

CLINICAL RESEARCH

Study of the Cognitive Evoked Potentials and Bioelectrical Brain Activity in Patients with Mild Cognitive Impairment Associated with Chronic Cerebral Ischemia

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Abstract

Chronic cerebral ischemia (CCI), as a manifestation of age-related pathology shows strong parameters of the morbidity rate among the elderly. Cognitive impairments are one of main expressions of this pathology. **The aim** of this study was to evaluate the neurophysiological parameters of the cognitive impairments in patients with various stages of discirculatory encephalopathy (DE) in the comparative aspect. The cognitive functions were studied in 60 patients (main group) possessing various degrees of CCI (stages I-III DE) on a comparative basis. Among them, 20 patients had stage I DE (Group 1), 22 patients had stage II DE (Group 2), and 18 patients had stage III DE (Group 3). The control group included 15 volunteers of comparable age without any manifestations of CCI. The mean age was 62.4±12.4 years. The etiological factors of DE in our observations were arterial hypertension and atherosclerosis of the cerebral vessels, without occlusion of the major artery of head. Based on the neuropsychological tests in 49 patients (81.6%) of the main group, we found cognitive impairments in various degrees of severity. Normal age-related memory loss was observed in 14.9% while mild cognitive impairment (MCI) was seen in 66.7% of the cases. Among the types of MCI, the disregulatory type was observed in 51.6% of patients with stage II-III DE, and the combined type was observed in 45.4% of patients with stage III DE. The EEG-pattern in patients with DE has some peculiarities that are expressed in the predominance of rhythmic slow wave activity and the reduction in the coherence of alpha rhythmic activity that results in a consequent disturbance of the integrated brain activity. Changes in cognitive evoked potentials (CEP P300) were expressed in the shortening of P300 peak latency and an increase in P300 peak amplitude and consequently, a reduction the latency/amplitude ratio in patients having MCI associated with DE.

Keywords: chronic cerebral ischemia; mild cognitive impairment; cognitive evoked potentials.

Introduction

Chronic cerebral ischemia (CCI), as a manifestation of age-related pathology shows strong parameters of the morbidity rate among the elderly. Cognitive impairments are one of main expressions of this pathology. As this is a reflection of the state of the community as a whole, from this perspective, this problem acquires a medico-social character. Cognitive impairments occur in a wide spectrum ranging from normal ageing to dementia. Scientists, today, evince great interest, neurologists in particular, in detecting the early appearances of cognitive impairments, and specifically, mild cognitive impairment (MCI) which represents a stage of cognitive impairments, prior to reaching the stage of dementia; however, they exceed the limits of the age norm. The

construct of mild cognitive impairment (MCI) has been proposed to designate an early, but abnormal, state of cognitive impairment [1]. As noted above, MCI occurs more often in patients with CCI and discirculatory encephalopathy (DE), stages I, II, and III [2-6].

The onset of memory loss complaints in elderly patients is a very important feature in the diagnosis of MCI. Investigations conducted in Russia revealed that only 17% of patients studied using the MMSE test (Mini-Mental Study Examination) had cognitive impairments within the age-related norms, 52% of patients had MCI and 30% showed dementia [3,7-9]. This enabled us to confirm that the frequency of MCI in the structure of the cognitive impairments in the elderly accounts for more than one-half of all the cases. Most cases revealed the transformation of MCI into dementia in a continuously increasing number of patients with MCI. According to some authors, this was indicative of the importance of studying this problem [3,5,8,10-13].

According to the data of the Canadian Study of Health and Aging, the rate of the incidence of MCI accounted for 11-17% among the old and senile. The date of this investigation showed

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that the risk of development of MCI occurred at 65 years of age and older; during one year it was 5%, whereas during four years of follow-up it rose to 19% [14]. The frequency rate of MCI associated with CCI accounts for about 10% in patients between 70 and 90 years, in 50% of patients with internal carotid artery occlusion, and in 70% of patients having previously suffered a stroke [13,14].

The progressive amnesic disorders appear to be the most frequent expressions of MCI. As a rule, they can combine with changes in the other cognitive spheres or remain isolated. Based on the neuropsychological profiles that R. Petersen [1] described four main types of MCI can be distinguished, which may be the predictors of some specific neurodegenerative diseases:

1. Amnesic MCI Single Domain (a-MCI-single domain)-isolated memory impairment; a-MCI-single domain often progresses to Alzheimer's disease.

2. Amnesic MCI Multiple Domain (a-MCI-multiple domain) - two or more cognitive domains are impaired, one of which is memory impairment; a-MCI-multiple domain is a predictor of vascular dementia, disease of Lewy bodies.

3. Non-Amnesic MCI Single Domain (na-MCI-single domain) - impairment in a single domain other than memory; na-MCI-single domain is a predictor of frontal-temporal dementia.

4. Non-Amnesic MCI Multiple Domain (na-MCI-multiple domain) - impairments in two or more domains but other than memory; na-MCI-multiple domain is a very rare subtype and a predictor of primary progressive aphasia.

The diagnosis of MCI, as a rule, is rather complicated, and it caused by several factors. For example, on neuropsychological testing, the parameters may be changed due to the effect of factors such as the education level of the patient, main disease duration and diagnostic sensitivity of this test during the identification of MCI. For example, some tests are insufficiently informative in the diagnosis of early forms of cognitive impairments. Cognitive evoked potential (CEP) is an important description of brain cognitive function. We selected CEP because it enables us to estimate the endogenous events occurring in the brain connected to the recognition and memorizing of the stimuli showed, in MCI patients.

The aim of this study was to evaluate the neurophysiological parameters of the cognitive impairments in patients with various stages of discirculatory encephalopathy in the comparative aspect.

Material and Methods

The cognitive functions were studied in 60 patients (main group) possessing various degrees of CCI (stages I-III DE) on a comparative basis. Among them, 20 patients had stage I DE (Group 1), 22 patients had stage II DE (Groupe 2), and 18 patients had stage III DE (Group 3). The control group included 15 volunteers of comparable age without any manifestations of CCI. The mean age was 62.4±12.4 years.

The etiological factors of DE in our observations were arterial hypertension and atherosclerosis of the cerebral vessels, without occlusion of the major artery of head.

Distribution of the patients based on the degree of cognitive defect was done in line with the classification of O.S. Levin

(2010), according to which there are different forms of MCI, as follows:

- amnesic type with the characteristic defect of episodic memory connected to the defect of memorizing (defect of perception, mediated memorizing and recognition) [4,14,15]; in the test for the free and directed verbal associations, a decrease in semantic speech activity was also possible;

- disregulatory (frontal) type, characterized by the prevalence of frontal lobe dysfunction, which may be connected to the primary pathology of the frontal cortex or is secondary in relation to the pathology of the deep structures (subcortical-frontal syndrome); in this type, a secondary decline of memory with a defect in perception is noted, however, with preservation of recognition and memorizing; the decrease in speech activity (especially a reduction in the number of phonetic associations) is also typical;

- the combined (multifunctional) type of MCI characterized by the association of the amnesic syndrome of the hippocampal type (with impairment of perception and recognition) with impairment of the regulatory or other cognitive functions;

- MCI with prevailing impairment of any other cognitive sphere, for example, visual-spatial or speech (*dysphasia*) impairments.

The diagnosis of DE was verified by the presence of the background disease (in our observations this was arterial hypertension stage II, atherosclerosis of the cerebral vessels or their combination), marked by the occurrence of the complaints of a cerebral character in combination with slight or pronounced focal symptoms, as well as by the presence of cognitive impairments. Patients with severe cognitive impairments and dementia were excluded from the study.

All the patients had undergone clinical-neurological investigations and neuropsychological tests in order to verify the presence and stage of cognitive defect. The stage of cognitive defect was determined by the MMSE (Mini-Mental State Exam) test, the Clock Drawing Test (CDT), the Bourdon-Wiersma test (visual perception and vigilance), and the Spielberger-Hanin test. The neurophysiological investigations included an EEG study (21-cables) and cognitive evoked potentials (CEP P300) on the electroencephalograph Neuron Spectrum 4 ("Neurosoft", Russia). Statistical analysis was performed using the statistical software «Statistica».

Results and Discussion

Based on the neuropsychological tests in 49 patients (81.6%) of the main group, we found cognitive impairments in various degrees of severity (Table 1).

Table 1.

Distribution of the patients according to degree of cognitive impairment

Degree of cognitive impairment	Stage of DE			
	I	II	III	Totally
Absence of cognitive impairment	11 (18.3%)	-	-	11 (18.3%)
Normal age-related memory loss	7 (11.66%)	-	2 (3.3%)	9 (15%)
MCI	2 (3.33%)	22 (36.67%)	10 (16.7%)	34 (56.7%)
Advanced cognitive impairment	-	-	6 (10%)	6 (10%)
Total	20 (33.33%)	22 (36.67%)	18 (30%)	60 (100%)

From the data presented in Table 1, it is evident that the distribution of cognitive impairments in the patients at different stages of CCI reveals unique features. We rarely observed the normal age-related memory loss (3.3%) in the patients with stage III DE, whereas it was found in 11.6% of patients with stage I DE. On the contrary, in the patients with stage III DE, the cognitive defect in 63.4% of cases achieved a degree of MCI, while in the patients with stage I DE, MCI was registered only in 3.3% of the cases. It should be noted that in these cases the MCI was represented by the amnesic subtype, which according literature data was frequently transformed into the Alzheimer's disease. Therefore, it is possible to say, that in this case, most likely, the cognitive impairment is combined with a neurodegenerative process. The greatest number of MCI was observed in the patients with stage II DE.

As noted above, MCI was observed in 66.7% of case. Distribution of the patients studied by the type of MCI based on O.S. Levin's classification is presented in Fig. 1.

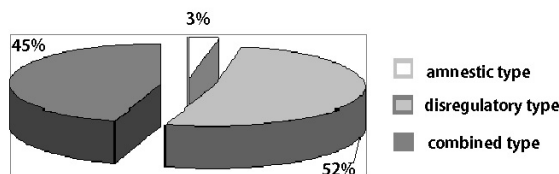


Figure 1.

Distribution of the patients according to MCI type

From the data presented, it is evident that the disregulatory and combined types of MCI occurred more frequently. In other words, MCI may be considered as an indicator of morpho-functional insufficiency of the brain associated with progressive CCI. Therefore, if at stage I DE, the normal age-related memory loss or its absence was noted more frequently, then during the progression of the main process, the disregulatory type (at stage II-III DE) or combined type (at stage III DE) of MCI was found more often. Based on these facts, we concluded that the stage of cognitive impairment reflected the stage of cerebral insufficiency. In this connection, the question arises regarding the development of more informative diagnostic criteria for MCI.

Neuropsychological tests appeared to be widely used in the diagnosis of cognitive impairment. These tests are used to perform the early cognitive impairment diagnosis and determine its severity degree. The simplicity of this diagnostic method is also advantageous. As shown above, the degree of the cognitive defect was defined by the MMSE test, the CDT, and the Bourdon-Wiersma test (visual perception and vigilance). Reactive anxiety and personal anxiety were measured using the Spielberger-Hanin test. Data of neuropsychological tests are presented in Figure 2.

The data presented in Fig.2 showed that MMSE score was 25.8±1.6 points in Group 1 patients that corresponded to MCI. In Group 2 patients, this score rose to 30 points. A detailed study of MMSE score revealed that in the patients with MCI functions such as memory and concentration of attention were damaged more frequently, which was typical for the combined and disregulatory types of MCI. The latter was confirmed by the Bourdon-Wiersma test too. The Bourdon-Wiersma test score in Group 1 patients was 4.3±0.4 points, while in the control group it was 5.6±0.6 points. An analysis of the reactive anxiety by the Spielberger-Hanin

test confirmed the presence of this anxiety in patients with MCI associated with CCI. The index of reactive anxiety in Group 1 patients was 47.6±8.4 points, whereas in the control group it was 31.2±4.1 points, which was evaluated as the norm. It is important to note that the differences were reliable. Personal anxiety by the Spielberger-Hanin test in patients with MCI and in the control group was 41.5±6.4 points and 38.0±5.8 points, respectively, and the differences were not statistically significant. In addition, the differences by the CDT were not statistically significant (7.8±8.3 and 9.4±0.6 points, respectively).

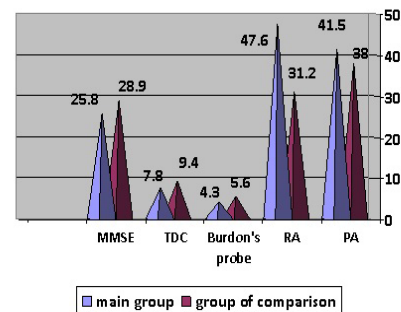


Figure 2.

Parameters of the neuropsychological tests in patients with CCI

In this study, the neurophysiological characteristics of MCI were investigated. The peculiarities of the bioelectric brain activity and parameters of cognitive evoked potentials (CEP P300) were studied using the EEG. The main parameters studied were P300 peak latency and P300 peak amplitude. Neurophysiological investigations were performed in patients with normal age-related memory loss and with MCI. In such cases, the distribution of the main rhythms of the brain, their power and zonal distribution were taken into account. These data are shown in Table 2.

Table 2.

EEG findings in patients with CCI

Parameter	Normal age-related memory loss (n=9)	MCI (n=40)	P
Theta-diapason			
PO lead	26.1±0.86	28.4±0.9	<0.001
PT lead	19.4±0.89	26.3±0.85	<0.01
Beta-diapason			
PO lead	52.9±0.3	57.4±0.6	<0.05
Alpha-rhythm			
PO lead	10.3±0.2	8.7±0.75	<0.001
Coherence of alpha-diapason			
PO lead	0.64±0.11	0.5±0.8	<0.05
FO lead	0.52±0.11	0.24±0.08	<0.05

An analysis of the EEG parameters revealed their dependence on the stage of cognitive impairment. The EEG in patients with stage II DE was accompanied by the intensification of the ascending activating effects of the nonspecific brain structures on the cortex of the large hemispheres that were expressed by the predominance of rhythmical slow wave activity ("theta") in the patients with MCI associated with DE.

A reduction in the coherence of alpha rhythmic activity in these patients indicated a disturbance in the links between the remote segments of the cortex as well as the intrahemispheric ones. This reduction in the optimization of the activity in the cortex resulted in damage of the cortical-subcortical links that were expressed in the integrated disorders in the brainwork. Clinically, this was expressed by the neuropsychological syndromes of the cortex of the frontal lobes. Besides, in the patients with stage II DE, we found agnosia and apraxia that reflect the predominantly cortical involvement of these disorders. Thus, the EEG changes revealed in the patients with DE were dependent upon the stage of cognitive defect and were specific in character. The results of the clinical investigations were confirmed in the analysis of parameters of CEP. Data are shown in Table 3.

Table 3.

Parameters of CEP (P300) in patients with CCI

Parameter	Group I (n=60)	Group II (n=15)
P300 peak latency, m/sec.	374*	361
P300 peak amplitude, μ W	5.2*	5.3
latency/amplitude ratio (R)	71.9*	68.1
N2 peak latency, ms	264.26	264.1
N3 peak latency, ms	461.28	459.8
N3-P3 peak-to-peak amplitude, μ W	6.19	6.12

* $P < 0.05$ between groups.

During the study of CEP we analyzed P300 peak latency, P300 peak amplitude, the latency/amplitude ratio (R), N2 and N3 peak latencies, N3-P3 peak-to-peak amplitude. The analysis of the dynamics of the neurophysiological parameters by the data of CEP (P300) showed reliable differences when compared with the control group. This was expressed by the shortening of P300 peak latency and an increase in P300 peak amplitude as a consequence of this decrease in the latency/amplitude ratio (R). Based on a study of other CEP parameters, the changes were not statistically significant between parameters of the main group and the control group that indicated the insufficient information of these parameters for the diagnosis and prognosis of MCI associated with DE. The results of the investigations indicated a reduction in the metabolic processes in the brain cells caused by DE that manifested clinically as a reduction in both parameters of neuropsychological tests and the parameters of P300 peak. Based on the results obtained, the following **conclusions** were drawn:

- Discirculatory encephalopathy was accompanied by cognitive impairments of various degrees of severity. Normal age-related memory loss was observed in 14.9% while MCI was seen in 66.7% of the cases.
- Among the types of MCI, the disregulatory type was observed in 51.6% of patients with stage II-III DE, and the combined type was observed in 45.4% of patients with stage III DE.
- The EEG-pattern in patients with DE has some peculiarities that are expressed in the predominance of

rhythmical slow wave activity and the reduction in the coherence of alpha rhythmic activity that results in a consequent disturbance of the integrated brain activity.

- Changes in CEP data were expressed in the shortening of P300 peak latency and an increase in P300 peak amplitude and consequently, a reduction the latency/amplitude ratio in patients having MCI associated with DE.

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