Short Comunications

Cognitive evoked potentials P300 and CNV in patients' with Parkinson disease

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ABSTRACT

A descriptive and traverse study was performed in patients with Parkinson's disease of the Neurology and Neurophysiology department of the Santiago General Hospital "Dr. Juan Bruno Zayas" from Santiago de Cuba, during the period from March 2017 to May 2018. The cognitive evoked potentials (P300-CNV) and a clinical neuropsychological evaluation were carried out.

Objective: To identify the relationship possible between cognitive evoked potentials and clinical-neuropsychological variables as diagnostic of the cognitive alterations that occur in patients.

Results: a significant prolongation of the latency, with a decrease in the amplitudes of the P300 and CNV with modifications in the morphology of the potential when the clinical neuropsychological evaluations were altered. These suggest that exist a delay in the cognitive processing of information, a decrease in the intensity of selective attention processes and hypofunction in cortical activation with asynchrony in the neurogenerators, in patients with Parkinson's disease, when the clinical and cognitive evaluations are altered.

Conclusions: the cognitive evoked potentials are useful, and complement the clinical and neuropsychological evaluation.

Key words: cognitive evoked potentials, CNV, P300, Parkinson's disease.

INTRODUCTION

Impaired cognitive functions in Parkinson's disease (PD) can occur at any stage, so identifying its presentation early can delay its transition to more severe phases; this is of great importance as it constitutes a very relevant risk factor for the development of dementia in the disease, compared to

those other Parkinson's patients without any type of cognitive impairment.[1] However, cognitive impairment may go unnoticed by both the patient, the family members and the professional, as it is usually very subtle, especially at the beginning, being progressive over time and affecting the activities of daily living in a large number of Parkinson's patients.[2]

The use of electrophysiological studies has the advantage over MRI neuroimaging and other studies, its high temporal resolution, as they represent the direct recording of the electrical activity of neural networks in the cerebral cortex.

Within the event related potentials (PRE) or endogenous evoked potentials, used to evaluate cognitive functions, the cognitive potential P300 (P300) and the negative variation contingency (CNV) have resulted in tests of greater applicability in clinical diagnosis; these are associated with variations related mainly to the intrinsic modulation of cerebral processes associated with perception mechanisms that change very little with physical parameters; which explains why they can reflect the mental changes caused by the disease and in normal aging.

The increase in prevalence and incidence with age, the greater survival of patients since the use of Levodopa, increases the possibilities of presentation of cognitive alterations in Parkinson's patients, which generates special attention by medical staff and the scientific community due to its high frequency and impact on the quality of life of patients and families.

Despite advances in the knowledge of its physiopathology in recent years, due to its multifactorial etiology, its final trigger and prevention remains an enigma. The diagnosis of suspicion is clinical and there are currently no specific diagnostic biological means and markers available to complement the clinical evaluation of this disorder. Therefore, in this research we intend to identify the possible relationship between the evoked potentials related to events and the clinical-neuropsychological variables as diagnostic means of the cognitive alterations produced in patients with Parkinson's disease.

METHODS

A transversal and descriptive study was performed on 30 patients with Parkinson's disease diagnosis who attended the Neurology and Neurophysiology consultation at the Santiago General Hospital "Dr. Juan Bruno Zayas" from Santiago de Cuba, who voluntarily accepted to be part of the study and who did not present neurophysiological, imaging and clinical signs that would guide the presence of a lesion at another level, not associated with the disease, had no disability (less than 5 on the Hoehn and Yahar scale) or severe cognitive impairment, during the period March 2017 to May 2018, patients had P300 and CNV evoked potentials and a neurological and neuropsychological evaluation with the Mini Mental State Examination.[3]

The electrophysiological studies were performed with Neuropack Four Mini equipment of Japanese manufacture, the surface electrodes of silver chloride (Ag-Cl) of 3mm diameter, were placed according to the international system 10-20.

For the P300 were located in Cz (Middle Central) - Channel 1, Pz (Middle Parietal) - Channel 2, the reference: Mastoids bilateral short-circuited. With impedance below 2 Ko, analysis time of 1000 ms, sensitivity: 50 uv and bandwidth: 1-50 Hz, type of stimulation: auditory (Tones), output: Bilateral, Intensity: 80 dB, frequent stimulus: 80% with frequency Tonal: 1 KHz. And infrequent stimulus: 20% and Tonal frequency: 2 KHz.

In the CNV two sensory stimuli were applied, the first stimulus S1 (Warning Stimulus) and the second stimulus S2 (Imperative Stimulus), were presented with a fixed time interval between them of 1 second. The patient responded by pressing a button manually to the second stimulus as quickly as possible. The analysis time was 5 sec, rejection level: +- 4 div, sensitivity: 50 uv, bandwidth: 1-50 Hz. The type of stimulation: Alert Stimulus (S1): Auditory. Tone, output: Bilateral, Intensity: 80 Db, phase: condensation. Output: bilateral, Imperative Stimulus (S 2): Visual (LED) and Output: Bilateral.

Data were presented in tables and graphs. The Pearson correlation coefficient was used to identify the possible correlation between the parameters of cognitive potentials with the clinical stage, evolution time and cognitive impairment. The student t test was used to identify differences in the parameters of cognitive potentials between Parkinson's patients and normal subjects, as well as between Parkinson's patients with attention and altered and unaltered memories. In all cases, a level of 5% significance was used.

RESULTS

The functional correlations of the components of the evoked cognitive potential P300 have been widely studied; there is consensus in most of the authors, in relating the discrimination capacity, with the latency of the N200 wave, the speed of information processing, with the latency of the P300 wave and the attention capacity, as well as the importance given to the task, with the amplitude of the P300 wave.[4.5] The meaning of the other components has not been fully clarified. In the generation of the CNV in humans is involved the Reticular Formation and correlates the morphology of the potential with its functional activity, on the other hand the processes of nonspecific attention and the level of cortical functional activation are related to the amplitude of the CNV.[6,7]

The non-motor symptoms are the least studied and least known in Parkinson's disease, in particular the alteration of higher mental capacities, either focal or multiple and the set of

decreases of different intellectual attitudes that can be associated with abnormal sensory, motor and personality modifications.

The relationship between the neuropsychological evaluation of cognitive impairment and the main parameters of cognitive potential P300 and CNV (Table 1) shows that for all components evaluated, values of longer mean latencies are obtained with a higher degree of cognitive impairment. This latency prolongation showed a very significant direct and proportional relationship for the N200 and the P300 ($p < 0.01$). The amplitude of the cognitive potential P300 and the CNV, shows a significant inverse relation tendency, although to a lesser extent in the CNV, to the decrease of the average amplitude of this component in patients with greater cognitive alteration. 50% of the patients (15) showed no cognitive impairment in neuropsychological evaluation and only 6 of the total showed moderate cognitive impairment.

Table 1. Results of the main parameters of P300 and CNV in patients with Parkinson's disease according to the neuropsychological evaluation of cognitive impairment

Cognitive Deterioration	N	Latency N200 (ms)		Latency P300 (ms)		Amplitude P300 (uv)		Amplitude CNV (uv)	
		$\overline{X}$	DS	$\overline{X}$	DS	$\overline{X}$	DS	$\overline{X}$	DS
No deterioration	15	224.4	8.28	345.8	12.08	13.0	2.47	27.3	2.02
Mild	9	235.3	7.68	361.6	11.16	7.68	2.27	10.38	3.83
Moderate	6	258.75	8.87	394.6	15.4	6.53	1.11	10.71	1.42

$p = 0.00018$ $p = 0.0033$ $p = 0.00521$ $p = 0.0237$ $p < 0.01$ $p < 0.05$

Source: Registries of the Department of Clinical Neurophysiology. General Santiago Hospital (ms): milliseconds (uv): microvolt

The amplitude of the P300 has been considered in clinical and experimental practice as an indicator of the intensity of the processes of selective attention, which is directly associated with the levels of expectation, attention and significance of the stimulus.[8] For its part, the magnitude of CNV amplitude is related to cortical functional activation level and non-specific attention processes.[9]

Table 2 shows the relationship between neuropsychological evaluation of attention and the main parameters of cognitive potential P300 and CNV. It can be seen that for all the components evaluated, values of longer mean latencies were obtained when attention was altered. This latency prolongation showed a non-significant relationship for latency N200 ($p = 0.06$), while it was significant for latency P300 ($p = 0.025$). The amplitude of the component of the P300 and CNV, show a much more significant inverse relation tendency, than the previous components ($p =$

0.015) and (p = 0.0041) respectively, to the decrease of the mean amplitude in the patients when the neuropsychological evaluation of the attention was altered. Patients[19] predominated without neuropsychological alteration of care.

Table 2. Results of the main parameters of P300 and CNV in patients with Parkinson's disease according to neuropsychological evaluation of care

Attention	N	Latency N200 (ms)		Latency P300 (ms)		Amplitude P300 (uv)		Amplitude CNV (uv)	
		$\overline{X}$	DS	$\overline{X}$	DS	$\overline{X}$	DS	$\overline{X}$	DS
Not altered	19	225.4	8.48	346.6	11.71	12.5	2.63	16.9	2.05
Altered	11	248.2	13.1	380.8	18.4	5.61	1.91	7.44	2.19
p = 0.06		p = 0.025		p = 0.015		p = 0.0041		p > 0.05	p < 0.05 p < 0.01

Source: Registries of the Department of Clinical Neurophysiology. General Santiago Hospital (ms): milliseconds (uv): microvolt

The relationship between the neuropsychological evaluation of memory and the main parameters of cognitive potential P300 and CNV (Table 3) shows that for all components evaluated, values of longer mean latencies are obtained when the memory was altered. This latency prolongation showed a significant direct relationship for N200 (p = 0.039); but not so for P300 (p = 0.053). Amplitude showed a significant inverse relationship, both for cognitive potential P300 (p = 0.0415) and CNV (p = 0.043), to the decrease in mean amplitude in patients with Parkinson's disease when neuropsychological evaluation of memory was altered. Patients[22] without neuropsychological memory alteration predominated.

Table 3. Results of the main parameters of P300 and CNV in patients with Parkinson's according to the neuropsychological evaluation of the memory

Memory	N	Latencia N200 (ms)		Latencia P300 (ms)		Amplitud P300 (uv)		Amplitud CNV (uv)	
		$\overline{X}$	DS	$\overline{X}$	DS	$\overline{X}$	DS	$\overline{X}$	DS
Not altered	22	227.0	8.49	349.6	12.4	11.49	3.25	15.6	3.46
Altered	8	255.2	10.8	387.7	16.04	4.87	1.34	6.30	1.32
p = 0.039	p = 0.0532		p = 0.0415	p = 0.043		p < 0.05	p > 0.05	p < 0.05	

Source: Registries of the Department of Clinical Neurophysiology. General Santiago Hospital (ms): milliseconds (uv): microvolt

The electrophysiological activity of the N200 is recognized by the authors as the activation of the subcortical regions, while the P300 is the activation of the cortical regions.[8] Flat comparisons show that N200 and P300 latencies are prolonged with respect to patients who do not have impaired neuropsychological evaluation of memory. It is of interest that the extension of the N200 component reaches statistical significance, with the extension of the P300 not showing the same significance, which coincides with the reports of other authors.[9] Discussion The results obtained in Table 1 demonstrate that the variables quantified in the potentials to cognitive events P300 and CNV, move away from their normal values, as cognitive deterioration increases, which is evidenced by the prolongation of the mean latency of the components N200, P300 and the tendency to decrease the amplitude of the components of P300 and CNV, which suggests that these components can be used both to detect and to evaluate the intensity of the cognitive alterations. The cognitive profile of Parkinson's patients has been discussed, and whether these deficits are due to a subcortical pathology or to a destruction of efferent fibers in the cortex.

The results obtained, which reveal a greater significance of N200 prolongation, support the concept of a subcortical base cognitive alteration, and there may be a relationship between cognitive alteration and motor dysfunction, which in turn is attributed to the loss of dopaminergic cells in the basal ganglia, although these results are not yet conclusive, as significant alterations of P300 latency prolongation and P300 and CNV amplitude were obtained to the extent that cognitive functions were altered. Another significant aspect is that it highlights that in patients with neuropsychological evaluation without cognitive impairment, latency values were obtained for N200 and P300 higher than the normative values, which were altered much more as the impairment of cognitive functions increased, suggesting a tendency to decrease the discrimination capacity and decrease the speed of information processing; so the N200 and P300 components could constitute an early electrophysiological marker in the detection of cognitive impairment in the early stages of the disease. Our results coincide with Balaban [10] and Sarikaya,[11] who agree on the usefulness of event-related potentials in the diagnosis of subclinical cognitive alterations present in Parkinson's patients. In patients with Parkinson's disease there are objective electrophysiological signs of a decrease in the intensity of the attention processes and the level of expectation, as well as a hypofunction of the cortical activation, as can be seen in Table 2. It has been established that the delay in cognitive speed preferentially affects the initial stage in the generation of this potential, considering that the reduction in amplitude is more marked between the N200-P300 peaks.

The reduction of the amplitude of the evoked cognitive potential in these patients has been reported in the literature consulted, depending on the value of the incentive or motivational stimulus; on the level of expectation of the subject, on how unexpected the stimulus is and on the degree of discrimination between frequent and infrequent stimuli that are clearly affected in

Parkinson's. The reduction of the amplitude of the evoked cognitive potential in these patients has been reported in the literature consulted, depending on the value of the incentive or motivational stimulus; on the level of expectation of the subject, on how unexpected the stimulus is and on the degree of discrimination between the frequent and infrequent stimulus that are clearly affected in Parkinson's.[8] Karayanidis and Andrews[12] also found a decrease in the amplitude of the P300 component, suggesting that the orientation response to new stimuli is impaired in patients, so that event-related potentials could provide, from a neurophysiological point of view, and in particular the amplitude parameters of the PRE, a quantitative measure of attention deficit in Parkinson's patients.

The significant reduction in the amplitude of P300 and CNV express a decrease in the intensity of attention processes and levels of expectation, as well as a hypofunction of cortical activation, which is consistent with the clinical state of patients characterized by hyporeactivity to sensory stimulation, reaching even, in the most severe cases, the inability to respond to environmental stimuli. From the electrophysiological point of view, the amplitude of cognitive evoked potentials has been correlated with attention disorders. However, the results of this study show that the latency of the N200 and P300 are modified when attention is altered, significantly in the case of the P300, which could suggest that the P300 latency that reflects the information processing time could constitute a sensitive temporal measure of nervous activity, of the assignment of underlying attention and of immediate memory; associated with cognitive action, which is modified by neuropsychological alterations in attention. The results shown in Table 3 suggest that the dysfunction of memory processes is preferably attributable to the subcortical dysfunction characteristic of this disease. The clinical and electrophysiological findings are evidence of the role of base nuclei in memory processes, preferably attributable to the alteration of subcortical structures involved in the formation of memory, such as the hippocampus, amygdale, dorsomedial nucleus of the thalamus, among others.[13]

CONCLUSIONS

The integral analysis of the results obtained shows a close relationship between the parameters of PRE P300 and CNV insofar as the clinical neuropsychological evaluations were altered; which suggests that these potentials turn out to be a sensitive alternative that complements the clinical-neuropsychological evaluation due to its feasibility in the evaluation of cognitive functions; contributing elements of objectivity in the interpretation of the physiopathological disorders associated with this disease.

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