systems; children receiving metabolic drugs (L-carnitine, phosphocreatine, mildronate, trimetazidine) for 3 months before the start of this study.

Exclusion criteria from the study: refusal to participate in the study at any stage; failure to perform study procedures; the occurrence of serious adverse events during the study.

The control group was formed in accordance with the following criteria: the first and second health groups according to the results of the medical examination; no history of a new coronavirus infection and negative ELISA results for specific antibodies against Sars-CoV-2; absence of objective and laboratory-instrumental manifestations from the CVS, central nervous system, autonomic nervous system and psychological disorders characteristic of PCS; signed informed consent.

Outcomes registration

- Clinical and anamnestic method with assessment of the severity of the infection, the presence of comorbid conditions, complaints and general condition during of examination;
- Physical examination, blood pressure measurement (auscultatory method on peripheral arteries, according to the draft clinical guidelines “Diagnosis and treatment of arterial hypertension in children and adolescents”) [18];
- Standard ECG on a SHILLER AT-5 device (Switzerland) at a tape speed of 50 mm/s;
- Echo-CG to assess the morphofunctional state of the myocardium on a Xario model SSA-66 device from TOSHIBA (Japan);
- Holter monitoring (HM) of ECG with assessment of heart rate variability (with calculation of temporal parameters [pNN50, rMSSD, SDNN] using the hardware-software complex “Cardiotechnika-04” NAO “Institute of Cardiological Technology” (Russia);
- Determination of the initial vegetative tone (according to the tables of Vein, modified by N.A. Belokon);
- Active orthostatic test, which was carried out according to the recommendations specified in the guide for doctors Belokon et al[4]. Pathological types of reactions: orthostatic tachycardia, orthostatic hypotension, orthostatic hypertension were determined according to the criteria of foreign authors [19–21].
- Assessment of the severity of PCS symptoms using a visual analog scale (VAS).
- Determination of quality of life (PedsQL™).

Primary outcome of the study

The presence of signs of PCS after 6, 12 and 24 weeks of follow-up.

Safety

In the process of the study, safety was also assessed: the total number of adverse events (AEs), stratified by severity and frequency; the frequency of adverse reactions; the frequency of serious adverse events (SAEs), including those associated with the use of the study drug/placebo; the proportion of subjects who registered at least one AE.

Ethics approval

The study was approved by the Local Ethics Committee of the Medical Institute of the National Research Ogarev Mordovia State University (Protocol No. 93 dated May 28, 2021). Inclusion in the study was carried out in accordance with the approved criteria upon receipt of signed informed voluntary consent for examination from the parent or legal representative of the child and the child who has reached the age of 15 years[5].

Statistical analysis

For statistical data processing the IBM SPSS Statistics v.25 was used. Compliance with the law of normal distribution was checked using the Shapiro–Wilk and Kolmogorov–Smirnov tests. For indicators with a distribution close to normal, the arithmetic mean (M) and standard deviation (SD), 95% confidence interval (CI) were calculated. The statistical significance of differences was determined for two groups using Student’s t-test, for three groups — using one-way analysis of variance (ANOVA). The direction and

[4] Belokon NA, Kuberger MB. Diseases of the heart and blood vessels in children. Moscow: Medicine; 1987. 446 p. Russian
[5] Federal Law No. 323-FZ dated November 21, 2011 “On the Basics of Public Health Protection in the Russian Federation”. Russian

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strength of the correlation between two quantitative indicators were assessed using Pearson's correlation coefficient. Qualitative indicators are presented both in absolute and relative values. To calculate the statistical significance of differences in qualitative characteristics, Pearson's χ^2 test was used. If the number of observations in any of the cells of the table was 10 or more, Yates› correction for continuity was used; if the number of observations was from 5 to 9, with the number of observations less than 5 in any of the cells — Fisher's exact test. The reliability of differences in the data obtained was established at the level of $p < 0.05$.

RESULTS

Baseline characteristics of patients

At the preliminary stage, we analyzed the data of medical records of 461 children, residents of Saransk aged 10–17 years (average age 13.8 ± 1.9 years), who underwent laboratory-confirmed COVID-19 during 2021–2022. 154 (33.4%) revealed indications of the appearance of new / persistence of existing symptoms of the acute phase 4 weeks after the coronavirus infection in the absence of established causes. In 29 of them (6.3% of the total number of children who underwent COVID-19), autoimmune or demyelinating diseases were diagnosed during the year with further in-depth examination, in 47 (10.2%) — cardiovascular, bronchopulmonary, uro-nephrological diseases, blood diseases, gastrointestinal tract, etc. were detected for the first time.

In 13 children and adolescents out of 78 with a diagnosis of exclusion of PCS, established according to the criteria of the Russian Scientific Medical Society of Internal Medicine and NICE, complaints disappeared after 12 weeks, and in 65 symptoms persisted for more than 12 weeks and there was actually PCS, the prevalence of which in the population of minor residents of Saransk was 14.1%. The prevalence of long-term COVID symptoms among 2634 students of Ogarev Moscow State University — residents of Saransk aged 18–25 years, was higher than among children and adolescents and amounted to 49.4% (1300 people) and 761 (28.9% of the total number of those who had been ill) were diagnosed with PCS.

Participation in the clinical study was offered to 98 patients aged 10–25 years with PCS who signed informed consent, of which 90 people met the inclusion criteria. Patients in the main group and the comparison group did not differ in age (14.5 ± 2.6 years and 15.6 ± 1.9 years, respectively) and gender composition (21 [46.7%] male and 24 [53.3%] female patients in the main group and 19 (42.2%) and 26 (57.8%) in the comparison group, respectively). Most often, the new coronavirus infection in children was mild, a moderate course was registered in 10 (23.3%) patients, and 13 patients underwent MIS-C.

Dynamics of clinical manifestations post-COVID syndrome against the background of complex therapy

The main clinical manifestations of PCS were comparable in the main group and the comparison group and were characterized by increased fatigue, headaches and muscle weakness — in 66.7–100% of the study subjects in the main group (Table 1). Less often (in 40.0–57.7%) there were appetite disorders / abdominal syndrome, sleep disorders, cognitive impairments (impaired memory, attention) and anxiety-depressive symptoms, cardialgia, these manifestations were recorded significantly more often in the main group compared with the control group (p = 0.00). A third of patients complained of decreased tolerance to physical activity, subfebrile temperature. Complaints of arthralgia, anosmia, hand tremor and hair loss were registered much less frequently. In the control group, only 3.3–6.7% of the examined individuals of the corresponding gender and age noted complaints, most often of increased fatigue and periodic headaches, which were relieved on their own.

The dynamics of clinical manifestations of PCS against the background of complex therapy are presented in Table 1. After 6 weeks of treatment, 42 (93.3%) patients in the main group had no complaints. In the remaining 3 (6.7%) patients in the main group and 15 (33.3%) patients in the comparison group, PCS symptoms were relieved by 12 weeks of follow-up. Symptoms of asthenia and dysosmia persisted longer.

Assessment of the severity of post-COVID syndrome symptoms using a visual analog scale

The results of assessing the severity of some PCS symptoms using VAS are presented in Figure 1.

In the main group, by 6 weeks of treatment, the severity of all symptoms decreased by 1.9–1.7 times (p = 0.00). Complaints of a cardiac nature of minimal severity remained only in 2 (4.4%) adolescents by the end of the active intervention, while for children, adolescents and young adults in the comparison group, a similar dynamic was registered only after 12 weeks of treatment. By 24 weeks of follow-up, clinical symptoms were completely absent in all groups.

Dynamics of changes in blood pressure

Initially, normal blood pressure values for the corresponding age, gender and height were recorded in 43.3% of children, adolescents and young adults in the main group. Hypotension was determined in the same percentage of children, and almost

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2 times less often hypertension of the 1 degree and high normal blood pressure. A similar picture was observed in the comparison group. After a course of treatment, hypotension was recorded in only 16.7% of children and adolescents ($p < 0.05$), and the number of examined individuals with high normal blood pressure decreased by almost 2 times ($p > 0.05$). In the comparison group, the representation of children and adolescents with hypotension also decreased in dynamics (from 46.7 to 33.3%, $p > 0.05$).

ECG dynamics

The initial heart rate (HR) according to the standard ECG in the study groups varied widely (Fig. 2): sinus bradyarrhythmia/sinus node dysfunction (migration of the rhythm driver, atrial rhythm) was recorded in 24.4–26.7% of the examined individuals, sinus tachycardia — in 28.9–31.1%. Sinus respiratory arrhythmia was detected in 11.1% of the examined individuals in the main group and 13.3% in the comparison group. By the end of the active intervention period in the main group, there was a significant (from 33.3% to 80%, $p = 0.00$) increase in the proportion of children, adolescents and young adults with sinus rhythm with normal HR (in the comparison group — from 31.1% to 38.9%). Restoration of sinus rhythm and normalization of HR occurred mainly due to improved sinus node function, while in the comparison group bradyarrhythmia/sinus node dysfunction persisted in 17.8%, tachycardia — in 20% and respiratory arrhythmia — in 11.1% of the examined individuals ($p > 0.05$). Although pathological HR values (increase > 98 percentile or decrease < 2 percentile) were not recorded in any of the examined individuals.

Determination of the initial vegetative tone

When determining the initial vegetative tone (modified tables of Vein), sympathicotonia and vagotonia were recorded in 8 (17.8%) and 21 (46.7%) of the examined individuals in the main group. In the comparison group, eutonia in 21 (46.7%) and vagotonia — in 15 (33.3%) predominated.

At the end of the course of treatment, both groups showed positive shifts in vegetative tone in the form of an increase in the representation of eutonia and a reduction in vagotonia and sympathicotonia. However, in the comparison group, the frequency of eutonia increased slightly (up to 57.8%), not reaching the corresponding values of the control group (70%), and sympathicotonia in 5 out of 9 patients changed to vagotonia. Whereas in the main group, complex therapy with L-carnitine significantly reduced the frequency of vagotonia — to 12 (26.7%) and sympathicotonia to 1 (2.2%), contributing to the normalization of vegetative tone in the absolute majority of patients — 32 (71.1%).

Results of the active orthostatic test

Patients in the main group and the comparison group were dominated by normal types of reaction (53.3% and 48.9%, respectively) to AST (classification of Belokon), but they were recorded less often than in the control group (76.7%). Hypersympathicotonic, hyperdiastolic and asympathicotonic types of reaction were noted in 6.7–24.4% and 8.9–28.9% of the examined individuals in the main group and the comparison group, respectively, while sympathoasthenic and asthenosympathetic variants were not found in our population. After 6 weeks of therapy in the main group, there was a significant decrease in the proportion of pathological and an increase in the normal type of reaction to AST (up to 91.1%, $p = 0.00$), hyperdiastolic and asympathicotonic types were not found, and the frequency of the hypersympathicotonic variant of the reaction decreased by 3 times. In the comparison group, the frequency of normal reaction to AST also increased, but less significantly, since all pathological types of reaction persisted, especially hyperdiastolic (Fig. 3).

Specific types of reaction: orthostatic hypertension, orthostatic hypotension, postural orthostatic tachycardia were noted in 3–11 (6.7–24.4%) and 2–13 (4.4–28.9%) patients in the main group and the comparison group, respectively, with a clear predominance of orthostatic postural tachycardia. After 6 weeks of therapy in the main group, postural orthostatic tachycardia syndrome persisted only in 1 adolescent girl (2.2%), while in the comparison group, despite the positive dynamics, there were 8 such patients (17.8%).

Echo-CG results

According to Echo-CG data presented in Table 2, mild LV dilatation (average value of left ventricular end-diastolic diameter (LVEDD) 1.5 (1.1; 1.8) Z-score) was noted in 6 (13.3%) patients, regurgitation on the mitral/tricuspid valve of the 1st degree was detected in 3 (6.7%), minor pericardial effusion — in 3 (6.7%) and dilatation of the coronary arteries — in 1 (2.2%) of the main group (mostly — in children and adolescents who underwent MIS-C). Comparable data were also typical for children, adolescents and young adults in the comparison group. By 6 weeks of treatment in the main group, there were no pathological changes, while in the comparison group, minor LV dilatation persisted in 6 out of 8 patients. In all patients in the main group, the ejection fraction increased within normal values. The values of the thickness of the posterior wall of the LV, the interventricular septum and the size of the right atrium did not have significant differences in the analyzed groups.

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Table 1 – Clinical manifestations of post-COVID syndrome in the study groups, *n* (%)

Clinical manifestations	Control (n = 30)	Main group (n = 45)		Comparison group (n = 45)	
		before treatment	6 weeks of therapy	before treatment	6 weeks of therapy
Increased fatigue	2 (6.7%)	45 (100%)* (p = 0.00)	3 (6.7%)# (p = 0.00)	45 (100%)* (p = 0.00)	12 (40.0%)# (p = 0.00)
Headaches	2 (6.7%)	40 (88.9%)* (p = 0.00)	1 (2.2%)# (p = 0.00)	42 (93.3%)* (p = 0.00)	14 (31.1%)# (p = 0.00)
Muscle weakness	0	30 (66.7%)* (p = 0.00)	2 (4.4%)# (p = 0.00)	32 (71.1%)* (p = 0.00)	13 (28.9%)# (p = 0.01)
Appetite disorder / abdominal syndrome	1 (3.3%)	26 (57.7%) * (p = 0.00)	1 (2.2%) # (p = 0.00)	24 (53.3%)* (p = 0.00)	12 (26.7%)# (p = 0.01)
Sleep disorder	0	25 (55.6%) * (p = 0.00)	0# (p = 0.00)	21 (46.7%)* (p = 0.00)	7 (15.6%)# (p = 0.00)
Cognitive impairments	0	22 (48.9%) * (p = 0.00)	1 (2.2%)# (p = 0.00)	21 (46.7%)* (p = 0.00)	6 (13.3%)# (p = 0.00)
Anxiety-depressive symptoms	0	16 (35.6%) * (p = 0.00)	0# (p = 0.00)	17 (37.8%)* (p = 0.00)	5 (11.1%)# (p = 0.00)
Emotional lability	1 (3.3%)	17 (37.8%)* (p = 0.00)	0# (p = 0.00)	18 (40.0%)*	9 (20%)# (p = 0.01)
Cardialgia	1 (3.3%)	18 (40.0%)* (p = 0.00)	0# (p = 0.00)	17 (37.7%)* (p = 0.00)	5 (11.1%)# (p = 0.00)
Subfebrile condition	0	14 (31.1%) (p = 0.00)	0# (p = 0.00)	15 (33.3%)* (p = 0.00)	3 (6.7%)# (p = 0.00)
Decreased tolerance to physical activity	0	16 (35.6%)* (p = 0.00)	0# (p = 0.00)	15 (33.3%)* (p = 0.00)	4 (8.9%)# (p = 0.00)
Anosmia / dysosmia	0	14 (31.1%)* (p = 0.00)	0# (p = 0.00)	13 (28.9%)* (p = 0.00)	2 (4.4%)# (p = 0.00)
Hand tremor	0	6 (13.3%)* (p = 0.03)	0# (p = 0.04)	5 (13.3%) (p = 0.05)	1 (2.2%) (p = 0.13)
Hair loss	0	6 (13.3%)* (p = 0.03)	0# (p = 0.04)	7 (15.6%)* (p = 0.02)	2 (4.4%) (p = 0.07)
Arthralgia	0	4 (8.9%) (p = 0.08)	0 (p = 0.13)	3 (6.7%) (p = 0.13)	1 (2.2%) (p = 0.48)
Feeling of palpitations	0	9 (20.0%)* (p = 0.01)	0# (p = 0.01)	8 (17.7%)* (p = 0.01)	6 (6.7%) (p = 0.48)

Note: * — differences from the corresponding indicators of children in the control group at $p < 0.05$; # — differences from the corresponding indicators of children in the main group/comparison group before and after treatment at $p < 0.05$ (according to McNemar's chi-square test).

Table 2 – Sizes of heart cavities and indicators of central hemodynamics in patients with post-COVID syndrome and children of the control group

Patient groups	LA, mm		LVEDD LV, mm		LVEF,%	
	before	after	before	after	before	after
Main group 10–14 years	22.5 ± 1.2	22.4 ± 1.1 (p = 0.46)	46.5 ± 3.4	44.0 ± 1.8* (p = 0.02)	70.2 ± 3.0	71.1 ± 2.2 (p = 0.66)
Comparison group 10–14 years	22.7 ± 1.6	22.5 ± 1.7 (p = 0.60) / (p = 0.89)	44.1 ± 4.8	43.4 ± 4.1 (p = 0.69) / (p = 0.71)	69.8 ± 3.0	69.1 ± 3.3 (p = 0.71) / (p = 0.16)
Main group 15–17 years	25.2 ± 3.3	23.9 ± 1.6* (p = 0.01)	47.1 ± 2.1	46.1 ± 1.2 (p = 0.10)	68.9 ± 2.3	68.4 ± 2.5 (p = 0.69)
Comparison group 15–17 years	24.4 ± 2.6	24.1 ± 1.9 (p = 0.81) / (p = 0.84)	47.4 ± 3.7	46.7 ± 3.2 (p = 0.64) / (p = 0.43)	69.1 ± 3.3	69.8 ± 3.0 (p = 0.80) / (p = 0.08)
Main group 18–25 years	25.1 ± 2.9	24.1 ± 1.5 (p = 0.05)	48.1 ± 2.1	47.1 ± 1.8 (p = 0.08)	67.7 ± 2.3	68.3 ± 2.2 (p = 0.75)
Comparison group 18–25 years	25.4 ± 2.4	24.8 ± 2.4 (p = 0.77) / (p = 0.56)	49.3 ± 4.3	48.3 ± 3.4 (p = 0.13) / (p = 0.29)	68.6 ± 2.1	68.8 ± 2.0 (p = 1.00) / (p = 0.12)

Note: LA — left atrium; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction. * — differences from the corresponding indicators of children in the main group/comparison group before and after treatment at $p < 0.05$ (according to Student's test); ** — differences from the corresponding indicators of children in the main group and the comparison group after treatment at $p < 0.05$.

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Table 3 – Some indicators of Holter monitoring in children, adolescents and young adults with post-COVID syndrome

Indicators	Duration of the average daily QTc interval, ms	Frequency of detection: episodes of supraventricular rhythm accelerated/ replacement	supraventricular/ ventricular extrasystole	episodes of migration of the rhythm driver/ sino-atrial blockade
Main group before treatment	422.8 ± 12.8	19 (42.2%)	6 (13.3%) / 1 (2.2%)	23 (51.1%)
Main group after 6 weeks	401.8 ± 19.7* (*p* = 0.01)	1 (2.2%)* (*p* = 0.00)	0	9(20%)* (*p* = 0.00)
Comparison group before treatment	418.3±13.8	20 (44.4%)	5 (11.1%) / 2 (4.4%)	26 (57.8%)
Comparison group after 6 weeks	401.4 ± 16.8* (*p* = 0.02) / (*p* = 0.70)	12 (26.7%)* (*p* = 0.01) / (*p* = 0.00)**	5 (11.1%) / 2 (4.4%)	17 (37.8%)* (*p* = 0.01) / (*p* = 0.06)

Note: * — differences from the corresponding indicators before treatment are significant at $p < 0.05$; ** — differences from the corresponding indicators of children in the main group and the comparison group after treatment at $p < 0.05$.

Table 4 – Some indicators of Holter monitoring in children, adolescents and young adults with post-COVID syndrome

Indicator	Age: 10–14 years		15–17 years		18–25 years	
	Post-COVID	Healthy peers	Post-COVID syndrome	Healthy peers	Post-COVID syndrome	Healthy peers
pNN50	25.7 ± 5.7 (*p* = 0.97)	25.8 ± 5.1	24.0 ± 3.0 (*p* = 0.01)*	28.6 ± 7.2	23.3 ± 8.0 (*p* = 0.01)*	30.0 ± 3.5
rMSSD	51.4 ± 8.1 (*p* = 0.01)*	59.6 ± 6.1	57.4 ± 6.7 (*p* = 0.02)*	62.5 ± 3.5	55.5 ± 8.9* (*p* = 0.03)	68.2 ± 3.6
SDNN	141.7 ± 14.7 (*p* = 0.11)	155.0 ± 16.2	139.3 ± 16.1* (*p* = 0.02)	160.1 ± 12.8	144.6 ± 19.2* (*p* = 0.01)	170.8 ± 16.2

Note: * — differences from the corresponding indicators of children in the control group at $p < 0.05$.

Table 5 – Dynamics of life quality indicators in children, adolescents and young adults with post-COVID syndrome during treatment

Indicator	Main group		Comparison group		Control group
	Before treatment	After	Before treatment	After	
Physical functioning	87.5 ± 5.7* (*p* = 0.00)	97.8 ± 2.5# (*p* = 0.00)	88.8 ± 5.3* (*p* = 0.00)	92.8 ± 4.6# (*p* = 0.01)** / (*p* = 0.003)	99.4 ± 1.0
Emotional functioning	65.33 ± 17.9* (*p* = 0.00)	95.5 ± 4.2# (*p* = 0.00)	67.4 ± 6.3* (*p* = 0.00)	91.5 ± 6.9# (*p* = 0.00) / (*p* = 0.33)	98.8 ± 1.4
Social functioning	89.8 ± 8.3* (*p* = 0.00)	96.7 ± .5# (*p* = 0.00)	88.9 ± 9.2* (*p* = 0.00)	92.0 ± 6.5 (*p* = 0.48) / (*p* = 0.07)	98.4 ± 1.8
School functioning	69.3 ± 6.5* (*p* = 0.00)	84.6 ± 7.6# (*p* = 0.00)	71.1 ± 4.5* (*p* = 0.00)	84.3 ± 6.3# (*p* = 0.00) / (*p* = 0.52)	98.3 ± 1.9

Note: * — differences from the corresponding indicators of children in the control group at $p < 0.05$; # — differences from the corresponding indicators of children in the main group and the comparison group before and after treatment at $p < 0.05$; ** — differences from the corresponding indicators of children in the main group and the comparison group after treatment at $p < 0.05$.

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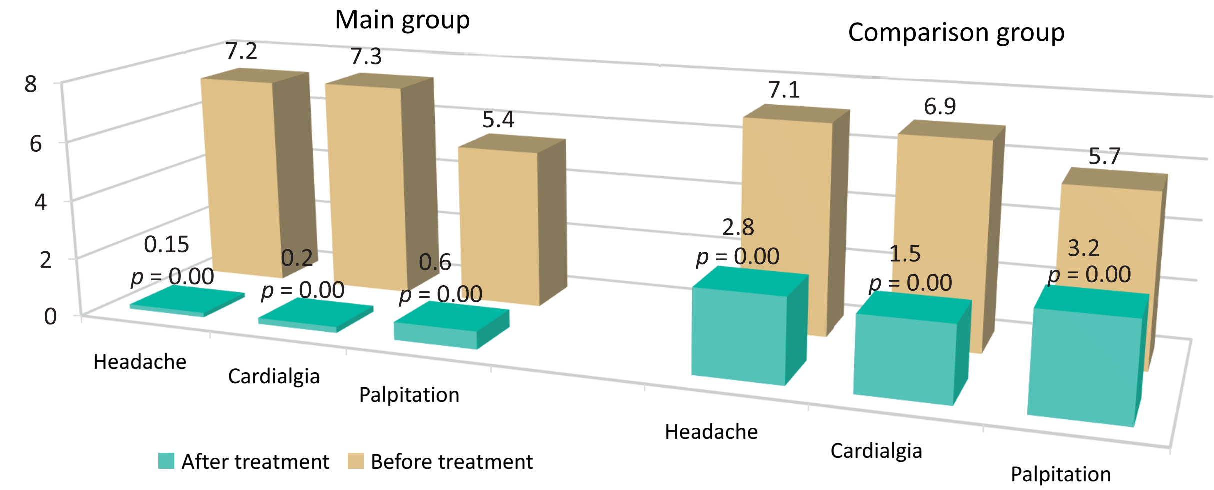

Figure 1 – Dynamics of the severity of headaches, cardialgia, palpitations during treatment in children of the main group.

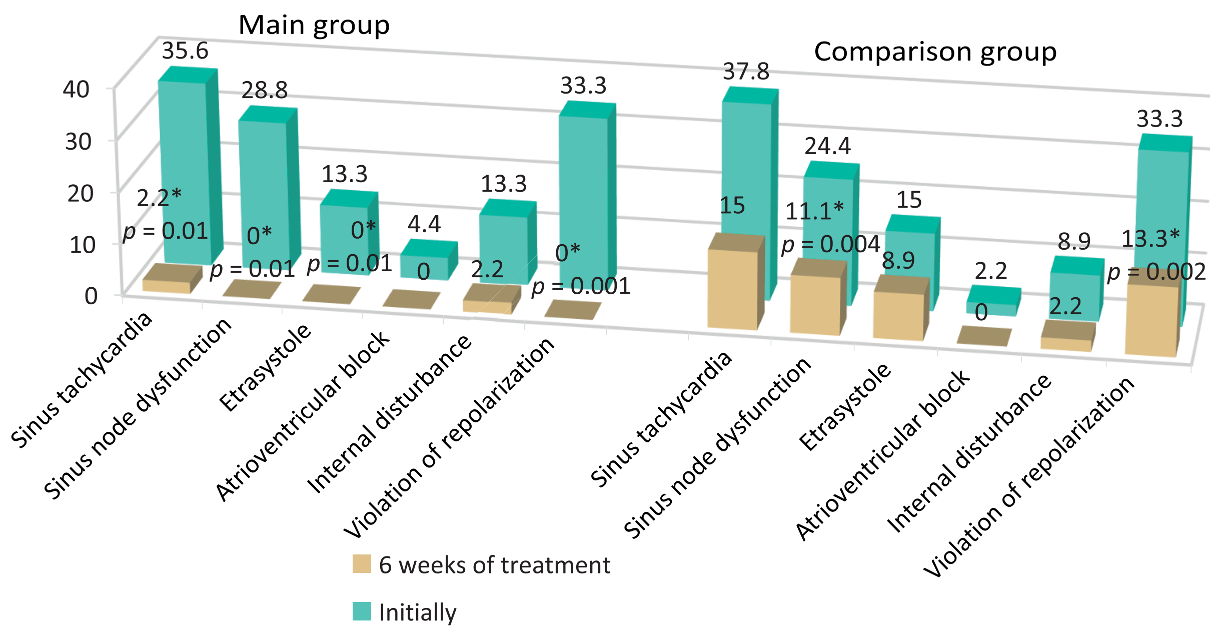

Figure 2 – Dynamics of ECG disorders in children, adolescents and young adults in the main group and the comparison group during treatment.

Note: * — differences from the corresponding indicators of children in the comparison group at $p < 0.05$.

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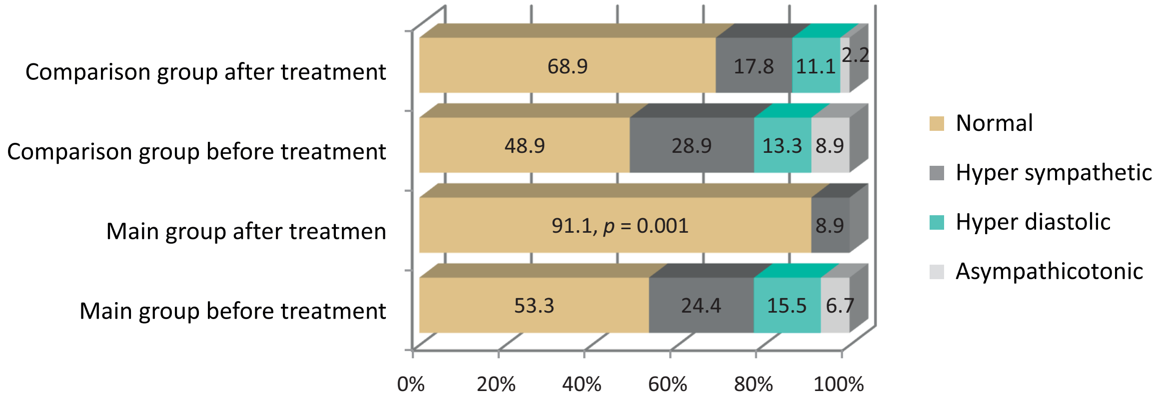

Figure 3 – Representation of types of reaction to the orthostatic test in individuals of the main group and the comparison group during therapy.

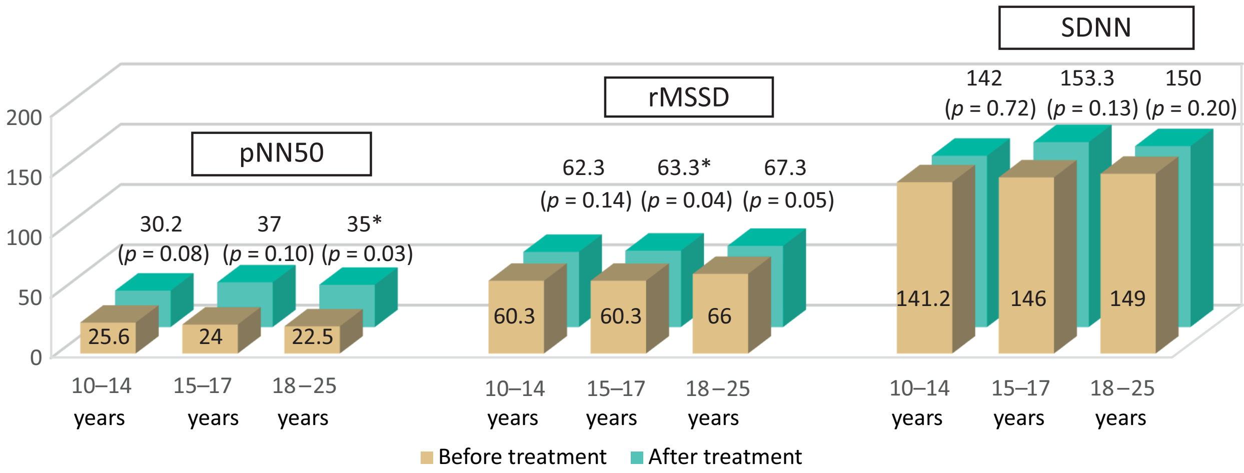

Figure 4 – Indicators of temporal analysis of heart rate variability in dynamics in patients of the main group.

Holter ECG monitoring with assessment of heart rate variability

The initial HR values (during the day and at night) during HM ECG in the main group and the comparison group did not differ significantly and tended to bradycardia (in comparison with children and adolescents in the control group), more pronounced in patients 10–14 years old — 72.7 ± 9.9 vs 79.5 ± 7.5 per min. Patients with PCS registered single extrasystole (atrial in 13.3%, ventricular — in 2.2%) with a frequency of 1385.6 ± 97.3 and 1513.8 ± 102.3 per day for patients in the main group and the comparison group (which in most patients was monomorphic and only in 2 — polymorphic in nature and in 1 adolescent episodes of allorhythmia of the trigeminy type were detected). In 32–36 patients in each group (71.1–77.8%), signs of sinus node dysfunction were detected (episodes of migration of the rhythm driver, sinoatrial blockade, supraventricular replacement rhythm), and clinically significant rhythm pauses (1432–1692 ms) were recorded in 3 (6.7%) patients with PCS (Table 3).

The inclusion of L-carnitine in addition to standard therapy led to the restoration of HR, a reduction in the frequency of registration of bradyarrhythmias and a decrease in the “density” of extrasystole ($p = 0.01$). The representation of ectopic complexes and the number of episodes of non-sinus rhythm in the comparison group changed insignificantly.

The average daily value of the QTc interval according to HM was initially higher in children, adolescents and young adults who had a new coronavirus infection — 429.1 ± 11.6 ms vs healthy peers — 399.3 ± 18.8 ($p = 0.01$). Non-specific repolarization disorders were leveled out by 6 weeks in both study groups. One 10-year-old child who underwent MIS-C with myocarditis and coronary arteritis had flattening of the T wave and ST depression up to 150 μV according to HM ECG, which were leveled out after a course of complex therapy with the additional use of L-carnitine.

Indicators of temporal analysis of heart rate variability (HRV) according to HM in all age categories were initially reduced in 26 (57.8%) patients in the main group and 27 (60%) individuals in the comparison group (Table 4), and the average SDNN values regardless the age were lower in patients with PCS compared to healthy peers. By 6 weeks of treatment, the average group values of pNN50, rMSSD, SDNN significantly increased in all children, adolescents and young adults in the main group, approaching the indicators of healthy peers. A similar dynamic was observed in the comparison group, but the differences did not reach statistical significance. By the end of the observation, the main indicators of temporal analysis of HRV corresponded to reference values in 39 (86.7%) and only in 14 (31.1%) patients in the main group and the comparison group, respectively ($p = 0.00$) (Fig. 4).

Quality of Life Assessment (PedsQL™)

Cardiac disorders in patients with PCS were associated with psychological problems and a decrease in quality of life according to the PedsQL™ questionnaire. At the same time, emotional and social functioning was more reduced in adolescents aged 15–17 years, and physical and school functioning — in children aged 10–14 years. When assessing physical functioning, we identified statistically significant differences depending on the presence of rhythm and conduction disturbances ($p = 0.013$). As follows from the data presented in Table 5, there was a statistically significant increase in quality of life indicators in all areas (physical, emotional, social, school functioning) in patients of the main group, while in the comparison group, the indicator of emotional and school functioning significantly improved.

In general, after 6 weeks of treatment, the therapy with the additional use of L-carnitine led to the absence of complaints, normalization of objective status, laboratory and instrumental data in 42 (93.3%) patients of the main group, and in the comparison group, similar results were obtained in 66.7% ($p < 0.05$).

Adverse events

No adverse events requiring drug withdrawal, significant deterioration of clinical, instrumental and biochemical parameters (ALT, AST, urea, creatinine, glucose) during drug administration were registered.

DISCUSSION

Despite the lower rates of morbidity, severity and mortality, health problems after a new coronavirus infection could not but affect the population of children and adolescents. According to the literature, the prevalence of long COVID (including ongoing symptomatic COVID) and PCS varies from 1.6 to 78% (depending on age and diagnostic criteria) [22]. The prevalence of PCS in our study was 14.1% among minors and 28.9% among individuals aged 18–25 years, which corresponds to the age trends in the formation of PCS, but is generally somewhat lower than according to Russian studies [23, 24], but, at the same time, higher than according to the results of the meta-analysis by Wulf Hanson et al., which established that 3 months after a new coronavirus infection, 2.8% of the subjects under 20 years of age had at least 1 symptom of PCS [3].

The likelihood of developing PCS practically does not correlate with the severity of acute COVID-19, but is higher in seropositive patients [5, 25]. Our study included only patients with laboratory-confirmed new coronavirus infection, but only 23.3% of them had a moderate course of the disease in the acute period, the rest had a mild or asymptomatic course. Although, it should be noted that 13 patients out of 45 patients included in the study with a diagnosis of U09.9 — Condition after COVID-19, had a history of MIS-C associated with a new coronavirus infection [26].

According to the literature, it is the lesion of the CVS, along with the involvement of the gastrointestinal tract, that is the leading organ manifestation of MIS-C and often determines the life prognosis [27]. At the same time, repolarization disorders on the ECG, arrhythmias and conduction blocks, increased activity of cardio-specific enzymes, myocardial dysfunction, pericardial effusion and dilatation of the coronary arteries, which are determined in 67–90% of children with MIS-C, can persist for more than 12 weeks from the moment of infection manifestation [28] and "result" in the development of independent nosological forms — myocarditis, pericarditis, arterial hypertension, coronary artery aneurysms.

Adult patients after a coronavirus infection have a 1.6 times higher risk of developing a new cardiovascular disease, including rhythm disorders, non-ischemic / ischemic cardiomyopathy, cerebrovascular and thrombotic diseases [29]. Similar information for the pediatric population was first presented in a recent review by Zhang et al. [30], who demonstrated that after a new coronavirus infection in children and adolescents, there is an increased risk of developing arterial hypertension, rhythm disorders, myocarditis, heart failure, cardiomyopathy and thromboembolic disorders. Moreover, patients aged

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5–20 years demonstrated a higher risk of developing cardiovascular disorders (especially arrhythmias) compared with children under 5 years of age. In our study, the presence of certain cardiovascular diseases was an exclusion criterion, but the frequency of cardiac manifestations of PCS (chest pain, palpitations, syncope) was 1.71%, which fully corresponded to the data of the review [30].

CVS damage in long-term COVID in children, in contrast to MIS-C, is described in a small number of studies, according to which cardiovascular consequences occurred in 8.7–14.5 patients [31–33]. The most common symptoms were increased or decreased blood pressure and postural tachycardia syndrome. According to our data, arterial hypo- and hypertension at rest and abnormal reactions to orthostasis were detected in 3–16 patients (6.7–24.4%). Among electrophysiological abnormalities, sinus tachy- and bradycardia, repolarization disorders are most often described [34]. The work of Delogu et al. also presents data on a slight prolongation of QTc (within the normal range) in the long-term COVID group, as well as a change in heart rate variability with a predominance of parasympathetic activity [34].

However, in general, the examined children, adolescents and young adults with PCS, were dominated by complaints of an asthenic nature, which is fully consistent with the known literature data, about the most frequent detection in children and adolescents with long-term COVID-19 of increased fatigue (up to 87%) and headache (up to 80%) [32, 35]. Although severe headache may be due to a decrease or increase in blood pressure, and increased fatigue and decreased tolerance to physical activity, in part, is mediated by myocardial dysfunction and the development of rhythm disorders. This is confirmed by the presence of a direct moderate correlation between symptoms from the CVS and a decrease in quality of life: in particular, the number of extrasystoles and impaired physical functioning (r = 0.469).

Given the complex nature of pathogenesis, the treatment of PCS is currently only being developed [36]. In adult patients, tranquilizers of the benzodiazepine group, antidepressants (tricyclic and serotonin reuptake inhibitors), nootropics, vitamins (especially groups B, C and D), antioxidants, and energy-tropic drugs are used. In children, the protective effect of aminoacetic acid (glycine) and its combinations with glutamic acid and L-cysteine (eltacin) has been shown [37].

L-carnitine has demonstrated its effectiveness in the acute period of COVID-19, providing antioxidant, immunomodulatory, suppressing TNF-α, IL-6, and IL-1, as well as cardioprotective effects [38]. In a study by Scaturro et al., it was found that the combination of physical exercises with L-acetylcarnitine therapy in patients with PCS can significantly improve the quality of life and eliminate the manifestations of depression [39]. We have previously shown the ability of L-carnitine to correct psychological disorders that are part of the clinical spectrum of PCS manifestations [40].

Study limitations

The limitations of this study include the lack of a preliminary calculation of the sample size, due to the limited number of children who have had laboratory-confirmed COVID-19. In addition, a possible limitation of this work is the lack of comparative analysis in groups (depending on age), which is an independent task and the subject of another publication.

CONCLUSION

The effectiveness of L-carnitine in correcting the frequency and severity of the main manifestations of PCS — vegetative, cardiovascular, psychoneurological disorders and asthenic disorders in children, adolescents and young adults has been demonstrated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Larisa A. Balykova, Marina V. Shirmankina, Anna V. Krasnopolskaya — data collection and processing, writing of the text; Stanislav A. Ivyansky, Anna A. Stradina, Tatyana M. Duvayarova, Daniil S. Rodionov — data collection and processing, editing of the text of the article. All the authors confirm that their authorship meets the ICMJE international criteria (all the authors have made substantial contributions to the conceptualisation, research and preparation of the article, and have read and approved of the final version before the publication).

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AUTHORS

Larisa A. Balykova – Doctor of Sciences (Medicine), Professor, Vice-Rector for Innovation in the field of Biotechnology and Medicine, National Research Ogarev Mordovia State University; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0002-2290-0013. E-mail: larisabalykova@yandex.ru

Marina V. Shirmankina – Assistant Lecturer of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-9049-5662. E-mail: shirmankina99@mail.ru

Anna V. Krasnopolskaya – Candidate of Sciences (Medicine), Assistant Professor of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 000-0003-3990-9353. E-mail: abalykova@mail.ru

Stanislav A. Ivyansky – Candidate of Sciences (Medicine), Assistant Professor of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0000-0003-0087-4421. E-mail: stivdoctor@yandex.ru

Anna A. Stradina – Pediatrician of Children's Polyclinic No. 4 (Saransk, Russia). ORCID ID: 0000-0003-1208-9949. E-mail: gofj@mail.ru

Tatyana M. Duvayarova – Assistant Lecturer of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0009-0008-0564-9534. E-mail: zolnickova.tatjana@yandex.ru

Daniil S. Rodionov – 6^{th}-year student of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0009-0009-6773-0124. E-mail: Daniil.serg.rod@gmail.com