Features of Cognitive Dysfunction in Young People with Post-Covid Syndrome

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Abstract: This article discusses the features of cognitive dysfunction in young people with post-COVID syndrome. Further research is needed in this direction. It can be said with confidence that the clinical picture of neurological diseases and syndromes caused by coronavirus infection corresponds to our usual ideas, in contrast to the results of neuroimaging and laboratory methods of additional examination.Of course, additional studies are needed on large groups of patients to finally understand the mechanisms of complications, the degree of their connection with COVID-19 and the development of schemes for their treatment and subsequent rehabilitation.

Keywords: *cognitive dysfunction, post-COVID syndrome, neurological diseases, coronavirus infection.*

1. Introduction

After the completion of the acute phase of COVID-19, the subsequent course of the disease and the dynamics of its clinical manifestations differ. Changes in the mental and physical components of health are closely related to each other, while cognitive impairment is largely independent of other manifestations of post-COVID syndrome (PCS). It can be assumed that there are differences in the mechanisms of formation of manifestations of PCS, which will ensure the stratification of patients and the implementation of personalized rehabilitation measures (1,6,10,13,18,20).

The manifestations of PCS are diverse, characterized by symptoms from various body systems, but neurological (neuropsychic) disorders are especially important: cognitive impairment, asthenic, vegetative, and anxiety disorders, leading to a decrease in the quality of life of patients and a slowdown in the rate of recovery (7,11,12 ,14,15,16).Various manifestations of PCS occur in the majority of patients who have undergone COVID-19: a third of patients have increased fatigue, and a fifth have cognitive impairment (5,12,17,19,20). These disorders can be observed in patients with varying severity of the underlying disease.

Further research is needed in this direction. It can be said with confidence that the clinical picture of neurological diseases and syndromes caused by coronavirus infection corresponds to our usual ideas, in contrast to the results of neuroimaging and laboratory methods of additional examination.Of course, additional studies are needed on large groups of patients to finally understand the mechanisms of complications, the degree of their connection with COVID-19 and the development of schemes for their treatment and subsequent rehabilitation.

In this regard, in our work, we focused on the study of cognitive impairment (CI) as in neurological pathology in PCS. Cognitive or “endogenous” potentials reflect electrical processes due to the brain’s own activity.Their formation is due to processes associated with mental cognitive functions, such as memory, expectation function, discrimination, information processing, decision making, reaction choice. The essence of the analysis of the cognitive processes of the brain lies in the fact that not just reactions to one or another afferent stimulus are distinguished, but endogenous events occurring in the brain associated with the recognition and memorization of the stimulus are analyzed19 (2,3).

A modern method for isolating endogenous events, which has made it possible to improve the analysis and understanding of cognitive processes, is the study of the cognitive potential of P300. This type of evoked potentials (EP) has recently been increasingly used in clinical practice in assessing the preclinical stage of CI and various types of dementia (3,4). Since 1993, the P300 technique has been included in the recommendations of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (International Federation of Societies for Electroencephalography and Clinical Neurophysiology) for the study of EAP (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1993) (table 1).

Table 1

P300 EP registration parameters recommended by the International Association of Clinical Neurophysiologists for clinical use (quoted in: Gnezditsky V.V., Korepina O.S., 2011)

Parameter	**Recommended values**
Stimulus parameters tone frequency Rise / decline Duration Intensity Interstimulus interval	2000 Hz with 20% (significant) 1000 Hz with 80% (not significant) 10 ms 50ms 60 dB SPL* 2 c
Subject parameters and instructions Position Eyes Instructions	sitting Closed Counting/pressing a button/tapping a finger on a meaningful stimulus
Registration and averaging parameters electrodes Referent grounding Bandwidth Age of Analysis Artifact Suppression	Fz, Cz, Pz, EOG** A1/A2 or M1/M2 Fpz 0.01-0.5 to 30 Hz 750ms >±100 µV ≥20 for meaningful stimulus

Number of averages	Superposition of two separately selected series of 20 averages
Reproducibility	

**Sound pressure level (sound pressure level); **electrooculographic*.

The P300 technique is based on the presentation in a random sequence of series of two auditory stimuli that do not differ sharply in parameters. In the usual selection of responses to these different stimuli, without the condition of their identification, long-latency auditory EPs (V-wave) are recorded, which differ slightly from each other due to the difference in stimulus parameters (2,3). However, the situation changes dramatically when the instruction is given that one of the stimuli will be significant and must be identified and counted. At the same time, the physical properties of the stimuli do not change. When separating and averaging in such a series of responses to insignificant stimuli, a wave similar to that in the usual sequence is recorded. At the same time, the nature of responses to significant stimuli differs sharply from the usual series by the appearance of a large positive wave (or complex) in the 300 ms region (3.4).

The selection of responses under conditions of recognition of stimuli that differ from others in some parameters can be done for any modality of the stimulus: auditory, visual (for a pattern and for a flash), somatosensory. A more reliable selection of these responses occurs when using auditory tone clicks with a different tone (2,3).

Currently, there are conflicting data on which structures are involved in the generation of certain P300 components. Many authors (10,11) note the maximum expression of P300 in the vertex region, which is probably why the assessment of the C3,C4 channel pattern has become routine in many laboratories (5,6). P300 EPs have a wide distribution topography over the surface of the head with a predominance in the fronto-central and less often in the parietal-central regions (3).

In order to reduce the redundancy of the information obtained during routine research, the number of channels by which the main amplitude-frequency parameters are estimated, as a rule, is reduced. However, the schemes used for analysis in different laboratories differ significantly.The International Association of Encephalography and Clinical Neurophysiology recommends P300 recording parameters for clinical use (see Table 1) where Fz, Cz, Pz active electrodes are used. In Russian laboratories, the most common is the scheme of active electrodes C3, C4 (3,4).

According to multichannel recordings, P300 is maximally expressed in the following areas: frontal (F3, F4) - 45%, central (C3, C4) - 45%, parietal (P3, P4) - 10% (5). At the same time, there is a significant interhemispheric asymmetry: P300 prevails in amplitude on the left in 64% and on the right in 36% of cases.

Due to the lack of a generally accepted methodology for studying CEP, the purpose of our study was to establish a rational EP lead scheme for assessing cognitive functions using the P300 method by analyzing the system of multi-channel recordings of CEP P300 in patients with CI against the background of post-covid syndrome (PCS).

Purpose of the study. To analyze the parameters of P-300 in young people with post-COVID syndrome, depending on gender.

2. Material and research methods.

The study included 87 young patients aged 18 to 44 years (mean age 31.9±12.1 years) with post-covid syndrome (PCS) (Fig. 1). The patients were divided into two groups: group I consisted of 36 women (41.4%), group II - 51 men (58.6%), the gender index was 1.4:1.0. The control group (CG) included healthy individuals comparable with those of the main group in terms of sex and age characteristics (n=20; mean age 32.4±7.3 years; gender index 1.0:1.2).

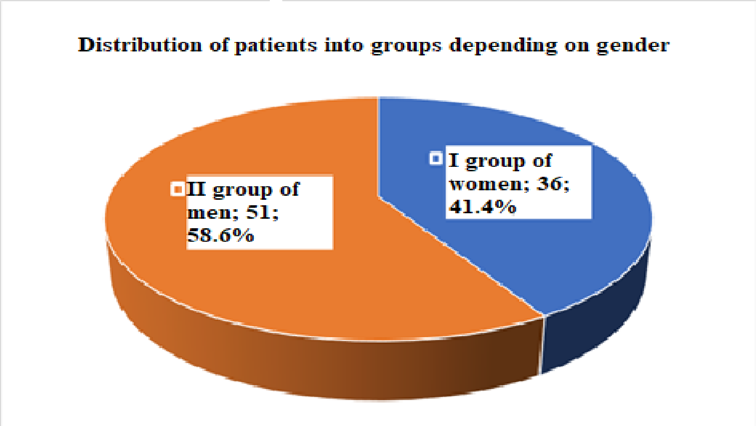

Figure 1. Distribution of patients by sex.

The diagnosis of post-COVID syndrome was included in the International Classification of Diseases (ICD-10), heading code U09.9 "Post-COVID-19 condition, unspecified", which also includes the post-COVID state (8). Patients were observed in the conditions of the neurological and therapeutic departments in the regional hospital of the city of Andijan.

In a comprehensive clinical examination of patients, a generally accepted clinical examination of the somatic status, a neurological examination using the MMSE scale, Luria's "10 words" test, and Schulte's + method were used.

Along with clinical and neurological studies, they were included in the block of studies, in addition to EEG recording and studies of cognitive evoked potentials (P300). Cognitive evoked potentials (CEPs) were chosen because they allow the assessment of endogenous events occurring in the brain and associated with the recognition and memorization of presented stimuli (2).

To register and isolate auditory evoked potentials (AEPs), a standard technique was used, which consisted in synchronous averaging of 18–22 EEG fragments in monopolar leads (F3, F4, C3, C4) using an EEG 16S electroencephalograph, a personal computer, and programs for studying evoked activity. brain. Among the insignificant double stimuli, which were given in a random order in a ratio of 3:1, there were more rare single sound signals (which were determined as significant), upon recognition of which the subject pressed the button located under the right hand. The P300 component was recorded with a time constant of 0.3 s and a frequency band of 0.2-75 Hz, an analysis epoch of 750 ms. The number of averagings for a significant stimulus was 20. The averaging was automatically performed for the presented significant and non-significant stimuli. The responses received were filtered in the frequency range from 0.5 to 30 Hz. The main peaks of the cognitive evoked potential were identified - P1, N1, P2, N2, P3, N3. The latent period of the P300 component was calculated as the latent period of the P3 peak in ms, the P300 amplitude was calculated as the interpeak amplitude of N2-P3 in μV (2).

Statistical processing of the results of clinical and instrumental studies of our patients was carried out using the methods of variation statistics in the Microsoft Office Excel-2019 software package with the determination of the mean and mean arithmetic errors by the method of moments ($M \pm m$), standard deviation (σ).

Statistical significance of the results was assessed using Student's test of significance (t) for parametric distribution and Fisher's test (F) for nonparametric data distribution. Differences were considered significant at 95% confidence interval ($P \leq 0.05$).

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3. Research results.

Complaints about memory disorder in the form of forgetfulness were presented by 56.3% of patients, while an objective study revealed memory loss in 85.5% of cases. Memory impairments were predominantly modal-nonspecific in nature and were primarily due to pathological inhibition of traces by interfering influences. The degree of impairment varied from mild (75.8%) to moderate (11.5%) severity. Mild disturbances were found only with the use of sensitized samples. The absence of mnestic disorders was recorded in 11.5% of cases.

The severity of CI on the MMSE scale in patients with PCS was studied. As can be seen from Table 3.10, in groups of patients with moderate CI it was significantly higher compared to CG. Also, significant differences in the score severity of MCI according to the MMSE scale was significantly higher in patients in group 2 compared to the first (Table 2).

Table2 Questionnaire results MMSE

CG degrees	**Group I, women, n=36**			**II group, men, n=51**		
	MMSE points), M ±σ	**n**	**%**	**MMSE points), M ±σ**	**n**	**%**
no cognitive impairment	32,4+0,7	31	86,1%	31,7+0,6	41	80,4%
Light CG	2,5±0,2	4	11,1%	23,1±1,2	8	15,7%
Moderate CG	17,3±2,8	1	2,8%	15,6± 0,4 *	2	3,9%

When conducting a test for memorization of 10 words, a slight decrease in memorization productivity was noted compared to the control, patients reach the maximum results after 5-6 repetitions, while persons in the control group - after 3-4 repetitions (Table 3).

In 98% of cases, modal-nonspecific disorders of voluntary attention were also revealed. The memorization curve in the 10-word test reflected the lack of activation support, a decrease in the concentration of voluntary attention and its increased exhaustion.

Noteworthy is the relative preservation of the volume of short-term memory in group I with a slight decrease in long-term memory, which indicates the absence of pronounced disturbances in the phase of direct reproduction. The number of errors is comparable to the control group.

Table3Patient testing results with the test "10 words" Luria

study interval	**I group**	**II group**	**CG**
Immediately after learning	5,6±0,3	5,1±0,33	7,2±0,21
After 10 minutes	8,2±0,29	6,9±0,35 *	6,5±0,26
In 20 minutes	7,0±0,29	6,5±0,38 *	5,9±0,28

The reproduction of numerical series in the control group was better compared to patients who underwent COVID-19, this difference was significantly significant (p=0.04). The reproduction of numerical series in direct order in patients of group II was impaired to a greater extent compared to group I, these differences were more pronounced in female patients. The revealed changes in patients with different groups had a statistically significant difference when comparing some indicators.

After analyzing the assessment of the stability of attention and performance according to the Schulte method (Fig. 2), we found a fairly large variability in the data. The studied groups of patients who underwent COVID-19 significantly differed in the efficiency of work with the control group (p = 0.001). The scatter in the time of passing the Schulte tables in patients of groups II and III increased as the complexity of the task increased.

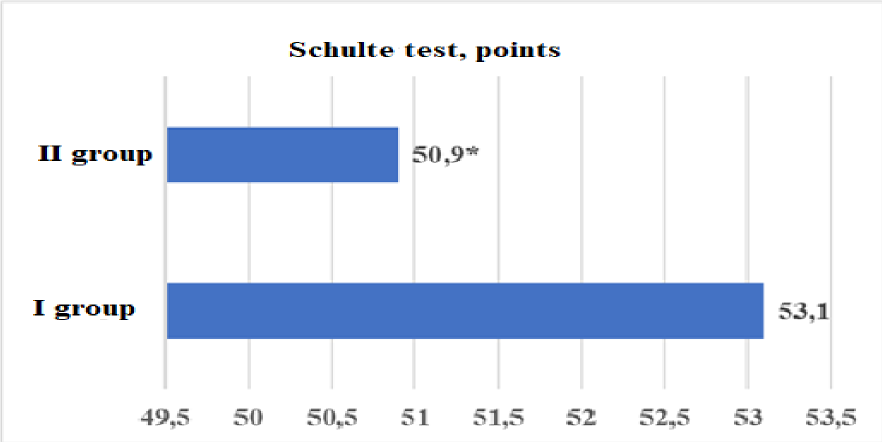

Figure 2. Results of testing according to the Schulte method

The exhaustion of attention according to the method of Schulte's tables in patients of group I and in healthy people fluctuated in the same ranges, while in patients of group II there was a dependence in which exhaustion increased as the test was performed. The work efficiency of patients in group I was 56.09%, in group II - 48.17%.

Table 4 shows that CVP indicators in patients with post-COVID syndrome (PCS) and in the control group (CG) had some distinctive features. There were significant differences in the latency of the P300 indicator.

For the rest of the analyzed indicators, the differences were not significant. When comparing the CEP values in patients with ACL and controls, we found a noticeable lengthening of the latency values in all leads. The differences in the indicators were significant when comparing the indicators between the CG and groups I and II, the differences in the indicators of the first group and the CG were unreliable.

Table 4 STM indicators in patients with PCS and CG

		Latency Options (ms)		
Method P300	**perception**	**identification**	**making decisions**	**RAM**
Examined groups	**N1**	**P2**	**N2**	**Ample N2/P3**
I group	235,5±1,3	347±2,1	109±1,9	19,8±0,9
II group	242,5±1,3	354±2,2	110,3±2,4	18,1±0,5
CG	233,6±1,6	333,7±2,1	104,8±2,6	20,7±0,8

Thus, the study of cognitive functions in the examined patients revealed the following: the sex of patients with PCS correlated with more pronounced cognitive impairment. Therefore, the determination of cognitive evoked potentials provides an opportunity to obtain additional information about the cognitive status of patients with PCS.

According to the results of other researchers, vascular dementia occurs more often in males than in females, especially in the age group up to 75 years [1,4]. This regularity, most likely, is also characteristic of the early - pre-dementia forms of vascular cognitive disorders, in particular the syndrome.Distinctive characteristics of CR in patients with PCS of different sexes can be explained by their initial features of the morphofunctional organization of the brain, as a result of which men have better visuospatial abilities compared to women, and women have better speech abilities and verbal memory [1].

When comparing P-300 values in patients with PCS compared with the control group, depending on gender, the following results were obtained. Table 5 clearly demonstrates the differences in the main KVP indicators for women and men. Thus, there were significant differences in the latency of P300. In men, this indicator was 397.85±63.21 ms, while in women it was 368.75±53.01 ms.

Table 5 Parameters of P300 evoked potentials in young people with PCS depending on gender

Options	Leads	I group	II group	CG
Latency P3, ms	C3	368,75±53,01 *^	397,85±63,21 *	351,9±24,3
	C4	367,62±52,63 *^	389,25±61,34 *	341,8±26,3
Amplitude N2/P3, μV	C3	7,50±3,30	7,81±3,29	5,2±3,28
	C4	7,59±3,0	7,6±2,9	5,6±2,91
Latency N2, ms	C3	255,81±34,14	285,91±39,1	268,4±41,7
	C4	251,18±32,67	271,18±22,7	269±47,2
Latency N3, ms	C3	460,40±77,82	465,40±78,27	457,2±54,3
	C4	461,86±79,84	465,68±74,48	451,7±60,3
Amplitude N3/P3, μV	C3	6,98±4,41	6,83±4,18	6,1±6,37
	C4	6,84±3,76	6,84±3,69	8,25±6,89

*Note: significant difference * - between CG - men and men; ^ - between CG - women and women.*

For the rest of the studied parameters, the differences were not significant. When comparing the indicators in the study of CEP in patients with PCS, an increase in latency in all leads was noted (Table 2).

4. Conclusion

In the study of cognitive functions in the examined patients, the following was revealed - the male sex correlated with more pronounced cognitive impairment. Therefore, the determination of cognitive evoked potentials provides an opportunity to obtain additional information about the cognitive status of patients with PCS.

The results of neuropsychological testing of patients with PCS were compared with modern criteria for pre-dementia disorders [1]. In the structure of cognitive disorders (KP) in patients with PCS, LCR significantly prevailed, which, according to the study, were more pronounced in males ($p<0.05$). The percentage of patients with PCS without cognitive impairment was approximately the same in men (80.4%) and women (86.1%). Thus, according to the results of neuropsychological testing, the overall CR score (according to the MMSE scales and the 10-word test according to Luria) turned out to be significantly higher in males ($p<0.05$).

Neuropsychological examination and cognitive evoked potentials are important methods for assessing the state of higher mental functions in patients with PCS and allow assessing the degree of involvement of the affected brain regions in the pathological process, as well as the functional state of the brain as a whole. The study showed differences in neuropsychological parameters depending on gender; in the group, men had significantly more pronounced CI and a lower rate of conduction of evoked cognitive potentials in the brain, in contrast to women.Moreover, the indicators on the MMSE scale in the group of women with PKS were also significantly higher than the corresponding indicators of the examined men with PKS. It should be assumed that the presence of post-covid syndrome triggers an early and accelerated process of cerebral ischemia, and males are at risk.

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