Peculiarities of Cognitive Disorders in Adult Patients with Epilepsy

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

Short Research Article

ABSTRACT

Aim: The basic aim of the article is to study the state of cognitive functions in patients with epilepsy due to clinical characteristics and a pharmacological group of received anticonvulsive medicines using MMSE test and examination of cognitive induced potential P300.
Place and Duration of Study: The Department of Neurology at Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan, between April 2012 and April 2013.
Methodology and Study Design: The study was conducted on the basis of the neurological department of the city hospital number 7 in Tashkent (Uzbekistan). 75 patients with epilepsy at the age from 21 to 42 being under treatment at hospital were examined. The average age of patients in the debut of the disease was 32 ± 9.3 years. The clinical form of the disease and epileptic seizures were determined based on the International Classification of epileptic seizures and the International Classification of epilepsy and seizures. Clinical assessment of cognitive functions was performed using MMSE (Mini Mental State Examination) test. Besides this method of research of cognitive evoked EEG potential to acoustic stimulation, and the assessment of potential latencies of P300, which reflects the cognitive processes of attention and perception, N200 was used, reflecting the process of initial identification of the stimulus.
Results: The results indicated the presence of more severe cognitive disorders in patients who

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were sick for more than 5 years, with symptomatic epilepsy, generalized convulsive seizures and taking barbiturates. It was established by assessing cognitive function method, that examination of potential P300 is more sensitive in comparison with MMSE test.

Conclusion: Our results clearly demonstrate the extension of the latent period of the components of P300 complex at all examined patients, shows a decline in the integral functions of the central nervous system and the mechanisms of information processing occurring in epilepsy. While taking AEDs, cognitive deficit increases in the following order valproates – carbamazepine – barbiturates.

1. INTRODUCTION

Cognitive disorders are ought to be obligate component of the clinical epilepsy and have a significant impact on the quality of life of patients [1-4]. Having analyzed the special literature, we conclude that the level of severity depends on the duration of the disease, clinical types of seizures, and the clinical form of the disease [5-8]. According to the diagnostic criteria, cognitive disorders prevail in symptomatic and bound to be less pronounced in the idiopathic form of the disease [9-12]. Besides, the development and characteristics of cognitive disorders are affected by the very type of anticonvulsant therapy and anticonvulsant that is used [13-16].

It should be noted that many of the works devoted to the study of cognitive functions in patients with epilepsy, based on purely clinical research methods. The number of papers on the use of objective neurophysiological methods of analysis of cognitive disorders in patients with epilepsy in special literature is not enough. One of the objective methods for the determination of cognitive disorders is the study of cognitive evoked potential P300. Neurophysiological study of this indicator in some neurological diseases, including epilepsy, is the informative neurological method which allows objectively estimate the function of attention and the speed of information processing [17-20].

The aim of this work was the research of cognitive functions in epilepsy, depending on the clinical characteristics of the disease and the pharmacological group received anticonvulsants using clinical and neurophysiological methods.

2. MATERIALS AND METHODS

The study was conducted on the basis of the neurological department of the city hospital number 7 in Tashkent (Uzbekistan) within 2 years.

The study involved 75 patients with epilepsy aged 21 to 42 years old who were hospitalized. The average age of the surveyed patients was 32.0±9.3 years.

The analysis of the data was carried out taking into account the clinical forms of epilepsy and epileptic seizures, duration of the disease, pharmacological groups of received drugs.

A clinical form of the disease was determined based on International Classification of epilepsy and seizures (New Delhi, 1989). In 46 patients (61.3%) symptomatic epilepsy (SE) was diagnosed, in 29 patients (38.7%) – idiopathic epilepsy (IE). The cause of symptomatic epilepsy in 68.7% of cases was due to traumatic brain injury (TBI) in the remaining cases (31.3%) the cause of the FE was the secondary encephalitis.

In 14 (18.7%) patients the disease duration was up to 1 year, in 22 (29.3%) patients the disease was between 1 and 5 years, and 39 (52.0%) patients the disease duration was over 5 years (Table 1).

In 31 (41.3%) patients generalized seizures were observed, in 44 (58.7%) – partial seizures. Examined patients received the following antiepileptic drugs (AEDs) as mono-therapy - Depakine, Carbamazepine, Benzonal.

So, in 31 (49.3%) patients Depakine was listed in their treatment regime, 24 (32.0%) patients were treated with carbamazepine, and 14 (18.7%) patients received Benzonal (Table 1).

The period of observation was 2 years, within which all patients repeatedly passed EEG test, the examination of cognitive functions was conducted under MMSE scale, the technique of cognitive evoked potentials P 300.

The control group of healthy individuals (30 men) has been examined for comparison with a relevant by age group of patients. The criteria for

inclusion into the group of healthy – no subjective complaints and objective neurological symptoms.

Table 1. Clinical characteristics of examined patients

	Number of patients	
	n	%
Form of epilepsy (E)		
Symptomatic (E)	46	61,3
Idiopathic (E)	29	38,7
Duration of the disease		
up to 1 year	14	18,7
1-5 year	22	29,3
over 5 years	39	52,0
Types of seizures		
Generalized	31	41,3
Partial	44	58,7
Mono-therapy AED		
Depakine	37	49,3
Carbamazepine	24	32,0
Benzonal	14	18,7

2.1 MMSE Test

For the syndromic diagnosis of cognitive disorders Mini-Mental State Examination (MMSE – Mini Mental State Examination) was used, which includes 11-questions, testing orientation in time and place; repetition of words (perception), serial counting (concentration), auditory-verbal memory, speech (naming objects, repetition of the phrase), understanding of the order, reading, writing, drawing. Performances under each order were scored.

Assessed data according to MMSE scale (total score - the state of cognitive functions) [7]

- 28-30 points – Norm. No cognitive impairment
- 24-27 points – Cognitive impairment
- 20-23 points – Dementia of mild degree
- 11-19 points – Dementia of moderate degree
- 0-10 points – Severe dementia

2.2 Methodology of Cognitive Evoked Potentials (CEP)

Evoked potentials (EP) represent the electrical processes in the brain related to the mechanisms of perception and information processing.

The research method P300 is based on the supply at a random sequence of two series of stimulus, some of which are significant and not

significant (to which a subjected to the test must respond), where these stimulus differ from each other by parameters, but not sharply. When you select responses to the significant rare stimulus the nature of the responses will differ from the usual series by the appearance of a large positive wave in the area of 300 ms (Fig. 1).
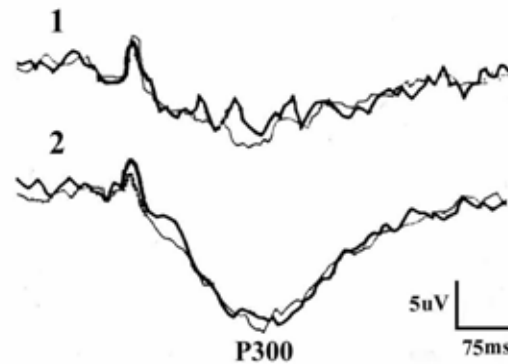

Fig. 1. CEP in response to not significant (1) and significant (2) stimulus

In normal allocation of responses mostly to auditory stimulus without the requirement of their recognition long-latency auditory evoked potential (V-wave) appears Also, V-wave is the sensory part of the response (perception) when the procedure P300 is used followed by P300 complex with peaks N2 and P3, reflecting the process of identification of rare significant stimulus. First, perception begins – V-wave, then the identification and differentiation (component N2) – in the time interval 180-325 ms, decision making and storing (P3) – in the interval 300-400 ms after a visual or auditory stimulus demonstration (Fig. 2).

P300 complex is associated with cognitive processes in stimulus processing, including the assessment of its importance, activation of attention resources by listing events in the memory. The increase of latent period P300 can be considered as the evidence of mental processes slowing, connected with this component, i.e. the categorization of events, activation of attention resources, listing the event in the memory. Decrease of P300 amplitude may indicate a decline in memory [1,2,5].

Investigation of cognitive evoked potentials (CEP) was performed by the 4-channel electro-neuro-myography with the function of analyzing the evoked potentials (Neuro-MVP-4 company,

Russia) in case of an unexpected situation (odd-ballparadigm) and under conditions of active perception of the stimulus. Registration was carried out by two channels: active scalp electrodes were set at C3 and C4 according to international system "10-20", the reference electrodes were on the points M1 and M2. The ground electrode was placed at the point FPz.
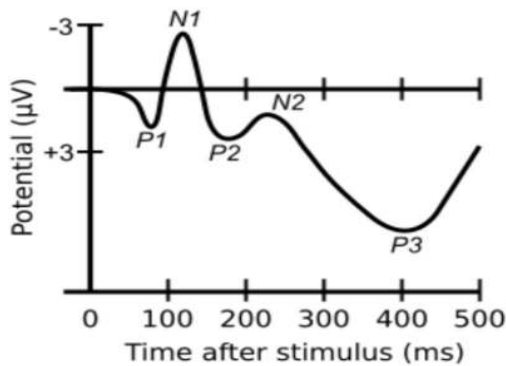
Fig. 2. V- wave and P300 complex

Investigation was carried out under a standard technique in a situation arising due to an unexpected event (in response to non-verbal auditory stimulation). Stimulation conditions: Binaural, period of stimulus – 50 ms, the intensity – 80 dB, the period between stimuli – 1 s. Registration settings: the stimulus frequency of tone is 2 000 Hz with 30% (significant), 1000 Hz with 70 % (not significant). The period of the analysis – 750 ms [1].

The patient is in a sitting position with his eyes closed, presses the button with the right hand on a significant stimulus. Evoked potentials were separately averaged to significant stimuli and the average time of reaction was calculated. Quantitative analysis was used for P300 changes in the central parietal leads (C3, C4).

For significant stimuli the following indicators were determined by each channel:

- latent period (LP) of P300 wave per ms
- latent period (LP) of N200 wave per ms
- latent period (LP) of the interval N200 – P300 per ms

In addition to quantitative assessment attention should be also paid to the changes of response forms, the wave amplitude change during the first and second series of averaging.

The research results were statistically processed on a personal computer using a standard package SPSS. For the analysis of dependent samples Student's t-test for paired samples and the Wilcoxon test were used. For all kinds of statistical analysis the differences were considered statistically significant at the level of significance $p < 0.05$.

3. RESULTS AND DISCUSSION

Results of comparing the data of the control group with the main group of patients with epilepsy have shown that all the investigated parameters between healthy and sick people with epilepsy have significant differences. In the group of sick patients was a significant decrease of performance score under the MMSE test (29.18 points) and elongation of N200, P300 latencies and P300 - N200 interval – respectively 201.87 ms; 304.51 ms; 102.64 ms – demonstrates the presence of cognitive disorders in epilepsy (Table 2). At the same time, one-way dynamic of the data of MMSE clinical test and neuro-physiological parameters confirms informative value of cognitive evoked potentials investigation for objective assessment of a degree of cognitive disorders intensity.

Table 2 shows that when comparing the control group and the group of patients there is significant inverse correlation dependence between elongation of latencies by indices of the P 300 method parameters and MMSE test scores.

Further, we compared the studied parameters between the groups of patients with idiopathic and symptomatic forms of epilepsy (Table 3). It was revealed that by clinical signs, i.e., by the MMSE test, there are no significant differences between the groups. Thus, in patients with symptomatic E score by MMSE questionnaire was 26.81 points, and in patients with idiopathic form of E – this score was 25.4 points.

However, by neuro-physiological indicators significant differences in all parameters with greater severity of these disorders were revealed, i.e. with a more pronounced elongation of latencies of cognitive evoked potentials in patients with symptomatic form of epilepsy (N200 = 240.19ms, P 300 = 353.12 ms interval (N 200 - P 300) = 112.93 ms). Indicators of N200, P300 latencies and P300- N200 interval in patients with idiopathic epilepsy were respectively – 250.29 ms; 393.12 ms; 142.83 ms.

Table 2. Indicators of MMSE test and P 300 method in healthy persons and patients with epilepsy

Tested groups	MMSE (points)	N 200 Latency (ms)	P 300 Latency (ms)	P300- N200 interval (ms)
Control group	29,18±0,5	201,87±9,3	304,51±9,6	102,64±2,3
Patients with epilepsy	26,10± 1,1	245,24±10,2*	373,12±7,3*	127,88±1,3*

*Note: Here and below, * - significant differences between compared groups (p <0.05)*

Table 3. Indicators of MMSE test and P 300 method depending on the form of epilepsy

Tested groups	MMSE (points)	N 200 Latency (ms)	P 300 Latency (ms)	P300- N200 Interval (ms)
Form of epilepsy (E)				
1. Symptomatic E	26,81±0,8	240,19±8,5	353,12±5,7	112,93±2,8
2. Idiopathic E	25,40±1,4	250,29±13,2	393,12±6,7*	142,83±0,9*

Thus, this confirms the known criteria of differential differences between idiopathic and symptomatic forms of epilepsy, according to which in the form of symptomatic epilepsy mental disorders are significantly more pronounced.

We have also carried out a comparative analysis of the state of cognitive functions between the groups of patients with prevailed either generalized or partial forms of epileptic seizures (Table 4). According to Table 4 under clinical characteristics, i.e. by MMSE test, significant differences were not revealed – 25.33 points in group 1 and 26.08 points in the second one. However, the neuro-physiological investigations revealed an elongation of latency of evoked potentials N200 and P300 and significant extension of the duration period N 200 - P 300 in patients with generalized form of seizures. The above mentioned indicators were respectively – 253.15 ms; 388.26 ms; 135.11 ms. The same indicators in second group of patients with partial seizures reduced to 237.33 ms; 357.98 ms; 120.65 ms.

Next, we compared the results of the study of cognitive indicators in patients with epilepsy, depending on the duration of the disease, dividing all patients into three groups: A duration of up to one year, from one to five years and above five years (Table 5).

As it is seen from Table 5, the severity of cognitive impairment, both by clinical and neuro-physiological parameters is rising with an increase in duration of the disease. It has been noted that patients with disease duration of more than five years compared to the group with disease duration up to one year have significant differences according to all main indicators. For example, according to this table in 3 groups of patients N200, P300 latencies and P300 - N200

interval are, respectively, 250.43 ms; 389.34 ms; 138.91 ms that is significantly higher than the same indicators in group 1 – respectively – 239.16 ms; 344.71 ms; 105.55 ms. When comparing groups 1 and 3, there are also great differences in MMSE test – in group 1 this indicator was about 27.87 points, which is significantly higher than the same indicator in group 3 – 24.97 points.

As Table 5 shows that comparing all three groups, we see inverse correlation dependence between elongation of latencies according to parameters of P300 method and MMSE test scores. Particularly this inverse correlation is important when comparing the 1 and 3 groups of patients (Table 5).

At the same time, we found out that there are no highly significant differences between the groups of patients with disease duration up to five years and over five years. Thus, we may conclude that when comparing data between the groups of patients with duration of more than five years and up to five years, significant differences were not found.

Given the above it can be concluded that the duration of the illness generally affects the severity of cognitive impairment in the first 5 years, but with the duration of the disease for more than five years the period of the disease does not essentially affect the severity of cognitive disorders.

One of the most important tasks of our research is to compare the severity of cognitive disorders in patients taking the three main groups of drugs – valproate, carbamazepine and barbiturates. As seen from the presented data, in general there are some significant differences between the compared groups (Table 6).

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Table 4. Indicators of MMSE test and P 300 method depending on the type of seizures

Tested groups	MMSE (points)	N 200 latency (ms)	P 300 latency (ms)	P300- N200 Interval (ms)
Types of seizures				
1. Generalized	25,33±0,9	253,15±11,3	388,26±8,5	135,11±1,7
2. Partial	26,89±0,8	237,33±8,9*	357,98±9,0*	120,65±2,1

Table 5. Indicators of MMSE test and P 300 method, depending on the duration of epilepsy

Tested groups	MMSE (points)	N 200 Latency (ms)	P 300 Latency (ms)	P300- N200 interval (ms)
Duration of disease				
1. Up to 1 year	27,87±1,9	239,16±11,6	344,71±7,9	105,55±1,6
2. 1-5 years	25,43±0,8*	246,15±9,6	385,31±8,2*	139,16±0,8*
3. Above 5 years	24,97±0,6#	250,43±10,4#	389,34±9,4#	138,91±0,7#

*Note: Here and below, * - significant differences between 1 and 2 compared groups (p <0.05), # - significant differences between 1 and 3 compared groups (p <0.05), ^ - significant differences between 2 and 3 compared groups (p <0.05)*

Table 6. Indicators of MMSE test and P 300 method, depending on the used AEDs

Tested groups	MMSE (points)	N 200 Latency (ms)	P 300 Latency (ms)	P300- N200 interval (ms)
Monotherapy AED				
1. Valproate	27,01±1,3	240,13±9,3	349,5±7,4	109,37±0,9
2. Carbamazepine	26,24±1,5	246,25±8,8	381,32±8,1*	135,07±1,3*
3. Benzonal	25,02±2,0#	249,34±10,7#	388,56±8,7#	139,22±0,6#

First of all, the attention is drawn to the fact that in the group of patients treated with Benzonal there is a clear downward tendency in the score indicators of cognitive functions under the MMSE test (25.02 points) and the relatively high value of latency elongation of researched electrophysiological potentials (N 200 = 249.34 ms; P 300 = 388.56 ms and N 200 - P 300 interval = 139.22 ms).

The most pronounced differences are observed in indicators of MMSE, potentials of N 200 P 300 latencies and also in difference of latencies (P300- N200) between the groups treated with valproate and barbiturate (respectively – 27.01 points; 240.13 ms; 349.5 ms; 109.37ms – in group 1 against the same indicators, respectively – 25.02 points; 249.34 ms; 388.56 ms: 139.22 ms – in group 3).

As for the differences between the groups treated with volproat and carbomazepin, in the absence of essential differences under MMSE test, significant differences were found within the following neuro-physiological parameters – the length of the P 300 complex and the duration of the N 200 - P 300 interval, in group 1 these indicators were 349.5 ms; 109.37 ms, respectively, but in group 2 – 381.32 ms; 135.07 ms - accordingly.

4. CONCLUSION

Thus, the extension of the latent period of the P300 complex components at all examined patiens shows a decline in the integral functions of the central nervous system and the mechanisms of information processing occurring in epilepsy.

The results of investigation led to the following conclusions:

1. Cognitive functions in patients with epilepsy significantly changed and are at the level of cognitive disorders (according to MMSE scale), which has been confirmed in indicators of neurophysiological researches of P300.
2. The most significant cognitive changes were revealed in patients with symptomatic form of epilepsy, in patients with generalized seizures and with disease duration about 5 and more years, it can be the result of more pronounced specific degenerative-dystrophic process in the brain tissues with disorder of neuronal spatial and temporal relations.
3. While taking AEDs cognitive deficit increases in the following order valproaty – carbamazepine – barbiturates.

4. Under Epilepsy there is inverse correlation dependence between elongation of latencies according to parameters of P 300 method and MMSE test scores.
5. The method of cognitive evoked potentials P300 is informative in the diagnosis of cognitive disorders in epilepsy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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