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COGNITIVE IMPAIRMENT IN CHRONIC CEREBRAL ISCHEMIA AND THE POTENTIAL OF NEUROPROTECTIVE PEPTIDE-BASED THERAPY

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Abstract.
Background. Chronic cerebral ischemia (CCI) is one of the leading causes of vascular cognitive impairment, resulting in progressive decline in cognitive functions, reduced quality of life, and increased risk of vascular dementia. Moderate cognitive impairment represents a clinically significant stage characterized by partial reversibility of neuronal dysfunction.
Objective. To evaluate cognitive impairment in patients with stage II chronic cerebral ischemia and to assess the effects of peptide-based neuroprotective therapy with Cortexin on cognitive outcomes.
Materials and Methods. Twenty patients with stage II CCI and moderate cognitive impairment were enrolled. Diagnosis was based on A.I. Fedin's classification and neuroimaging findings (CT/MRI). Cognitive functions were assessed using the MMSE and MoCA scales. In addition to standard therapy, patients received Cortexin 10 mg intramuscularly twice daily for 10 days.
Results. Cognitive improvement was observed following therapy, with more pronounced effects in younger patients. Cortexin demonstrated good tolerability and no significant adverse events.
Conclusions. Cortexin may be considered an effective and safe component of комплексной therapy for cognitive impairment associated with chronic cerebral ischemia, particularly at early stages of cognitive decline.
Keywords: chronic cerebral ischemia, cognitive impairment, vascular cognitive disorders, Cortexin, neuroprotection.

КОГНИТИВНЫЕ НАРУШЕНИЯ ПРИ ХРОНИЧЕСКОЙ ИШЕМИИ ГОЛОВНОГО МОЗГА И ВОЗМОЖНОСТИ ИХ МЕДИКАМЕНТОЗНОЙ КОРРЕКЦИИ НЕЙРОПЕПТИДНОЙ ТЕРАПИЕЙ

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Аннотация.
Актуальность. Хроническая ишемия головного мозга (ХИГМ) является одной из ведущих причин развития когнитивных нарушений сосудистого генеза, приводящих к снижению качества жизни, социальной дезадаптации и прогрессированию сосудистой деменции. Особый клинический интерес представляет стадия умеренных когнитивных расстройств, при которой сохраняется потенциальная обратимость нейрональной дисфункции.
Цель исследования. Изучить особенности когнитивных нарушений у пациентов с ХИГМ II стадии и оценить влияние нейропептидного препарата кортексин на динамику когнитивных функций при курсовом применении.
Материалы и методы. В исследование включены 20 пациентов с ХИГМ II стадии и умеренными когнитивными расстройствами. Диагноз устанавливался на основании клинической классификации А.И. Федина и данных КТ/МРТ. Когнитивный статус

оценивался с использованием шкал MMSE и MoCA. На фоне стандартной терапии пациенты получали кортексин в дозе 10 мг дважды в сутки внутримышечно в течение 10 дней. **Результаты.** Установлено достоверное улучшение когнитивных показателей после курса терапии, более выраженное у пациентов младшего возраста. Препарат продемонстрировал хорошую переносимость и отсутствие клинически значимых побочных эффектов. **Выводы.** Кортексин является эффективным и безопасным компонентом комплексной терапии когнитивных нарушений при хронической ишемии головного мозга, особенно на ранних этапах когнитивного дефицита.
Ключевые слова: хроническая ишемия головного мозга, когнитивные нарушения, сосудистая когнитивная дисфункция, кортексин, нейропротекция.

SURUNKALI MIYA ISHEMIYASIDA KOGNITIV BUZILISHLAR VA ULARNI NEYROPEPTID ASOSIDAGI DORI VOSITALARI BILAN KORREKSIYA QILISH IMKONIYATLARI

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Annotatsiya.
Dolzarbligi. Surunkali miya ishemiyasi (SMI) tomirli kelib chiqishga ega kognitiv buzilishlarning asosiy sabablaridan biri bo‘lib, u aqliy faoliyatning pasayishi, hayot sifati yomonlashuvi va vaskulyar demensiya rivojlanishi bilan kechadi. O‘rtacha darajadagi kognitiv buzilishlar bosqichi klinik jihatdan muhim bo‘lib, bu davrda neyronal funksiyalarning qisman qaytuvchanligi saqlanadi. **Tadqiqot maqsadi.** SMI II bosqichli bemorlarda kognitiv buzilishlarni o‘rganish va кортексин preparatining kognitiv funksiyalar dinamikasiga ta’sirini baholash. **Material va usullar.** Tadqiqotga SMI II bosqichli va o‘rtacha kognitiv buzilishlari bo‘lgan 20 nafar bemor kiritildi. Tashxis A.I. Fedin tasnifi va KT/MRT ma’lumotlari asosida qo‘yildi. Kognitiv holat MMSE va MoCA shkalalari yordamida baholandi. Asosiy terapiya fonida bemorlarga кортексин 10 mg dan kuniga ikki mahal mushak ichiga 10 kun davomida yuborildi. **Natijalar.** Davolashdan so‘ng kognitiv ko‘rsatkichlarning yaxshilanishi kuzatildi, ayniqsa yosh bemorlarda yaqqolroq namoyon bo‘ldi. Preparat yaxshi o‘zlashtirildi va nojo‘ya ta’sirlar aniqlanmadi.
Xulosa. Кортексин surunkali miya ishemiyasida kognitiv buzilishlarni kompleks davolashda samarali va xavfsiz dori vositasi hisoblanadi.
Kalit so‘zlar: surunkali miya ishemiyasi, kognitiv buzilishlar, tomirli kognitiv disfunktsiya, кортексин, neyroproteksiya.

Introduction. Chronic cerebral ischemia (CCI), also referred to in the post-Soviet neurological tradition as discirculatory encephalopathy, remains one of the most prevalent and socially significant neurological syndromes in middle-aged and elderly populations. It represents a progressive cerebrovascular disorder caused by long-standing insufficiency of cerebral blood flow, leading to diffuse and multifocal ischemic damage of the brain parenchyma. The clinical importance of CCI lies not only in its high prevalence but also in its role as a major etiological substrate for ischemic stroke, vascular dementia, and persistent neurological disability [1,2]. Among the wide spectrum of clinical manifestations of CCI, cognitive impairment occupies a central position. Cognitive disorders in chronic cerebral ischemia range from mild cognitive impairment to severe vascular dementia and often precede overt focal neurological deficits. These impairments typically affect attention, executive functions, processing speed, memory, and visuospatial abilities, reflecting the predominant involvement of subcortical-frontal circuits and diffuse white matter pathology [3,4]. Importantly, cognitive decline in CCI is frequently underestimated in routine clinical practice,

especially in patients without a history of stroke, despite its substantial impact on quality of life, social functioning, and treatment adherence.

From a pathophysiological standpoint, cognitive impairment in CCI results from a complex interaction of chronic hypoperfusion, endothelial dysfunction, blood–brain barrier disruption, neuroinflammation, oxidative stress, mitochondrial dysfunction, and progressive neuronal apoptosis [5]. Structural neuroimaging studies consistently demonstrate leukoaraiosis, lacunar infarcts, cortical and subcortical atrophy, and microangiopathic changes, which correlate with the severity of cognitive deficits [6]. Functional neuroimaging further reveals impaired connectivity within large-scale cognitive networks, particularly the default mode and executive control networks [7]. Given the multifactorial mechanisms underlying cognitive impairment in CCI, therapeutic strategies aimed solely at correcting systemic hemodynamic factors are often insufficient. Modern neurological practice increasingly emphasizes the need for pathogenetically grounded neuroprotective and neurometabolic interventions capable of modulating neuronal survival, synaptic plasticity, and neurotrophic support [8]. In this context, peptide-based neuroprotectors have attracted considerable interest.

Cortexin is a complex of low-molecular-weight polypeptides derived from the cerebral cortex of cattle, capable of crossing the blood–brain barrier and exerting multimodal effects on the central nervous system. Experimental and clinical studies indicate that Cortexin demonstrates neuroprotective, antioxidant, antihypoxic, neurometabolic, and neurotrophic properties [9,10]. The drug modulates the balance of excitatory and inhibitory neurotransmitters, stabilizes neuronal membranes, reduces glutamate-induced excitotoxicity, and enhances the expression of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) [11]. Despite the long-standing use of Cortexin in neurological practice across Eastern Europe and Central Asia, questions remain regarding the optimal dosing regimens, duration of therapy, and its specific impact on cognitive domains in patients with different stages of chronic cerebral ischemia. Of particular interest is the potential benefit of repeated or long-term course therapy in patients with moderate cognitive impairment, a stage at which therapeutic interventions may still significantly alter the trajectory of cognitive decline. The present study was conducted at the Department of Neurology of Samarkand State Medical University and aimed to investigate the characteristics of cognitive impairment in patients with stage II chronic cerebral ischemia and to assess the effects of Cortexin administered as part of long-term course-based neuroprotective therapy on cognitive outcomes.

Aim of the Study. The aim of this study was to evaluate cognitive impairment in patients with stage II chronic cerebral ischemia and to analyze the influence of Cortexin on cognitive functions when administered at a dose of 10 mg twice daily intramuscularly for 10 days, in combination with standard therapy, with repeated courses during follow-up.

Materials and Methods. A prospective observational clinical study was conducted at the Department of Neurology, Samarkand State Medical University. The study protocol was developed in accordance with institutional clinical research standards and conformed to the principles of the Declaration of Helsinki. All patients provided informed consent prior to participation. The study included 20 patients diagnosed with stage II chronic cerebral ischemia accompanied by moderate cognitive impairment. The cohort consisted of 5 men (25%) and 15 women (75%). The mean age of the patients was 62.4 years. Diagnosis of chronic cerebral ischemia was established based on the clinical classification proposed by A.I. Fedin (2016), taking into account clinical presentation, neurological examination findings, and neuroimaging data obtained from computed tomography and magnetic resonance imaging of the brain [12]. All patients demonstrated neuroimaging signs consistent with chronic cerebrovascular pathology, including diffuse white matter changes, periventricular leukoaraiosis, lacunar post-ischemic lesions, and cortical-subcortical atrophy of varying severity. Patients with a history of acute stroke within the previous six months, neurodegenerative diseases, severe psychiatric disorders, or decompensated somatic pathology were excluded from the study.

The majority of patients had multiple vascular risk factors. Arterial hypertension was present in most cases, often in combination with cerebral atherosclerosis and metabolic disorders. In 25% of patients, a history of vertebrobasilar insufficiency was documented. Another 25% of patients

demonstrated a combination of arterial hypertension, atherosclerosis, and diabetes mellitus. In 50% of cases, arterial hypertension coexisted with cerebral atherosclerosis without diabetes.

Table 1. Baseline Clinical Characteristics of Patients with Chronic Cerebral Ischemia (n = 20)

Parameter	Value
Mean age (years)	62.4
Male / Female	5 / 15
Arterial hypertension	75%
Cerebral atherosclerosis	75%
Diabetes mellitus	25%
Vertebrobasilar insufficiency	25%
Combined vascular risk factors	50%

Cognitive functions were assessed using standardized neuropsychological tools widely applied in clinical neurology. The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were administered at baseline and during follow-up visits. Moderate cognitive impairment was defined as MMSE scores below 25 and MoCA scores below 24, in accordance with accepted diagnostic thresholds [13,14]. Neuropsychological testing focused on global cognitive status as well as domains typically affected in vascular cognitive impairment, including attention, executive functioning, memory, and visuospatial abilities. All assessments were performed by trained neurologists to ensure consistency.

All patients received standard therapy for chronic cerebral ischemia according to current medical and economic standards of care. This included antihypertensive therapy, antiplatelet agents, lipid-lowering drugs, and metabolic support as indicated. In addition to baseline therapy, patients received Cortexin at a dose of 10 mg intramuscularly twice daily (morning and midday) for 10 consecutive days. The drug was administered as part of a course-based neuroprotective regimen. Patients were monitored for adverse events throughout the treatment period and during follow-up. Given the exploratory nature of the study and the limited sample size, statistical analysis focused on descriptive statistics and comparative evaluation of cognitive scores before and after treatment. Changes in MMSE and MoCA scores were analyzed in relation to age groups to assess age-dependent treatment effects.

Results. At baseline, all patients demonstrated moderate cognitive impairment. MMSE scores ranged below 25, while MoCA scores were consistently below 24. Cognitive deficits were most pronounced in domains of attention, executive control, and short-term memory, consistent with subcortical-frontal dysfunction characteristic of chronic cerebral ischemia. Following the first course of Cortexin therapy administered in combination with standard treatment, a positive trend in cognitive performance was observed in the majority of patients. Improvement was evident as early as the first scheduled follow-up visit. Patients younger than 50 years demonstrated more pronounced cognitive improvement compared to older patients. In this subgroup, MMSE scores increased to 26–27 points, while MoCA scores reached 24 points. In patients older than 50 years, improvement was present but less marked, with MMSE scores reaching approximately 25 points and MoCA scores increasing to 23 points.

Table 2. Dynamics of Cognitive Scores After Cortexin Therapy

Age group	MMSE (baseline)	MMSE (post-treatment)	MoCA (baseline)	MoCA (post-treatment)
≤ 50 years	<25	26–27	<24	24
> 50 years	<25	~25	<24	23

These findings suggest that cognitive impairment at earlier stages and in younger patients demonstrates greater reversibility and responsiveness to neuroprotective therapy. Cortexin was well tolerated by all patients. No allergic reactions, clinically significant adverse effects, or exacerbation of concomitant somatic diseases were recorded. General clinical status remained stable throughout the treatment and follow-up periods.

Discussion. The results of this study confirm the high prevalence and clinical significance of cognitive impairment in patients with stage II chronic cerebral ischemia. Even in the absence of overt dementia, moderate cognitive deficits substantially affect daily functioning and represent a critical therapeutic target. The observed improvement in cognitive scores following Cortexin therapy may be explained by the drug's multimodal mechanism of action. By enhancing neuronal metabolism, reducing oxidative stress, and modulating neurotrophic signaling pathways, Cortexin appears to improve synaptic efficiency and functional connectivity within cognitive networks [9,11]. The greater therapeutic response observed in younger patients and at earlier stages of cognitive decline supports the concept of a "therapeutic window" during which neuroprotective interventions are most effective [15]. Our findings are consistent with previously published data indicating the beneficial effects of peptide neuroprotectors in vascular cognitive impairment [16]. However, the present study emphasizes the importance of course-based therapy and integration with standard vascular risk management. Limitations of the study include the small sample size and the absence of a control group, which restricts the generalizability of the results. Nevertheless, the consistency of cognitive improvement and the favorable safety profile warrant further investigation in larger, controlled trials.

Conclusions. Cognitive impairment represents a core clinical manifestation of chronic cerebral ischemia and requires early identification and targeted therapy. The use of Cortexin as part of комплексной терапии in patients with stage II chronic cerebral ischemia at a dose of 10 mg twice daily intramuscularly for 10 days demonstrates a positive effect on cognitive dynamics, particularly in patients at earlier stages of impairment. The drug is well tolerated and can be recommended as a component of pathogenetically oriented treatment strategies aimed at slowing cognitive decline and improving quality of life.

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