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INFLUENCE OF PERSONALISED REHABILITATION ON COGNITIVE FUNCTIONS, PAIN SYNDROME AND BIOMARKERS IN PATIENTS WITH CHRONIC CEREBRAL ISCHEMIA

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ABSTRACT

The article presents the results of a clinical, laboratory and neuropsychological study aimed at assessing the effectiveness of an individualized rehabilitation program in patients with chronic cerebral ischemia stage I-II. The developed program included a cognitive-motivational module, physical training with biofeedback and nutraceutical support. According to the results of the 12-week intervention, the main group showed statistically significant improvements in cognitive functions (MoCA), a decrease in the severity of pain syndrome (VAS), an increase in the quality of life (SF-36), as well as a decrease in the levels of the proinflammatory cytokine IL-6 and homocysteine against the background of an increase in the neurotrophic factor BDNF. The results demonstrate the high effectiveness of an integrated approach to medical rehabilitation of patients with initial manifestations of chronic cerebrovascular insufficiency, which can help reduce the rate of progression of cognitive impairment and improve overall functional status.

KEY WORDS. *Chronic Cerebral Ischemia, Rehabilitation, Cognitive Functions, IL-6, BDNF, Homocysteine, Moca, Nutraceuticals.*

RELEVANCE

Chronic cerebral ischemia (CCI) stage I–II is one of the most common forms of cerebrovascular pathology, especially in old age, and is a leading cause of persistent loss of working capacity, cognitive impairment, and deterioration in quality of life [1,2]. According to epidemiological studies, the incidence of CCI among people over 50 years of age ranges from 15 to 30%, while the early stages of the disease remain underdiagnosed for a long time [3].

Modern concepts of the pathogenesis of CCI indicate a multifactorial origin of cerebral hypoperfusion, involving microcirculation disorders, oxidative stress, chronic inflammation and neurodegenerative processes [4,5]. A special role in the formation of cognitive deficit in CCI is played by inflammatory mediators, such as interleukin-6 (IL-6), as well as a decrease in the level of neurotrophic factors, particulary BDNF [6,7].

Despite advances in drug therapy for CCI, the effectiveness of standard treatment regimens in restoring cognitive function remains limited, necessitating the development of new, comprehensive, and personalized medical rehabilitation programs [8,9].

An interdisciplinary approach combining neuropsychological correction, physical activity, nutritional support and control of vascular-metabolic factors can have a pronounced neuroprotective and anti-inflammatory effect [10,11]. However, the literature contains fragmentary data on the use of such programs with the integration of clinical and laboratory monitoring, including biomarkers of neuroinflammation and neuroplasticity [12,13].

Thus, the study of the effectiveness of a personalized rehabilitation program for CCI stages I–II with an assessment of cognitive functions, biomarkers and neuroimaging parameters is a relevant scientific and practical direction that contributes to the early recovery of patients, increasing their daily activity and reducing the risk of progression of vascular dementia [14,15].

The aim of the study

To develop and evaluate the effectiveness of a personalized medical rehabilitation program based on biomarker stratification (IL -6, BDNF) in patients with chronic cerebral ischemia stage I–II in comparison with the standard approach, using a comprehensive assessment of pain, cognitive functions and quality of life.

MATERIALS AND METHODS OF RESEARCH

The study was prospective and controlled and was conducted at the clinical rehabilitation department in patients diagnosed with chronic cerebral ischemia (CCI) stage I–II. The work was carried out in accordance with the Declaration of Helsinki, the protocol was approved by the local ethics committee. All patients provided voluntary informed consent to participate.

The study included 115 patients aged 50 to 75 years (average age 62.4 ± 7.9 years), including 52 men and 63 women , who met the following inclusion criteria: - confirmed diagnosis of CCI stage I–II according to MRI and clinical and neurological

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examination (MoCA ≥15 points, patients with dementia were excluded); ability to participate in an active rehabilitation program. Exclusion criteria: MoCA <15 points or established dementia; acute vascular event within the last 6 months; decompensated somatic diseases; severe depression (HADS >11). Patients were randomized into two groups (Table 1).

Table 1
Characteristics of the study groups and features of the rehabilitation carried out

Group	Quantity (n)	Characteristics of the intervention
Main	68	Personalized rehabilitation program taking into account biomarker levels (IL -6, BDNF, MDA, homocysteine) and clinical assessment
Control	47	Standard rehabilitation program without individualization by biomarkers

The rehabilitation course lasted 8 weeks, with the load 3-4 times a week. All patients were assessed before and after the course.

Table 2 presents the main components of the personalized rehabilitation program used in the main group of patients. Each intervention was prescribed based on individual clinical and biochemical parameters.

Aerobic training was aimed at reducing systemic inflammation with elevated IL-6 and CRP levels. Cognitive training was used in patients with moderate cognitive impairment and reduced levels of neurotrophic support (BDNF). Physiotherapy included coordination, balance, and stabilization exercises and was prescribed for gait disorders. Psychoemotional support was indicated for anxiety-depressive manifestations (according to the HADS scale) and decreased quality of life. Dietary correction and antioxidant therapy were prescribed for elevated homocysteine and malondialdehyde (MDA) levels, indicating oxidative stress.

Table 2
Structure of a personalized medical rehabilitation program for patients with chronic cerebral ischemia

Component	Reason for appointment	Frequency
Aerobic exercise (walking, breathing)	Elevated IL -6, CRP	3 times a week, 30 min.
Cognitive training (MoCA <26)	Low BDNF, decreased MoCA	2 times a week, 25 min.
Physiotherapy (coordination, balance)	Impaired gait, coordination	3 times a week
Psycho-emotional support	HADS >7, decrease in SF -36	1 time per week (group or individual)
Dietary and antioxidant correction	Elevated homocysteine and MDA	As prescribed by a doctor

The program was flexible, modified as the patient's condition changed, and provided a personalized approach to restoring cognitive, metabolic, and psychophysiological parameters.

The effectiveness of the developed program was assessed before and after rehabilitation using the following methods: cognitive status - MoCA and MMSE; pain syndrome - visual analogue scale (VAS); quality of life - SF-36 questionnaire (two main scales: physical and mental health). As well as blood biomarkers: inflammation: IL-6, CRP, TNF-α; neurotrophic support: BDNF, NGF; neurodegeneration: homocysteine, NSE; oxidative stress: malondialdehyde (MDA), SOD.

All laboratory parameters were determined using standard enzyme-linked immunosorbent assays (ELISA). Student's t-test and ANOVA were used for comparison within and between groups. Delta values (Δ) were calculated as the difference between values before and after rehabilitation. The significance level was considered statistically significant at $p < 0.05$. Calculations were performed in SPSS 26.0.

RESULTS OF THE RESEARCH

The obtained data demonstrated significant differences in clinical and biological parameters between the main and control groups of patients with chronic cerebral ischemia after the rehabilitation course. The personalized program, developed taking into account inflammation biomarkers, neurotrophic support and metabolic status, was more effective than the standard approach. Below there are comparative results of cognitive tests, subjective assessment of the state, as well as laboratory parameters before and after the intervention, with an emphasis on delta changes and relative effectiveness.

Table 3
Comparative characteristics of patients before the start of rehabilitation

Indicator	MG (n=68)	CG (n=47)	p-value
Age, years	62.5 ± 7.8	61.9 ± 8.2	0.64
Men/women	31/37	21/26	0.89
MoCA, points	21.8 ± 3.5	22.1 ± 3.3	0.58
VAS, points	4.3 ± 1.2	4.2 ± 1.3	0.71
IL -6, pg/ml	4.8 ± 1.5	4.7 ± 1.6	0.77
BDNF, ng/ml	10.2 ± 2.7	10.5 ± 2.6	0.56

Analysis of the baseline data of patients in the main (MG) and control (CG) groups (table 3) showed comparability in terms of the main demographic, clinical, and laboratory parameters. The average age of the participants was 62.5 ± 7.8 years in the main

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group and 61.9 ± 8.2 years in the control group (p = 0.64), the gender structure was also identical (31 men and 37 women in the MG versus 21 and 26 in the CG; p = 0.89).

The cognitive function scores according to the MoCA scale were moderately reduced in both groups, without statistically significant differences (21.8 ± 3.5 in the MG and 22.1 ± 3.3 in the CG; p = 0.58). The assessment according to the visual analog scale of pain (VAS) was also comparable (4.3 ± 1.2 vs. 4.2 ± 1.3; p = 0.71).

The level of interleukin-6 (IL-6), a marker of systemic inflammation, was similar in both groups (4.8 ± 1.5 pg/ml in the MG and 4.7 ± 1.6 pg/ml in the CG; p = 0.77). The concentration of brain-derived neurotrophic factor (BDNF), reflecting the neurotropic potential, also did not differ statistically significantly (10.2 ± 2.7 ng/ml in the MG and 10.5 ± 2.6 ng/ml in the CG; p = 0.56). Thus, before the start of the rehabilitation intervention, the groups were homogeneous, which allows for a correct interpretation of the differences identified in the subsequent dynamics.

Table 4
Comparative characteristics of patients at the 6th week of rehabilitation

Indicator	MG (n=68)	CG (n=47)	p
MoCA, points	24.1 ± 2.8	22.8 ± 3.1	0.027
VAS pain scores	2.7 ± 1.1	3.5 ± 1.2	0,011
SF -36, total score	55.1 ± 6.2	50.6 ± 6.5	0,018
IL -6, pg/ml	3.8 ± 1.3	4.4 ± 1.4	0,021
BDNF, ng/ml	11.8 ± 2.6	10.8 ± 2.5	0,015
Homocysteine, µmol/l	14.1 ± 3.7	15.1 ± 4.1	0.032

Table 4 presents data reflecting the dynamics of the condition of patients in both groups 6 weeks after the start of the rehabilitation intervention. Statistically significant differences were found in all key indicators, indicating greater effectiveness of the comprehensive personalized program in the main group (MG) compared to the control group (CG).

Thus, cognitive functions according to the MoCA scale improved more significantly in patients in the MG (24.1 ± 2.8 vs. 22.8 ± 3.1 points, $p = 0.027$), and the pain level according to the VAS was significantly lower (2.7 ± 1.1 vs. 3.5 ± 1.2 points, $p = 0.011$). Quality of life according to the SF-36 total index was also higher in the main group (55.1 ± 6.2 vs. 50.6 ± 6.5, $p = 0.018$).

At the biomolecular level, patients in the MG showed a more pronounced decrease in the level of the proinflammatory marker IL-6 (3.8 ± 1.3 vs. 4.4 ± 1.4 pg/ml, $p = 0.021$) and an increase in the level of the neurotrophic factor BDNF (11.8 ± 2.6 vs. 10.8 ± 2.5 ng/ml, $p = 0.015$), which may indicate improved neuroplasticity. In addition, the level of homocysteine, associated with vascular cognitive impairment, was statistically lower in the main group (14.1 ± 3.7 vs. 15.1 ± 4.1 µmol/l, $p = 0.032$). Thus, the presented data confirm the positive effect of the developed personalized rehabilitation program on cognitive, pain and metabolic parameters in patients with chronic cerebral ischemia.

Table 5
Comparative characteristics of patients at the 12th week of rehabilitation

Indicator	MG (n=68)	CG (n=47)	p
MoCA, points	25.4 ± 2.9	23.5 ± 3.2	0,014
VAS pain scores	2.1 ± 0.9	3.2 ± 1.1	0,018
SF -36, total score	59.5 ± 6.8	53.9 ± 6.6	0.022
IL -6, pg/ml	3.2 ± 1.1	4.1 ± 1.3	0,011
BDNF, ng/ml	12.8 ± 2.5	11.1 ± 2.4	0,007
Homocysteine, µmol/l	13.3 ± 3.8	14.7 ± 4.0	0.036

Table 5 presents comparative indices of cognitive and somatic status, quality of life and biomarkers in patients of the main group (MG) and the control group (CG) at the 12th week of rehabilitation. According to the results of the rehabilitation course, significantly better results were observed in the MG compared to the CG. Cognitive functions (MoCA scale assessment) in the MG were higher (25.4 ± 2.9 vs. 23.5 ± 3.2, p=0.014), indicating a more pronounced improvement in memory, attention and executive functions. The intensity of pain syndrome according to the VAS scale was lower in the MG (2.1 ± 0.9 vs. 3.2 ± 1.1, p=0.018), indicating the effectiveness of the intervention in reducing pain. Quality of life according to the total SF-36 score was also higher in the main group (59.5 ± 6.8 vs. 53.9 ± 6.6, p=0.022), indicating an improvement in physical and psychoemotional state. The level of the inflammatory marker IL-6 was significantly lower in the MG (3.2 ± 1.1 vs. 4.1 ± 1.3, p=0.011), which demonstrates the anti-inflammatory effect of the program. The level of the neurotrophic factor BDNF was higher in the main group (12.8 ± 2.5 vs. 11.1 ± 2.4, p=0.007), which may be associated with improved neuroplasticity. The homocysteine level was lower in MG patients (13.3 ± 3.8 vs. 14.7 ± 4.0, p=0.036), which may reflect a decrease in vascular risk.

Thus, the data obtained at week 12 confirm the high effectiveness of the individualized rehabilitation program in relation to cognitive functions, pain syndrome, quality of life and neuroinflammatory markers.

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Table 6
Comparison of indicators in dynamics in the main and control groups (before and after rehabilitation)

Indicator	MG (n=68)	CG (n=47)	p (Δ)
MoCA (points)	21.8 ± 3.5 → 25.4 ± 2.9 (**Δ** =+3.6)	22.1 ± 3.3 → 23.5 ± 3.2 (**Δ** =+1.4)	0,014
VAS pain (score)	4.3 ± 1.2 → 2.1 ± 0.9 (**Δ** =–2.2)	4.2 ± 1.3 → 3.2 ± 1.1 (**Δ** =–1.0)	0,018
SF -36 (total score)	48.2 ± 6.5 → 59.5 ± 6.8 (**Δ** =+11.3)	47.6 ± 6.3 → 53.9 ± 6.6 (**Δ** =+6.3)	0.022
IL -6 (pg/ml)	4.8 ± 1.5 → 3.2 ± 1.1 (**Δ** =–1.6)	4.7 ± 1.6 → 4.1 ± 1.3 (**Δ** =–0.6)	0,011
BDNF (ng/ml)	10.2 ± 2.7 → 12.8 ± 2.5 (**Δ** =+2.6)	10.5 ± 2.6 → 11.1 ± 2.4 (**Δ** =+0.6)	0,007
MDA (µmol/L)	3.9 ± 0.9 → 3.1 ± 0.8 (**Δ** =–0.8)	3.8 ± 1.0 → 3.6 ± 0.9 (**Δ** =–0.2)	0,021
Homocysteine (µmol/l)	15.7 ± 4.1 → 13.3 ± 3.8 (**Δ** =–2.4)	15.9 ± 4.2 → 14.7 ± 4.0 (**Δ** =–1.2)	0.036

Note: Δ is the delta change (the difference between values before and after rehabilitation); all intra-group changes in the main group are statistically significant ($p < 0.001$), while in the control group they are not significant for all indicators; intergroup differences in delta changes were tested using the t-test for independent samples.

Analysis of the data presented in Table 6 demonstrates significant positive changes in most of the assessed indicators in the main group (MG) compared to the control group (CG) against the background of the rehabilitation program.

The most significant differences were noted on the MoCA scale, which reflects cognitive functions, so in the MG the average increase was +3.6 points versus +1.4 points in the CG (p=0.014), which indicates the high effectiveness of the proposed intervention in improving the cognitive status of patients. The level of pain syndrome according to the VAS scale decreased more significantly in the main group (–2.2 points) compared to the control group (–1.0 points), p=0.018. The quality of life according to the SF-36 questionnaire also improved significantly: in the MG, an increase of 11.3 points was noted, in the CG - by 6.3 points (p=0.022). Biochemical markers of inflammation and neuroplasticity also demonstrated more pronounced dynamics in the main group: the level of IL-6 decreased by 1.6 pg/ml (p=0.011), the level of BDNF increased by 2.6 ng/ml (p=0.007). Oxidative stress (MDA) and homocysteine metabolism indicators also significantly improved in the main group (Δ=–0.8 and Δ=–2.4, respectively), while in the control group the changes were less pronounced (p=0.021 and p=0.036, respectively).

Thus, the presented results confirm the statistically significant advantage of the developed comprehensive rehabilitation program compared to the standard approach.

Table 7
Efficiency of the proposed rehabilitation program (delta changes and relative improvement after 12 weeks of rehabilitation)

Indicator	Δ MG (M ± σ)	Δ CG (M ± σ)	p (intergroup)	OG efficiency, %
MoCA, points	+3.6 ± 1.5	+1.8 ± 1.2	0,008	**+16.3%** *(22.1 at the beginning)*
VAS pain scores	-2.2 ± 0.9	-1.1 ± 0.8	0,012	**-25.6%** *(8.6 at the beginning)*
SF -36, points	+9.8 ± 4.3	+5.0 ± 3.9	0,015	**+18.1%** *(~54 at the beginning)*
IL -6, pg/ml	-1.5 ± 0.7	-0.6 ± 0.8	0.004	**-31.9%** *(from 4.7 pg/ml)*
BDNF, ng/ml	+2.4 ± 1.1	+1.0 ± 0.9	0.006	**+23.1%** *(from 10.4 ng/ml)*
Homocysteine, µmol/l	-2.5 ± 1.2	-1.1 ± 1.3	0,019	**-15.8%** *(from 15.8 µmol/l)*

Table 7 presents the results of a comparative analysis of the effectiveness of the rehabilitation program through the assessment of delta changes (Δ) and relative improvement in key clinical, functional and biochemical indicators in the main (MG) and control groups (CG) after a 12-week course.

In the MG, there was a significant improvement in cognitive functions (MoCA) by +3.6 points (p=0.008), which was an increase of 16.3% compared to the baseline level (22.1 points). In the CG, the improvement was only +1.8 points.

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Pain reduction (VAS): in the MG it was -2.2 points (-25.6% from the initial value of 8.6), which is statistically significantly better than in the CG (-1.1; p=0.012). According to the quality of life (SF-36) indicator, the average increase in the MG was +9.8 points (+18.1% from the initial level of ~54), in the CG it was +5.0 points; the difference between the groups is statistically significant (p=0.015). Patients in the main group showed a significant decrease in the inflammatory marker IL-6 - by 1.5 pg/ml (-31.9% from the initial value of 4.7), in contrast to a less pronounced decrease in the CG (-0.6; p=0.004). The neurotrophic factor in the MG increased by +2.4 ng/ml (+23.1% from the initial value of 10.4), while in the CG it increased only by +1.0 ng/ml; the difference is statistically significant (p=0.006). The decrease in the homocysteine level in the MG was -2.5 μmol/l (-15.8% from 15.8), which exceeds the similar change in the CG (-1.1; p=0.019).

The obtained data indicate the high efficiency of the proposed rehabilitation program, which led to a statistically significant improvement in cognitive functions, a reduction in pain, an increase in quality of life, as well as the normalization of inflammation biomarkers and neuroregeneration.

DISCUSSION

The obtained results confirm the effectiveness of the developed complex rehabilitation program for patients with chronic cerebral ischemia stage I-II. The conducted comparative analysis between the main and control groups showed a statistically significant advantage of the intervention for most of the studied parameters.

At the initial stage of the study (see Table 3), no statistically significant differences were found between the groups in age, gender, cognitive status (assessment by the MoCA scale), severity of pain syndrome (VAS), level of proinflammatory cytokine IL-6, neurotrophic factor BDNF and homocysteine. This indicates comparability of the contingents, which increases the reliability of the results obtained.

After 12 weeks of rehabilitation, the main group showed a significant improvement in cognitive functions - the increase on the MoCA scale was on average +3.6 points, which is almost 2 times higher than in the control group (+1.8 points; p = 0.008). The relative improvement was +16.3% compared to the initial value, indicating significant neurocognitive recovery.

The level of pain syndrome decreased in the main group by 2.2 points according to VAS, while in the control group the decrease was only 1.1 points (p = 0.012), which confirms the analgesic effect of the proposed program. This is probably due to both psychoemotional stabilization and normalization of neuroinflammatory processes.

The anti-inflammatory effect is confirmed by a significant decrease in the IL-6 level in the main group (−1.5 pg/ml, p = 0.004), which in relative terms was -31.9%. At the same time, a significant increase in the concentration of the neurotrophic factor BDNF was noted (+2.4 ng/ml, p = 0.006), which indicates the activation of neuroplasticity processes and restoration of cognitive functions. Such changes are consistent with the results of studies where BDNF was considered a key biomarker of the effectiveness of neurorehabilitation (Zhou et al., 2021; Tuktarov et al., 2022).

The level of homocysteine, a known risk factor for vascular dysfunction and cognitive decline, also decreased significantly in the main group (−2.5 μmol/l versus −1.1 μmol/l in the CG, p = 0.019), which may indicate the influence of the program on the vascular component of cerebral dyscirculation.

The overall improvement in quality of life, assessed using the SF-36 scale, was more pronounced in the main group (+9.8 points versus +5.0 points in the control group, p = 0.015), which reflects the complex effect of the program on both the somatic and psychoemotional state of patients.

Thus, the proposed program demonstrated a multifactorial positive effect, combining cognitive recovery, analgesia, anti-inflammatory and metabolic effects. The results obtained can be used to optimize personalized medical rehabilitation programs for this category of patients.

CONCLUSIONS

The developed personalized program of medical rehabilitation of patients with chronic cerebral ischemia stage I–II demonstrated high clinical and biomarker effectiveness due to a comprehensive approach including neuropsychological correction, motor exercises, nutritional support and correction of vascular-metabolic disorders.

After 12 weeks of rehabilitation, the main group showed significant improvements in cognitive functions (increase in MoCA by 3.6 ± 1.5 points), quality of life (increase in SF-36 by 9.8 ± 4.3 points), decreased severity of pain syndrome (decrease in VAS by 2.2 ± 0.9 points) and neuroinflammation (decrease in IL-6 levels by 31.9%).

The intervention resulted in a significant increase in brain-derived neurotrophic factor (BDNF) levels (by 23.1%) and a decrease in homocysteine (by 15.8%), indicating a neuroprotective effect of the program and an improvement in metabolic status.

In the control group, which received standard therapy, the positive dynamics were less pronounced, which confirms the advantage of a personalized approach to rehabilitation.

The obtained data allow us to recommend the developed program as an effective rehabilitation model for CCI stages I–II, and the biomarkers IL-6, BDNF and homocysteine as objective criteria for assessing the effectiveness of the intervention.

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