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INFLUENCE OF SLEEP DISTURBANCE ON COGNITIVE FUNCTIONS IN CHRONIC CEREBRAL ISCHEMIA AND ITS CORRECTION

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ANNOTATION

Chronic cerebral ischemia (CCI) accounts for almost 2/3 of cerebrovascular diseases and causes cognitive impairment. In our article, we studied the influence of sleep disorders on cognitive functions. Patients took the drug melatonin to correct sleep disorders. 63 patients with CCI were examined. The mean age of the patients was 58.5±1.4 years. Patients were divided into 6 groups depending on the presence of sleep disorders and the stage of CCI disease. Sleep disorders and cognitive impairment were assessed using special questionnaires; in addition, the cognitive evoked potentials of P300 were studied. With an increase in the stage of CCI, cognitive indicators worsened according to the scales and parameters of cognitive evoked potentials P300. In patients with sleep disorders, there was a tendency to worsen sleep parameters according to the Epworth scale with an increase in CCI. In patients with CCI, sleep disturbances worsen cognitive functions. When treated with melatonin in patients with CCI, both sleep disorders and cognitive impairment improved.

Keywords: sleep disturbances, cognitive impairments, cognitive evoked potentials, chronic cerebral ischemia, melatonin.

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ВЛИЯНИЕ НАРУШЕНИЯ СНА И ИХ КОРРЕКЦИЯ НА КОГНИТИВНЫЕ ФУНКЦИИ ХРОНИЧЕСКОЙ ЦЕРЕБРАЛЬНОЙ ИШЕМИИ

АННОТАЦИЯ

Хроническая церебральная ишемия (ХЦИ) составляет почти 2/3 цереброваскулярных заболеваний и вызывает когнитивные нарушения. В нашей статье мы изучили влияние нарушений сна на когнитивные функции. Для коррекции нарушений сна пациенты принимали препарат мелатонин. Было обследовано 63 пациента с ХЦИ. Средний возраст пациентов составил 58,5±1,4 года. Пациенты были разделены на 6 групп в зависимости от наличия нарушений сна и стадии заболевания ХЦИ. Расстройства сна и когнитивные нарушения оценивались с помощью специальных опросников, кроме того, исследовались когнитивные вызванные потенциалы P300. С увеличением стадии ХЦИ ухудшались когнитивные показатели по шкалам и параметрам когнитивных вызванных потенциалов P300. У пациентов с нарушениями сна наблюдалась тенденция к ухудшению параметров сна по шкале Epworth с увеличением стадии ХЦИ. У пациентов с ХЦИ нарушения сна ухудшают когнитивные функции. При лечении мелатонином у пациентов с ХЦИ улучшались как нарушения сна, так и когнитивные нарушения.

Ключевые слова: нарушения сна, когнитивные нарушения, когнитивные вызванные потенциалы, хроническая церебральная ишемия, мелатонин.

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SURUNKALI MIYA ISHEMIYASIDA UYQU BUZILISHINING KOGNITIV FUNKTSIYALARGA TA'SIRI VA UNI KORREKSIYASI

ANNOTATSIYA

Surunkali miya ishemiyasi (SMI) serebrovaskulyar kasalliklarning deyarli 2/3 qismini tashkil qiladi va kognitiv buzilishlarni keltirib chiqaradi. Maqolamizda biz uyqu buzilishlarining kognitiv funktsiyalarga ta'sirini o'rgandik. Bemorlar uyqu buzilishlarini tuzatish uchun melatonin preparatini qabul qilishdi. SMI bilan kasallangan 63 bemor tekshirildi. Bemorlarning o'rtacha yoshi 58,5, 1,4 yoshni tashkil etdi. Bemorlar uyqu buzilishining mavjudligi va surunkali miya ishemiyasi kasalligining bosqichiga qarab 6 guruhga bo'lingan. Uyquning buzilishi va kognitiv buzilish maxsus anketalar yordamida baholandi; bundan tashqari, P300 ning kognitiv potentsiallari o'rganildi. SMI bosqichining oshishi bilan kognitiv ko'rsatkichlar P300 kognitiv uyg'otadigan potentsiallarning tarozi va parametrlariga muvofiq yomonlashdi. Uyqu buzilishi bo'lgan bemorlarda SMIning ko'payishi bilan Epvort shkalasi bo'yicha uyqu parametrlarini yomonlashtirish tendentsiyasi mavjud edi. SMI bilan og'rigan bemorlarda uyqu buzilishi kognitiv funktsiyalarni yomonlashtiradi. SMI bilan og'rigan bemorlarda melatonin bilan davolashda uyqu buzilishi ham, kognitiv buzilish ham yaxshilandi.

Kalit so'zlar: uyqu buzilishi, kognitiv buzilishlar, kognitiv uyg'otuvchi potentsial, surunkali miya ishemiyasi, melatonin.

Introduction

According to the World Health Organization (WHO), most of the world's population has a life expectancy of over 60 years. According to WHO estimates, by 2050 the number of people over 60 in the world population will reach 2 billion [24]. Currently, with the increase in life expectancy of people, cerebrovascular diseases also increase.

Currently, among the cerebrovascular diseases that cause a decrease in cognitive activity, chronic cerebral ischemia (CCI) is the most common, accounting for almost 2/3 of all cerebrovascular diseases. [1]. In CCI, multifocal or diffuse ischemic lesions develop in the brain, manifesting themselves as a complex neurological and neopsychological lesion and tending to gradually increase [7]. Cognitive impairment (CI) of mild and moderate severity may be an early sign of CCI [17, 14, 16, 23]. The study of CI is carried out by the ERP R300 method. The temporal-limbic and stem-reticular structures take an active part in realizing the P300 potential [8, 5].

Normative values of P300 vary depending on age. At the same time, from the age of 7 to 18-20 years, the speed of passage of impulses increases and the latency of P300 decreases, and then the latency of P300 increases. In this case, the latent period of P300 increases by 1.25 ms per year, while the amplitude decreases by 0.1 mV [3, 12]. This decrease is explained primarily by the thinning of the myelin sheath and [6] at the same time by the reduction of dendrites in the process of natural aging, a decrease in the density of synaptic connections [3, 4]. The P300 method has a number of advantages in the objective assessment of the process and is important in the early detection of cognitive disorders. Using this method, it is useful to distinguish between cognitive impairment, dementia, and other functional changes [10, 18, 19]. An association between P300 and sleep disorders has been noted in several studies [10, 11, 22] .

In CCI, also reveals sleep disturbances. Of great interest is the problem of the relationship between dissomnic disorders and the development of CCI. It has been established that with age, sleep disorders occur in an increasing number of people. [24,25,26]. According to the results of a number of epidemiological studies, 30% of people in all age groups of the population have problems with sleep; about 95% of people over 60 years of age have various problems with sleep. Symptoms of insomnia occur three times a week in 16-21% of cases, in 10-28% of cases these symptoms are expressed, 8-18% are dissatisfied with their sleep. Every fourth elderly patient often or constantly takes sleeping pills [2,9,13,16,15]. The causal relationship between cognitive impairment and sleep disturbance in CCI is complex and varied. On the one hand, sleep disorders can stimulate cerebrovascular disorders, and, on the other hand, CCI causes changes in the duration and structure of sleep [19].

It is assumed that the age-related decrease in the level of melatonin secretion plays a role in the development of the mentioned sleep disorders and in itself can be the cause of a number of disorders characteristic of old age with damage to the brain, internal organs, the immune system, and the development of oncological diseases. Results from some investigators in patients treated with melatonin (3 mg) with CCI show positive changes in CI over 24 days [27].

Purpose of research: Study of cognitive changes in patients with sleep disorders in CCI by method ERP P300 and evaluation of the effect of melatonin on its correction.

Research materials and methodology:63 patients (36 men and 27 women) were examined. The mean age of the patients was 58.5±1.4 years. Patients were first divided into two groups depending on the presence of sleep disorders, and then these two groups were further divided into three subgroups depending on the stage of CCI.

Table 1.

Patients with sleep disorders 1st group

	Characteristics of groups	Female	Male	Average 58.8±1.4
1	CCI 1st stage	n=3	n=7	53.3±1.7
2	CCI 2nd stage	n=5	n=6	60.8±1.6
3	CCI 3rd stage	n=6	n=7	61.5±1.1

Table 2.

Patients without sleep disorders 2nd group

	Characteristics of groups	Female	Male	Average 58.2±1.2
1	CCI 1st stage	n=3	n=7	54.3±1.0
2	CCI 2nd stage	n=5	n=5	59.8±1.2
3	CCI 3rd stage	n=6	n=4	60.5±1.3

Epworth Sleepiness Scale (ESS) to assess daytime sleepiness. The questionnaire assessed the level of daytime sleepiness in the range from 0 to 24 points (0-7 - no daytime sleepiness, 8-9 points - mild daytime sleepiness, 10-15 points - moderate daytime sleepiness; 15-20 points - high daytime sleepiness, 20 points and above - severe daytime sleepiness). [16].

The MMSE and MOCA questionnaires were used to assess cognitive activity [19]. It was assessed on the MMSE scale: orientation in time and space, repetition of words, serial calculation, repetition of

previously spoken words, naming of objects, repetition of complex phrases, execution of commands, understanding of written speech, free phrase speech, copying of geometric figures. The maximum total score is 30 points, which means no cognitive deficit. 24-27 points indicate mild cognitive impairment, 20-24 points are interpreted as mild dementia, 11-19 points mean dementia, 0-10 points mean severe dementia.

The Montreal Scale of Cognitive Function Assessment (MOCA) is better calculated than the MMSE scale in detecting moderate cognitive impairment. The maximum score is 30 points. A score below 26 points indicates mild impairment (19-25 points) and dementia is considered (11-21 points) [28].

Neuro-MEP 4 (Neurosoft, Russia) is used in the Neurological Clinic "General Med Standart" for direct cognitive activity of patients using the instrumental diagnostic method. The methodology of R300 research is based on the "odd point" paradigm, where two stimuli are presented in random order, among which are "insignificant" (often) and "significant" (rare) stimuli, which are the following results. Stimulation in the form of a random event in response to auditory stimuli was used to register ERP. Auditory stimuli were used in the form of clicks with a frequency of 1000 Hz for insignificant stimuli and a probability of 70–80%, for significant stimuli, 2000 Hz and a probability of 20–30%. The duration of the stimuli was 50 ms, the intensity was 80 dB, and the period between stimuli was 1 s. Binaural stimulation was used. The epoch of analysis is 750–1000 ms. The number of averages is 30–70 separately for significant and insignificant stimuli. Frequency band – 0.5–30 Hz. Responses to significant stimuli were of clinical importance. First, the P300 component was verified by comparing responses to significant and non-significant stimuli. Responses to a significant stimulus had mid-latency components in response to the stimulus itself and then directly to the P300 cognitive complex itself. After the components were verified, the latency of the P300 component were evaluated.

All patients took melatonin at a dose of 3 mg for 1 month and their cognitive functions assessed. For statistical analysis, parametric and non-parametric methods used, depending on the nature of the data. The given indicators are as the arithmetic mean and standard deviation (M±m). When systematizing and statistical processing, $p<0.05$ was taken as significance.

Results: During the examination, all patients were divided into groups depending on the presence of sleep disorders and the stage of CCI disease, and the results were analyzed.

The most common cause of CCI in the group of patients without sleep disorders was atherosclerosis (45.4%, n=15), less often arterial hypertension (39.4%, n=13) and their combination (27.3%, n=9). In the group of patients with sleep disorders, the most common cause of CCI was atherosclerosis (40.0%, n=12), less often arterial hypertension (33.3%, n=10), type 2 diabetes mellitus (16.7%, n=5), and their combination (10.0%, n=3).

Patients with sleep disorders: When studying daytime sleepiness according to the Epworth questionnaire in patients with CCI 1 stage indicators of the upper limit of the normal range for this scale were revealed, with a deterioration of two and two and a half times in patients with CCI of the second and third stages, respectively ($p<0.05$). After a month of therapy with melatonin, the results showed significant ($p<0.05$) positive dynamics detected in the groups of CCI of the 2nd and 3rd stages of disease (Table 3).

Table 3.

The results of daytime sleepiness in patients with sleep disorders on the Epworth scale

Before treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage	After treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage
Epworth scale (points)	7.1 ± 0.7	14.2 ± 1.0 *	17.7 ± 0.3 ●○		6.8 ±0.1	12.1 ±0.5	13.4 ±0.5

note: *-$p<0.05$ – for groups CCI 1st stage and CCI 2nd stage; ●-$p<0.05$ - for groups CCI 1st stage and CCI 3rd stage; ○-$p<0.05$ - for the CCI 2nd stage and CCI 3rd stage.

According to the Montreal Cognitive Function Scale (MOCA), patients with CCI at the first stage had normal values, while patients with CCI at the second and third stages had moderate CI, while the level of CI increased with increasing stage of the disease. According to the MMSE scale, patients with CCI of the first and second stages scored the same scores, while in patients with CCI of the third stage, the scores scored were significantly worse, which correlated with the data obtained from the MOCA test (see Table 4)

Table 4.

Results cognitive impairment in patients with sleep disorder by MMSE questionnaire and by ERP P300

Before treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage	After treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage
MMSE	25.2±0.4	25.0±0.5*	21.9±0.9 ●○		27.1±0.1	26.2±0.3	24.1±1.0*
MOCA	28.0±0.5	26.3±0.4*	20.8±0.3 ●○		28.2±0.2	26.8±0.2	22.9±0.8
P300 Latency	348.1 ±15.4	375 .0 ±17.2 *	382.0 ±16.3 ●		342.7 ±5.7	368 ±11.2*	378 ±9.6

note: *-$p<0.05$ – for groups CCI 1st stage and CCI 2nd stage; ●-$p<0.05$ - for groups CCI 1st stage and CCI 3rd stage; ○-$p<0.05$ - for the CCI 2nd stage and CCI 3rd stage.

In the study of ERP P300 in patients with CCI of the first stage, the latency of the P300 peak were within the normative values, while in patients with CCI of the second stage, an increase in latency of P300 were detected, and in patients with CCI of the 3rd stage, the indicators were significantly worse than the standard values ($p<0.05$). After correcting sleep disorders with melatonin, patients experienced an improvement, they noted positive changes in their memory ability. These changes were also revealed in a decrease in the latency of ERP P300 (Table 4).

Patients without sleep disorders

When analyzing indicators on the Epworth scale in patients with CCI without sleep disorders after melatonin therapy, it was revealed that there was a slight improvement in all groups (Table 5).

Table 5.

Results daytime sleepiness of patients without sleep disorders by Epworth scale

Before treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage	After treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage
Epworth scale (points)	2.7 ± 0.7	3.5 ± 1.0 *	4. 1 ± 0.3 ●○		2.6 ±0.3	3.4 ±0.8	4.0 ± 0.5

note: *-p<0.05 – for groups CCI 1st stage and CCI 2nd stage; ●-p<0.05 - for groups CCI 1st stage and CCI 3rd stage; ○-p<0.05 - for the CCI 2nd stage and CCI 3rd stage.

When studied the CI of patients with CCI without sleep disturbance using a questionnaire (MMSE and MOCA), the data obtained indicate that patients with CCI of the 1st stage had borderline normative indicators, and patients with CCI of the 2nd and 3rd groups had moderate cognitive changes, and sleep disturbances compared with stage 1 patients. After 1 month of taking melatonin, the study of ERP P300 in patients revealed a shortening of the latent periods in all groups, which indicates an improvement in cognitive functions.

Table 6.

Results cognitive impairment in patients without sleep disorder by MMSE questionnaire and by ERP P300

Before treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage	After treatment	CCI 1st stage	CCI 2nd stage	CCI 3rd stage
MMSE	27.2 ± 0.4	26.0 ±0.5*	23.9 ±0.9 ●○		27.7 ± 0.5	27.5 ± 0.8	26.1 ± 0.1
MOCA	28.0 ± 0.5	26.3 ±0.4*	23.8 ±0.3 ●○		28.3 ± 0.1	27.4 ± 0.6	25.6 ± 0.3
P300	340.1	368.0	375.0		339.4	360.5	367.1
Latency	±10.4	±9.2*	±12.3 ●		±9.8	±6.4	± 9.8

note: *-p<0.05 – for groups CCI 1st stage and CCI 2nd stage; ●-p<0.05 - for groups CCI 1st stage and CCI 3rd stage; ○-p<0.05 - for the CCI 2nd stage and CCI 3rd stage

CONCLUSIONS:

1. As the CCI level increases, the cognitive indicators increase according to questionnaires and cognitive evoked potential P300 (latency);

2. In patients with sleep disorders, it was found that with increasing CCI disease stage, indicators on the Epworth scale have a tendency to worsen;

3. Sleep disturbance in CCI patients leads to deterioration of cognitive performance.

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