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PATHOGENETICALLY DETERMINED DIAGNOSIS AND METHODS OF CORRECTION OF CEREBROVASCULAR DISORDERS IN PATIENTS WITH THE CONSEQUENCES OF COVID-19

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Key words: cerebrovascular pathology, coronavirus infection, cerebral ischemia, autonomic system, vestibular disorders, cognitive impairment, damage to the nervous system, cerebral circulation.

ПАТОГЕНЕТИЧЕСКИ ОБУСЛОВЛЕННАЯ ДИАГНОСТИКА И МЕТОДЫ КОРРЕКЦИИ ЦЕРЕБРОВАСКУЛЯРНЫХ НАРУШЕНИЙ У БОЛЬНЫХ С ПОСЛЕДСТВИЯМИ COVID-19

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Ключевые слова: цереброваскулярная патология, коронавирусная инфекция, ишемия головного мозга, вегетативная система, вестибулярные нарушения, когнитивные нарушения, поражение нервной системы, мозговое кровообращение.

Изучены когнитивные функций, состояние вегетативной нервной системы, вестибулярные расстройства и ауторегуляция мозгового кровообращения у пациентов с цереброваскулярной патологией и перенесших COVID-19. Выявлено, что вышеперечисленные нарушения являются ключевыми и коморбидными при недостаточности мозгового кровообращения у людей, перенесших COVID-19, и коррелируют со степенью поражения мозга. Их прогрессированию способствует перенесенная коронавирусная инфекция с последующей декомпенсацией ишемии, особенно вследствие прямого поражения сосудистой системы ЦНС.

Применение β-Фенил-ГАМК улучшает память, концентрацию внимания с восстановлением когнитивных функций, влияет на центральные вестибулярные структуры за счет улучшения их васкуляризации, оказывает гармонизирующее вегетотропное, антидепрессивное действие, а также стабилизирует или нормализует патологические показатели цереброваскулярной реактивности.

COVID-19 OQIBATLARI BO'LGAN BEMORLARDA SEREBROVASKULYAR KASALLIKLARNING PATOGENETIK DIAGNOSTIKASI VA TUZATISH USULLARI

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Kalit so'zlar: serebrovaskulyar patologiya, koronavirus infektsiyasi, miya ishemiyasi, vegetativ tizim, vestibulyar buzilishlar, kognitiv buzilishlar, asab tizimining shikastlanishi, miya qon aylanishi.

Serebrovaskulyar patologiyasi bo'lgan va COVID-19 bilan kasallangan bemorlarda kognitiv funktsiyalar, avtonom asab tizimining holati, vestibulyar kasalliklar va miya qon aylanishining avtoregulyatsiyasi o'rganildi. Yuqoridagi buzilishlar COVID-19 bilan kasallangan odamlarda serebrovaskulyar etishmovchilikda asosiy va komorbid ekanligi va miyaning shikastlanish darajasi bilan bog'liqligi aniqlandi. Ularning rivojlanishiga, ayniqsa, Markaziy asab tizimining qon tomir tizimiga to'g'ridan-to'g'ri zarar etkazilishi sababli, ishemiyaning dekompensatsiyasi bilan o'tgan koronavirus infektsiyasi yordam beradi.

B-fenil-GABA dan foydalanish xotirani yaxshilaydi, kognitiv funktsiyalarni tiklash bilan diqqatni jamlaydi, Markaziy vestibulyar tuzilmalarga ularning qon tomirlarini yaxshilash orqali ta'sir qiladi, uyg'unlashtiruvchi vegetativ, antidepressant ta'sirga ega, shuningdek serebrovaskulyar reaktivlikning patologik ko'rsatkichlarini barqarorlashtiradi yoki normallashtiradi.

In Ukraine, there is a tendency to increase the prevalence and incidence of cerebrovascular pathology of (CVP), both acute cerebral strokes (ACS) and chronic progressive forms [1-4].

All these problems are aggravated as a result of the coronavirus infetion (COVID-19) pandemic. Statistical indicators indicate that there is a high probability of the development of ACS in the first days of the clinical course of the acute respiratory syndrome as a result of infection with the SARS-CoV-2 virus and persists after the end of the acute period of this disease, which is an order of magnitude higher than when infected with the influenza virus [5-7].

A significant number of young people are registered in the structure of the morbidity of ACS against the background of transferred COVID-19 [7,8].

It is known that ACS is an age-dependent disease with a gradual “accumulation” of mainly several risk factors for the implementation of a vascular accident. The absence of this kind of “prehistory” and young age significantly complicate the therapy and rehabilitation received [9,10,11]. The development of ACS has been recorded in the long-term period after infection with SARS-CoV-2 [12,13,14].

The clinical picture of ACS is dominated by cognitive disorders [15], which persist and progress during the recovery period [5,9,10], making it difficult to carry out pathogenetically based pharmacological correction of all periods of stroke, including rehabilitation [16,17]. Drug correction is based on an understanding of the pathogenetic mechanisms of the disease,

but at the present stage of development, the development of science is predominantly empirical in nature. [18]. It should be noted that chronic cerebral ischemia (CCI) is the main supplier of a significant amount of ACS [19]. Thus, it is necessary to pay special attention to the most widespread chronic disorders of cerebral hemorrhage in order to avoid the culprit of gross organic judicial changes in the central nervous system, such as ACS, which is the most urgent this problem of clinical medicine and neurology [19-22]. Moreover, in addition to mnestic disorders and cephalgic syndrome [23,24], conductive and vestibular dysfunction (VD), the developments of which are evident in the clinical picture of vascular dysgemia, the central nervous system correlates with these stages damage to the brain [25,26].

The clinical diversity of dizziness is associated with age-related changes in the sensory system, a decrease in the compensatory capabilities of central balance mechanisms, including due to CCI, cerebrovascular insufficiency with a predominant lesion of the vertebrobasilar region, and problems primarily of cervical origin. in the form of degenerative-dystrophic processes in the spine [27,28]. In addition, the functioning of the vestibular system has a complex mechanism, including specific reception, tetrad of orientation in space, auxiliary sensory systems, vestibular projections to the central nervous system (CNS) with their representation in the cerebral cortex [26]. Disorders of the autonomic system that affect vascular reactivity are leading in this type of VD and require additional methods for diagnosing dizziness syndrome, which affects the adequacy and timeliness of therapeutic intervention, prevention, etc.

Thus, the progression of CCI is facilitated by the development of coronavirus infection with the frequent appearance of non-motor symptoms in the form of cognitive, psychoemotional and other CNS disorders, which leads to a deterioration of the patient's condition with a high probability of developing more severe vascular lesions of the CNS, including CCI [5,9,10,15,17,29,30]. Although the question of including VD among the main symptoms of COVID-19 in the acute period remains open, its significance in people who have had COVID-19 is beyond doubt, where the most common neurological symptom in such patients is dizziness.A strong correlation between SARS-CoV-2 infection and dizziness has been reported, but the mutual mechanisms are not fully understood and require further study [25–31].

We consider it important to pay attention to the possible routes of penetration of the SARS-CoV-2 virus into the central nervous system: olfactory nerves and pathways, cellular invasion (monocytes, macrophages) like a "Trojan horse", endothelial cells, blood-brain barrier. Transsynaptic transmission through peripheral nerves with the possible use of kinesin axonal transport and paracellular migration has also been suggested [32-37].

All of the above affects the state of the vestibular system, which is the first to respond to changes in the functioning of the autonomic nervous system (ANS), formations of the brain stem, where the vestibular nuclei and their pathways are located. In this way, it is possible to activate some degenerative diseases of the central nervous system with anosmia, motor, cognitive, psycho-vegetative disorders, systemic and non-systemic dizziness, disorders of statolocomotor, balance [37].

Another important mechanism of infectious damage to the nervous system is clinical manifestations associated with hypercoagulability due to systemic inflammation, cytokine storm leading to endothelialitis, and other factors leading to vascular damage to the CNS [9,10,13,14,36]. Everything that we noted above is fully consistent with the pathophysiological mechanisms of virus-induced lesions of the nervous system, given that we conducted our own diagnostic and treatment efforts from a pathogenetic point of view.

Damage to the vestibular apparatus is accompanied by a decrease in blood flow in the vestibular structures, which are very sensitive to ischemia. In addition, hemodynamic changes easily occur as a result of vasospasm, endothelial damage, and thrombosis among other vascular problems in coronavirus infection [13,14,36,37].

The aim of the study. Study of the state of the autonomic system, cognitive functions, functional state of the vestibular apparatus and autoregulation of cerebral blood circulation in patients with cerebrovascular pathology, which was formed against the background of the consequences of COVID-19.

Materials and methods.

Along with the clinical and neurological examination, the somatic sphere of the patients was studied with the involvement of the necessary specialists.

We examined 108 patients (49 men and 59 women) aged from 32 to 60 years (mean age 43.6±1.6 years) who had COVID-19, including those with compensated CCI (group I, n=24) and subcompensated stage (group II, n=38) and 46 patients (group III) who suffered an ischemic stroke in the post-Covid period, which was confirmed by neuroimaging methods. The duration of the stroke varied within the early recovery period. Speech and writing were preserved in all patients. The control group (CG, n=20) consisted of relatively healthy people who underwent professional selection. Informed consent to participate in these clinical observations was obtained from all patients.

The study of cognitive functions was carried out using a short scale of mental state - Mini-Mental State Examination (MMSE) [38], a battery of tests for studying frontal dysfunction - Frontal Assessment Batter (FAB) [39], a test for memorizing 10 words according to A.R. Luria for the study of short-term and long-term memory [40,41]. All groups were tested twice: at the beginning of the study and three months later.

The state of the ANS was studied using a questionnaire [40], in addition, autonomic characteristics were studied using a table of express diagnostics of autonomic tone (VT), reactivity test (VR) and autonomic support of activity (VSA) [40,42,43]. The Hospital Anxiety and Depression Scale (HADS) was used to identify the presence and severity of anxiety and depressive disorders in patients [44]. The study of indicators of cerebrovascular reactivity of the cerebral arteries was carried out in triplex mode on an Ultima-PA ultrasound scanner (RADMIR, Ukraine). The following reactivity coefficients were studied:

1) hypercapnic load, reactivity coefficient KrCO2;
2) hyperventilation load, reactivity coefficient KrO2;
3) vasomotor reactivity index - IVMR;

4) functional nitroglycerin test, reactivity coefficient - KrFNT. In order to study the possibilities of drug correction of brain disorders in patients with CVD, the effect of taking the drug Phenibut (β-Phenyl-GABA), as a nootropic of complex action with a wide spectrum of pharmacological activity, was studied [45]. The possibility of long-term use at any age without side effects is largely due to its affinity for the body's natural metabolites. In cases of post-stroke cognitive deficit, the following are especially important: adaptogenic, anti-stress, antiarrhythmic and hypotensive effects, improvement of cerebral hemodynamics in cerebral ischemia, normalization of autonomic regulation in cerebral angiodystonia. In addition, phenibut (β-phenyl-GABA) is used for post-stroke seizure and spasticity syndrome (affinity with baclofen) [46]. The drug was prescribed to patients of all groups for three months, one tablet (250 mg) 3 times a day. The obtained results were statistically calculated using the parametric ANOVA test and the non-parametric Kruscall-Wallis test. Statistical differences were considered probable at $p < 0.05$.

Results and their discussion.

Patients with CCI complained of dizziness (non-systemic

- 51.6%, or systemic - 48.4%), caused by physical exertion (25.8%), head movements (38.7%), orthostatic changes (14.5%) fluctuations (usually an increase) in blood pressure (9.7%).

The start of accompanying pathological mechanisms of vestibulopathy were: vascular-vegetative headache (75.8%) with vasomotor (24.2%), ischemic-hypoxic (48.4%), venous (27.4%) components. Localization: diffuse (40.3%), in the occipital (33.9%), parietal (14.5%), frontal (11.3%) regions. Algic syndrome was manifested by pain in the neck (69.3%) and mainly during movements, muscle weakness (58.1%), including with irradiation to the shoulder and the corresponding hand (37.1%); back pain (56.4%); cardialgias (37.1%) and other pain phenomena. The tension of the muscles of the shoulder girdle and neck had a reflex-tonic or generalized character in 48.4% of cases with pronounced vegetative accompaniment and with angiospasm of superficial, local and main vessels.

In addition, the most significant symptoms were - increased blood pressure (59.8%), noise in the head (38.7%), decreased hearing (30.6%), orthostatic hypotension (19.3%). In a number of cases - asthenia (41.9%), emotional lability (58.1%), as well as cognitive disorders (70.9%) and dyssomnias (40.3%).

In an objective study of vestibular-postural conduction [9,25,26] moderate vestibular disorders in Romberg's pose in the form of instability and swaying prevailed (69.3%). Fine-sweeping nystagmus, as well as nystagmoid movements without visible VDs at the time of the study, were established.

In the III group of patients who suffered an ischemic stroke in the post-covid period, 35 patients (76.1%) complained of dizziness of a mainly systemic nature, in combination with orthostatic disorders (24 - 52.2%), impaired coordination (20 - 43.5%), ataxic manifestations (12 - 26.1%) and in some cases - the phenomenon of frontal ataxia.

Headache was registered in 32 patients (69.6%), mainly migraine-like (25-78.1%) or venous-discirculatory (7-21.9%) in nature. Algic syndromes were associated with movement disorders in the neck (15 - 32.6%), in the limbs with localization in the joints (12 - 26.1%), as well as in the form of thoracalgia (10 - 21.7%), cardialgia (5 - 10.8%).

No pronounced focal neurological symptoms were recorded. Minor extrapyramidal disorders were registered in 9 (19.6%) patients, the presence of a moderate pyramidal syndrome with slight spasticity in 9 (19.6%), paresis in 8 (17.4%), manifestations of anisoreflexia in 12 (26.1%), facial asymmetry in 8 (17.4%), oral automatism reflexes in 13 (28.3%) patients. 10.9% had manifestations of pseudobulbar disorders.

Vegetative characteristics: VT was pathological - in 94 (87.0%) patients, at the same time, with a shift towards the vagal orientation - 45.3%; sympathicotonia prevailed in 41.7%, eutonia persisted in 12.9% of cases.

The obtained data indicate that in the conditions of CCI, autonomic changes prevail in the direction of sympathicotonia ($p<0.05$) with a tendency to decrease with subcompensation (II group, Fig. 1). At the same time, with increasing decompensation (III group), vagotonia prevailed significantly (by 6 times) (86.9%, $p<0.05$).

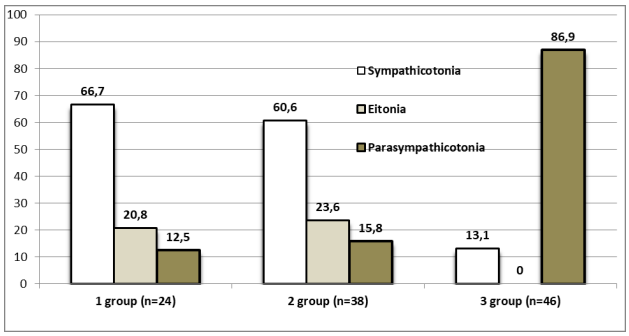

Fig. 1. Relative distribution of the number of patients depending on VT by group

Pathological VR in 92 (85.1%) patients, of which it was insufficient in 47 patients (51.1%) and increased as ischemic brain damage increased (25.0%, 51.6%, 67.6%, respectively by groups). At the same time, in each group of patients, their number from excessive VR significantly exceeded the corresponding indicator when compared with such an indicator in practically healthy individuals ($p<0.05$, Table 1).

Insufficient VR was diagnosed in a significantly larger number of patients of the I and II clinical groups compared to this indicator in the control ($p<0.05$). And we found pathological VR in all and most of the examined patients, which was absent in practically healthy individuals ($p<0.01$).

Table 1.
Distribution of the number of patients depending on VR by group

Groups of patients	The number of patients with the detected			
	Excessive VR	Insufficient VR	Paradoxical VR	Pathological VR
Control (n=20)	1	1	0	2
I gr. (n=24)	18#	6	0	24##
II gr. (n=38)	12#	16#	3	31##
III gr. (n=46)	12#	25#	0	37##
In general among groups of patients	42 (45,6%)	47 (51,1%)	3 (3,3)	92 (100,0%)

Notes: # - p<0.05 and ## - p<0.01 - probable differences of the studied indicators compared to the corresponding indicators in the control group (Kruscall-Wallis statistical test).

Maximum changes (100.0% pathological VR indicators) in 1 group with a probable predominance of excessive reactivity ($P<0.05$).

VSA in 93 patients (88.5%) was pathological: excessive (45.2%) or insufficient (54.8%). There is a clear increase in the number of patients with pathological support of activity (all groups): excessive VSA (I and II groups), insufficient VSA (II and III corpses), which revealed statistical probability when compared with such indicators in practically healthy individuals (in all cases $p<0.05$; Table 2).

Table 2.
Distribution of the number of patients depending on ultrasound examination by group

Groups of patients	The number of patients with detected vegetative support of activity		
	Excessive	Insufficient	Pathological
Control (n=20)	1	2	3
I gr. (n=24)	15#	6	21##
II gr. (n=38)	17#	13#	30##
III gr. (n=46)	10	32#	42##
In general among groups of patients	42 (45,2%)	51 (54,8%)	93 (100,0%)

Notes: # - p<0.05 and ## - p<0.01 - probable differences of the studied indicators compared to the corresponding indicators in the control group (Kruscall-Wallis statistical test).

As in cases with VR indicators, the insufficiency of VSA increased depending on the compensation of ischemic brain damage (group I) to decompensated cases (group III), (28.6%, 43.3% ($P<0.05$), 76, 2% ($P<0.05$) respectively by group).

Clinically significant depression (11 or more points), according to HADS, was registered in 34.3% of cases, and the distribution

among groups was uneven: the maximum in group I – 66.7%, in group II – 39.5% (p < 0.05) and with the degree of ischemic damage to the CNS, the number of cases significantly decreased - up to 13.0% in the III group (p < 0.05).

As for cognitive impairment according to the test by A.R. Luria, a clear tendency to decrease the performance of the word recall test was observed in all examined groups of patients depending on the degree of damage to the CNS (p <0.05). In group I, the average values of the test at all stages of word presentation were significantly higher than in groups II and III. Significant fluctuations of these indicators were also registered depending on the stage of ischemic brain damage, a violation of selectivity, a narrowing of the volumes of immediate and delayed reproduction were noted. (Fig. 2).

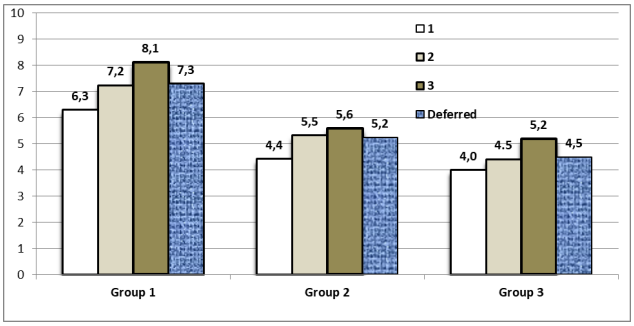

Fig. 2 Dynamics of the average number of memorization of 10 words in three (short-term) and in delayed (long-term memory) presentations in patients in groups depending on the compensation of ischemic processes.

When studying short-term and long-term memory, depending on the progression of the pathological process in the brain, an increase in the insufficiency of intellectual operations was revealed, among which a decrease in the level of generalization took a prominent place. Various dysmnestic disorders were emphasized. Productivity of arbitrary memorization of verbal material was reduced compared to normative data (p<0.05).

A significant decrease in the volume of long-term reproduction was registered, which also indicates a violation of verbal memory.

According to the data obtained on the MMSE scale, the average score is in the range of mild cognitive disorders (25.5±0.6 points - I group), as well as mild dementia (23.6±0.2 and 20.9±0.4 points in groups II and III, respectively), and in group III these values border on moderate dementia with a decrease in points on all items of the mental status assessment scale. This kind of intellectual disorders form vascular dementia, which in some observations came to the fore. In the I group, MMSE results were reduced due to concentration of attention, copying. In the II group - memory, sequence of commands, etc.

When studying the average indicators of the "Frontal Dysfunction Battery" (FAB) test in the examined groups, the following were recorded: moderate cognitive disorders with impairment of praxis, spatial activity (group I), severe cognitive disorders with impairment of activity control, programming, praxis, material function (group II) and dementia (III group) where the CNS functioning is reduced in relation to each categorical generalization (Table 4).

An important aspect of the study of vascular disorders is the careful registration of indicators of cerebrovascular reactivity of cerebral arteries, both for prognosis and for monitoring the effectiveness of treatment [47-51].

In patients of I, II and III groups, a decrease in CrCO2 indicators was observed (CG – 1.28±0.06; 1st group – 1.17±0.04, II group – 1.14±0.03, III group – 1, 10±0.03). CrO2 values in group I did not change significantly, in groups II and III they were significantly reduced without a significant difference between these groups (CG - 0.36±0.03, group I - 0.34±0.04, group II - 0, 26±0.02, p<0.05; III group – 0.24±0.02, p<0.05).

The lack of significant changes in reactivity to O2 in group I compared to groups II and III can be explained by the fact that the vasoconstrictor regulation mechanism in patients with vascular pathology is exhausted later than the corresponding vasodilator one.

The values of IVMR as an integral indicator of stability of cerebral autoregulation were slightly reduced in group I (62.9±7.5, CG - 71.5±6.9), and also sharply decreased in groups II and III (group II - 51.2 ±4.6, p<0.05; III group - 42.1±3.9, p<0.05). These changes were mostly characteristic of patients of the III group.

Also, in groups II and III, approximately equally, there was a significantly pronounced hyporeactivity to TNF (CG - 0.16±0.02, group II - 0.05±0.01, p<0.05; group III - 0 .01±0.05, p<0.05), which is the most sensitive indicator of violations of the vasodilatation function at various stages of CVP (Table 3).

Table 3.

CVR indicators in patients with CVP

Groups of patients	CrCO2	CrO2	IVMR	CrTNF
Control (n=20)	1,28±0,06	0,36±0,03	71,5±6,2	0,16±0,02
I gr. (n=24)	1,17±0,04	0,34±0,04	62,9±6,5	0,11±0,01
II gr. (n=38)	1,14±0,03	0,26±0,02*	51,2±4,6*	0,05±0,01*
III gr. (n=46)	1,10±0,03	0,24±0,02*	42,1±3,9*	0,06±0,01*

Notes: * - p<0.05 – probable differences of the studied indicators compared to the corresponding indicators in the control group (ANOVA statistical criterion).

It can be assumed that the exhaustion of the reserves of the vasoconstrictor component in organic vascular lesions of the brain occurs later than similar changes in the vasodilator component. Changes in the reactivity of the myogenic circuit as CCI progresses are similar to the data of the metabolic circuit of autoregulation, and a decrease in IVMR indicators is a marker of autoregulation disruption and correlates with the degree of ischemic brain damage.

After the treatment, most patients noted a significant improvement in well-being. Complaints of unsteadiness while walking and instability in the vertical position decreased by 49.1% in the CCI groups. The number of cases of dizziness decreased by 1.5 times (P<0.05), including system - by 40.0%.

In addition to restoring the functioning of the vestibular analyzer with the elimination of the above-mentioned and other accompanying vegetative symptoms, including violations of vasomotor regulation. The pronounced "vegetotropic" nature of the proposed therapy is confirmed by the normalization of both paroxysmal (pre-syncopal states, blood pressure lability, panic attacks and autonomic crises of other orientation) and permanent symptoms, emotional instability, meteotropy. In addition, the specific weight of people with eytonia increased (from 10.2% to 37.9%, P<0.05). The distribution by groups was: 45.8%, 26.3%, 13.0% of observations, respectively, which indicates an increase in the compensatory capabilities of the autonomic system depending on the degree of ischemic damage to the central nervous system against the background of the ongoing therapy. VR was normalized by 27.2% (P<0.05) and entered the range of normal distribution, the same changes occurred in VSA - by 25.8% (P<0.05).

In all groups, manifestations of clinically significant depression were eliminated in 40.5% (P<0.05). At the same time, the maximum normalization of the psycho-emotional background occurred in the CCI groups (43.7% and 40.0%), minimal positive changes - in group III (in 33.3% of observations).

Testing of short-term and long-term memory according to the method of A.R. Luria after therapy, registered an increase in the number of responses to the presented words in all presentations. The average values of the obtained data at all stages of presentation of words were higher than at the beginning of the study, and probable values were registered in I (by 12.9%) and II (by 13.8%) groups (Fig. 3). The maximum reproduction of words was achieved in groups after the third presentation (9.3±1.1; 6.5±1.2; 5.7±1.8 words, respectively) - 1.4 and 1.6 times higher in I group in comparison with II and III groups. Moreover, in the latter there was a tendency to improve the test results (by 8.8% in the third presentation). After treatment in the I group, the results of normal word memorization were achieved. Regarding long-term memory, there was also an increase in the number of word reproductions (by 14.1%, 11.9%, 6.3%).

Thus, the obtained data indicate an improvement in the state of short-term and long-term memory, stability of attention in all groups in the process of complex application of β-Phenyl-GABA, which affects the reproduction of cognitive functions in patients (Fig. 3).

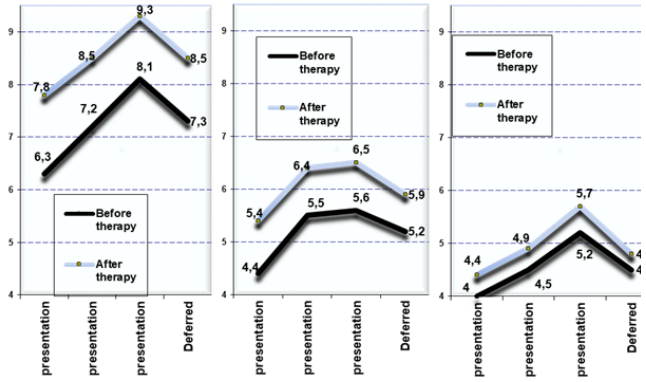

Fig. 3. Dynamics of the number of memorization of 10 words in three (short-term) and in delayed (long-term memory) presentations in patients of all examined groups: I group (first column), II (middle), III (right)

A study on the MMSE scale in patients of all groups after nootropic therapy revealed some improvement in results ($p<0.05$) (Table 4).

According to the data obtained on the MMSE scale, the average score is on the border of the ranges of "mild cognitive disorders" and the norm (27.9±0.5 points - I group), II group moved to the range of "mild cognitive disorders" (25.4±0.8 points), the III group improved the score, but maintained the level of "mild dementia" (table 4).

This kind of intellectual disorders form vascular dementia, which in some observations comes to the fore. In the I group, MMSE results were reduced due to concentration of attention, copying. In the II group - memory, sequence of commands. In the III group - voluntary attention, orientation in space, time, perceptual-gnostic functions, etc.

Table 4.

The effect of the applied treatment on the structure of neurocognitive disorders according to the indicators of the FAB and MMSE scales in the examined groups

Groups of patients	Treatment effectiveness criteria (M±	
	MMSE	FAB
I group		
Before treatment	25,5±0,6	15,8 ±0,5
After treatment	33,2±0,4#	20,6±0,7#
II group		
Before treatment	23,6±0,2	13,2±0,4
After treatment	30,6±1,1#	17,3±0,9#
III group		
Before treatment	20,9±0,4	10,9±0,7
After treatment	27,2±1,1#	14,6±0,8#

Notes: # - p<0.05 - probable differences of the studied indicators compared to the corresponding indicators in the control group (Kruscall-Wallis statistical test)

An improvement in the FAB frontal dysfunction test was recorded. Thus, in group I, cognitive functional capabilities increased by 1.4±0.3 points and returned to normal; in the II group - by 2.1±0.6 points and the FAB indicators moved from the range of severe to moderate cognitive disorders; and in group III - by 1.3±0.5, which corresponds to severe cognitive disorders (table 4). At the same time, after the treatment, those cognitive functions that were determined by the subtests "Speech speed", "Simple choice reaction" and "Difficult choice reaction" recovered better.

A positive effect of treatment on CVR indicators was also noted. The greatest effect was determined in patients of II and III groups according to KrCO2 indicators (II group – increase from 1.14±0.03 to 1.22±0.06, III group – increase from 1.10±0.03 to 1.19 ±0.05) (Fig. 4). The dynamics of the growth of KrO2 indicators was somewhat lower, but it should be taken into account that the changes in reactivity to the O2 sample were initially not as significant as to the CO2 sample (II group - an increase from 0.26±0.02 to 0.31± 0.03, III group – increase from 0.24±0.02 to 0.30±0.04). It should be noted that KrO2 indicators practically equaled the normative ones.

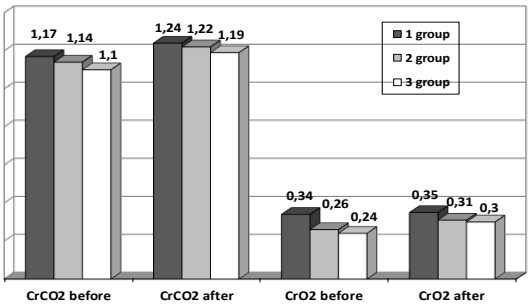

Fig. 4. The effect of the applied treatment on CVR indicators (KrCO2 and KrO2)

We consider the most significant effect of treatment on CVR to be stabilization of IVMR, as an integral indicator of cerebral autoregulation and the most significant predictor of II development (II group – increase from 51.2±4.6 to 59.5±5.4; III group – increase from 42.1±3.9 to 55.1±4.7) (Fig. 5). This indicates the prospects of using the drug in a complex scheme for the prevention of ischemic stroke in patients with CCI.

In the case of ischemic brain damage and infection with the SARS-CoV-2 virus, altering pathogenetic mechanisms are included, which contribute to the aggravation of the clinical picture of the studied pathology, the rapid progress of brain ischemia up to the development of ACS, including in young people, for whom it is not typical due to the absence of major risk factors for vascular accident. However, according to the literature and our observations, further study of the mechanisms of direct damage to the nervous and vascular system by the SARS-CoV-2 virus is necessary [9,10,15,21,30].

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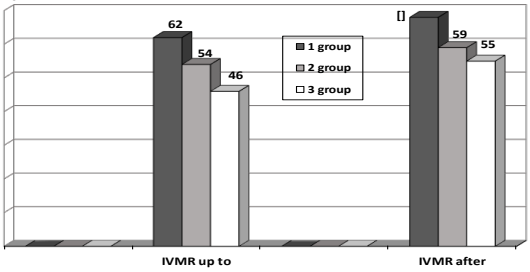

Fig. 5. The influence of the applied treatment on the dynamics of IVMR indicators

At the same time, mnestic disorders are observed, the prevalence of which in the recovery period of brain ischemia is a key pathogenetic link in the manifestation of residual organic and, as a consequence, functional lesions of the brain parenchyma [37]. In the course of our research, it was found that cognitive deficits take first place in the clinical picture and require careful diagnosis for timely correction and prevention of a negative impact on rehabilitation [30].

Cognitive deficits and the development of neuropsychological syndromes are the most common manifestations of cerebral circulatory failure in people who have had COVID-19, with the rapid formation of vascular dementia, in addition, exacerbation or development of neurodegenerative diseases of the central nervous system [52 ,53], so the MMSE and FAB scales were used.

Dizziness in the post-covid period and in the presence of CCI becomes significant due to the prevalence and altering effects on the CNS. It is necessary to take into account the presence of disorders of the ANS, which affects all links of the pathogenesis of the studied conditions, vascular reactivity, etc. [21,24].

It was found that VD is the most common syndrome in cerebral blood circulation insufficiency, which progresses against the background of the transferred coronavirus infection [37,52]. In addition to neurotropic, this is related to vascular damage in the structures of the vestibular apparatus [42,43], vegetative formations and dysfunction of the nervous system, which contribute to the development and support the long course of VD. Our studies also confirm the available data on the impact of coronavirus infection on the vestibular analyzer both in the acute and post-covid periods [54,55], with a mandatory change in the functional characteristics of the autonomic system [56], as well cerebral hemodynamics [57].

The main complaint and subjective experience of the examined contingent of patients was dizziness with the presence of a large number of triggers of a motor, vestibulo-postural, orthostatic, algic, reflex-tonic nature, as well as with vegetative and vascular reactions. In addition, a clinical picture of brain ischemia with characteristic symptoms of various stages of decompensation of the pathological process was registered. Systemic vertigo was more often manifested with the increase of organic symptoms with a maximum in group III, which can be interpreted as damage to the vestibular structures due to their ischemia, while in the compensated stage of ACI (group I) symptoms of non-systemic vertigo syndrome, characteristic of psychogenic manifestations of psychoneurasthenic syndrome, described in initial ischemia of the brain without gross damage.

In most patients, the main vegetative characteristics were pathological. Our data proved that in cases of compensated manifestations of autonomic dysfunctions, the sympathicotonic orientation of VT prevailed with a sharp change in polarity towards vagotonia during decompensation of the pathological process. Similar regularities were found in pathological variants of VR: from the predominance of excessive, and in cases of reduced compensatory capabilities, the ANS passed to insufficient VR. The same regularities are registered with regard to VSA.

In terms of psycho-emotional changes, clinically significant depression was most often detected in the first stages of CCI and less often in persons who underwent ACS. These data correspond to the proposition that depression is one of the first clinical markers of vascular encephalopathy. In cases of significant morphofunctional vascular disorders with similar developmental mechanisms and influence on neuronal activity, monoamine exchange, depressive experiences also occur.

When cognitive disorders were studied, significant fluctuations in the A.R. Luria test performance were also registered depending on the stage of ischemic damage of the CNS towards the narrowing of the volumes of immediate and delayed reproduction of words, both in groups and in comparison with normative indicators. According to MMSE data, it is possible to trace the formation of vascular dementia in groups. According to FAB indicators, moderate cognitive disorders related to disorders of praxis, spatial activity (group I), severe cognitive disorders with impaired control over activities, programming, praxis, material function (group II) and dementia (group III) up to a decrease in the functioning of the central nervous system according to each category generalization.

The decrease in reactivity according to IVMR indicators, as a sign of the search for the optimal sanogenetic variant of cerebral hemodynamics, is mainly due to the vasodilator component, and it fluctuated within significant limits. The given data indicate the importance of IVMR as an integral factor that reflects the dynamic properties of the homeostatic range of vascular autoregulation, including in the case of organic damage to its higher levels. According to our conclusions, reactivity in patients with CCI in the stage of subcompensation and patients with ischemic stroke in the anamnesis coincides, especially according to indices that reproduce the state of the vasodilator component of autoregulation - hypercapnic stress and functional nitroglycine test. Such a regularity may indicate the risk of developing stroke in patients with CCI according to the data of CVR studies. This is confirmed by other studies [47-51], which determined a decrease in reactivity indicators, especially IVMR, as predictors of the development of ischemic stroke. In our study, the most significant deviation of IVMR indicators was observed precisely in patients with ischemic stroke, as well as a significant decrease of this index in the subcompensated group of CCI, which also confirms the high probability of the development of i stroke in this group of patients.

After the treatment, the number of cases of dizziness, both systemic and non-systemic, decreased by two times. Taking into account the above-mentioned effects of β-Phenyl-GABA, it is possible to assume that the nootropic drug had a direct effect on the condition of the central mechanisms of the vestibular structures with the improvement of their vascularization.

The obtained data indicate an improvement in the state of short-term and long-term memory, stability of attention in all groups during the application of β-Phenyl-GABA, which affects the reproduction of cognitive functions in patients. According to the MMSE scale, the average score of neurocognitive disorders after treatment improved in all examined groups: on the border of "mild cognitive disorders" and normal (group I), group II moved to the range of "mild cognitive disorders", in group III the indicators increased, but remained at "mild dementia" levels.

When using β-Phenyl-GABA with a known vegetotropic effect,

it can be assumed that the harmonizing and sympatholytic effect, as well as improving the reactivity of cerebral blood flow, are associated with the functioning of the central nervous system and the cardiovascular system, which have a decisive influence on the pathophysiological mechanisms of the development and course of ischemic processes in post-epidemic period.

Considering the high influence of emotions on memory functions, the antidepressant effect of nootropic drugs was assessed. Favorable changes in the psychoemotional state of patients of all examined groups after treatment with β-Phenyl-GABA were established.

Conclusions

Cognitive, psycho-emotional, vestibular and autonomic disorders are key and comorbid with cerebral blood flow insufficiency in people who have suffered from COVID-19 and correlate with the degree of brain damage.

Suffered coronavirus infection contributes to the progression of the above-mentioned syndromes and further decompensation of ischemia due to direct damage to the CNS vascular system. The obtained data indicate that the use of β-Phenyl-GABA improves memory, concentration of attention with the restoration of cognitive functions, affects the central vestibular structures with the improvement of their vascularization, has a harmonizing vegetotropic, antidepressant effect, and also stabilizes or normalizes pathological indicators of cerebrovascular reactivity. mainly depending on the degree of brain damage, especially the index of vasomotor reactivity, which can be considered as a predictor of stroke.

We believe that further research on the correction of the above-mentioned pathological changes in chronic brain ischemia or after a stroke in the post-covid period should be directed to the study of the effects of the combined use of β-Phenyl-GABA with various rehabilitation measures to identify possible potential and synergistic effects.

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