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COGNITIVE EVENT-RELATED POTENTIALS (P300) AND COGNITIVE IMPAIRMENT IN DUCHENNE MUSCULAR DYSTROPHY

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Duchenne muscular dystrophy (DMD) is a progressing disorder characterized by muscle wasting and weakness due to the absence or alteration of the function of dystrophin that protects muscle cells from mechanical stress induced by a movement during contraction. The function of dystrophin isoforms expressed in the brain is not fully understood, but the presence of non-progressing cognitive impairment (including disorders of learning and memory) is a common feature in patients with DMD. To establish correlation between the cognitive event-related potential P300 and psychological evaluation with an intelligence test based on the Stanford and Binet Intelligence Quotient (IQ) in patients with DMD and a control group, the respective tests were performed in 31 patients with DMD and 30 controls. The mean age of the group with DMD was 9.35 ± 2.88 years, while that in control children was 9.43 ± ± 2.69 years ($P = 0.89$). The IQ was 90.77 ± 12.62 in the DMD group and 106.77 ± 9.62 in the controls ($P < 0.0001$). The amplitude of the cognitive potential P300 in leads Fz, Cz, and Pz showed no statistically significant differences between the groups. Thus, parameters of the P300 potential and cognitive assessment showed no relationship in patients with DMD *vs*. controls.

Keywords: Duchenne muscular dystrophy, cognition, event-related potentials, P300, Intelligence Quotient (IQ).

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a neuromuscular disease characterized by progressing weakness that eventually leads to disability and early death [1]. This pathology is due to the absence of a functional muscle protein, dystrophin; the reason is mutations in the *DMD* gene located in Xp21.2 [2]. It is believed that the function of muscle dystrophin is the protection from mechanical stress to muscle fibers during contraction. Dystrophin isoforms are also expressed in the brain, and their function is not completely known [3]. Dystrophin with the molecular mass of 427 kDa is expressed in cortical neurons and Purkinje cells of the cerebellum. Other four isoforms are also located in the CNS; these are Dp260 (located in the outer plexiform retinal layer), Dp140, Dp116 (Schwann cells), and Dp71. Non-motor manifestations of DMD have been described; these disorders may be due to CNS-located dystrophin isoform alterations affecting the ability to react to certain stimuli. It has been shown that the retinal Dp260 isoform mutation is associated with color (red and green) vision impairment [4]. Furthermore, a DMD-related non-progressing cognitive deficit has been reported, with one standard deviation below the reference Intellectual Quotient (IO) [5]. A recent study showed that there are brain volume abnormalities in DMD patients, with decreases in the total and gray matter brain volumes [6]. On the other hand, cognitive event-related potentials (CERPs), in particular the widely known P300 wave, are long-latency potentials associated with mental processes; they are generated in response to informative auditory, visual, motor, or specific-task stimuli.

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The P300 amplitude is related to the memory formation and indicates the amount of CNS activity related to the action of an information input. The latency of this potential reflects the stimulus sorting speed; it is independent of the reaction time behavior and can be used for the measurement of a cognitive function.

Parameters of P300 are affected in neuropsychiatric diseases, normal aging, and other cognitive disorders; these parameters can be used as indicators of mental changes corresponding to the cognitive impairment [7]. Cognitive deficit is associated with the P300 latency and amplitude changes.

Abnormalities of P300 potentials in myotonic dystrophy-affected individuals have been described [8], and cognitive deficiency in DMD patients has also been widely documented. Our objective was to establish whether there is a relationship between the parameters of the P300 cognitive potential and results of the psychological Stanford and Binet intelligence evaluation test in DMD patients and in a control group.

METHODS

An open, prospective, comparative, and analytical study was conducted at the "Luis Guillermo Ibarra Ibarra" National Institute of Rehabilitation (INR) in Mexico City. Five- to 15-year-old patients with DMD were included. Definite diagnosis was made according to STARnet MD criteria [9] (based on clinical features, CPK level, DNA study, and protein analysis by immunostaining). All participants were found to be able to understand the study and agreed to participate. Five- to 15-year-old healthy children with no illness history or a current illness involving the CNS, with normal auditory and visual potentials, were taken as the control group.

All participants in the study underwent a psychological evaluation and neurophysiological study including (i) recording of cognitive event-related potentials, (ii) that of auditory brainstem potentials, (iii) that of visual potentials, and (iv) Stanford and Binet Intelligence Test [10] with the assessment of IQ and estimation of the cognitive functions and dimensions (language, memory, conceptual thinking, reasoning, numerical reasoning, visual-motor area, and social intelligence). To record the audio and visual potentials, the Nicolet Biomedical Viking Select 9.0 (USA) equipment was used; for the measurements and analysis of cognitive potentials, P300 ANT Neuro and Cognitrace Eemagine computer software was used.

Visual and binaural acoustic stimulations were applied using a display module with a random-event (stimulating signal) reproducing the conditions and parameters described by the International Federation of Clinical Neurophysiology [11]. Stimulation tone parameters were composed of 75 dB-intensity 50-msec segments (10-msec-long raising and lowering phases). The tones were presented in randomized sequences with 80% of the common tones of 1000 Hz and 20% of the 2000-Hz infrequent tones. Significant stimuli presentation likelihood was 0.5 tone per one second. Interstimulus intervals randomly fluctuated within the range of 1.0 to 1.5 sec. The children were instructed to press a button immediately after presentation of the significant stimulus (higher pitch). The electrode impedance was kept below 5 kΩ.

An EEG cap with surface electrodes was used for recording of bioelectrical signals, as established by the international 10–20 system. The latencies at the maximum amplitude point of the evaluated component in the Fz, Cz, and Pz electrodes were measured.

For statistical analysis, screening was performed using descriptive methods to evaluate the sample characteristics. Frequency measures were determined for qualitative variables (maximum and minimum), and central tendency, and dispersion measures were estimated for numerical variables. The distribution curves were evaluated with the Kolmogorov–Smirnov test. For inferential statistics, the Student's *t*-test was used for those numerical variables that corresponded to the normal law; for those that did not fit such a curve, nonparametric tests were used. An adjusted chi-square was used for qualitative variables. A $P < 0.05$ was accepted to reject the null hypothesis; SPSS, version 18 software was used.

RESULTS

Sixty-one 5- to 14-year-old boys were included in the study. The DMD group comprised 31 children, whose mean age was 9.35 ± 2.88 years (M ± s.d.), while the controls were 30 children, and their average age was 9.43 ± 2.69 years ($P = 0.89$).

Eight children in the DMD group (25.8%) were found to be deficient in concrete thinking evaluation, while all 30 control children were normal ($P < 0.05$). In the language dimension, three DMD-affected children (9.67%) demonstrated below-normal levels, while the control-group boys were all normal ($P = 0.23$). In

T a b l e 1. Proportions of Children with Below-Normal Results (Sanford and Binet Evaluation) in the Examined Group

T a б л и ц я 1. Кількість дітей із оцінками нижче норми при використанні системи Стенфорда–Біне

Psychological sphere, dimension	DMD group (n = 31)	Control group (n = 30)	Intergroup comparison, P
Memory	12 (38.7%)	1 (3.22%)	**0.001**
Conceptual thinking	8 (25.80%)	0	**0.005**
Language	3 (9.67%)	0	0.23
Reasoning	10 (32.25%)	0	**0.001**
Numerical reasoning	12 (38.70%)	0	**0.001**
Visuospatial perception	4 (12.90%)	0	0.113
Social Intelligence	8 (25.80%)	2 (6.45%)	0.08

reasoning, ten DMD-affected children (32.25%) were deficient and none in the control group (P <0.001). In the field of numerical reasoning, twelve DMD-suffering children (38.7%) were below a normal range vs. none in the control group (P < 0.001). Four subjects of the DMD group (12.9%) were deficient in the spatial perception dimension vs. none in the control group ($P \leq 0.113$). For social intelligence, eight DMD-affected children (25.8%) were deficient vs. two (6.45%) in the control group (P < 0.08) (Table 1).

As was observed, children with DMD were stratified in a lower level compared to the controls (P < 0.001) according to the Stanford and Binet Intelligence Test (Table 2). The median IQ value for the DMD group was 90.77 ± 12.62, while in the control group this was 106.77 ± 9.62 (P < 0.0001); at the same time, both these values remained within a normal range.

The results of analysis of the cognitive potential P300 were the following. In site Fz, the mean amplitude in the DMD group was 7.48 ± 7.46 μV, while in the control group this was 7.80 ± 5.07 μV ($P \leq 0.48$). The mean latency of P300 in this site was 316.03 ± 34.05 msec in the DMD group vs 318.30 ± ± 23.92 msec in the control group, i.e., these values were practically equal to each other ($P \leq 0.74$). For the Cz electrode, the mean latencies in the above groups were 312.97 ± 32.79 and 318.30 ± 16.92 msec, respectively ($P \leq 0.89$). The mean P300 amplitude in this site in the DMD group was 7.83 ± 5.24 μV, while in the control group this was 6.03 ± 3.41 μV (the difference did not reach the significance level; P < 0.11). For electrode Pz in the DMD and control groups, the average latencies were 320.81 ± 31.06 and 314.57 ± 23.41 msec, respectively (the difference also was below the significance level; $P \leq 0.378$). In the Pz, the mean amplitudes in DMD and control children were 10.07 ± 7.26 and 10.49 ± 7.58 μV ($P \leq 0.83$) (Table 3).

Thus, there were some intergroup differences between mean values of the P300 latency and amplitude, but in any case these dissimilarities were statistically insignificant.

T a b l e 2. Distribution of Cognitive Levels (According to the Stanford–Binet Intelligence Test) in the Examined Group

T a б л и ц я 2. Розподіл когнітивних рівнів згідно з тестом Стенфорда–Біне

Cognitive level	DMD (n = 31)	control (n = 30)
Top	1 (3.22%)	3 (10.00%)
High Normal	0	10 (33.33%)
Normal	18 (58.06%)	16 (53.33%)
Normal-low	7 (22.58%)	1 (3.33%)
Borderline	2 (6.45%)	0
Deficient	3 (9.67%)	0
	P	**0.001**

T a b l e 3. Average Parameters of the P300 Cognitive Potential

T a б л и ц я 3. Середні значення параметрів когнітивного потенціалу P300 в обстежених групах

Lead, parameter	DMD (n = 31)	control (n = 30)	P
Fz			
Amplitude, μV	7.48 ± 7.46	7.80 ± 5.07	0.48
Latency, msec	316.03 ± 34.05	318.30 ± 23.92	0.74
Cz			
Amplitude, μV	7.83 ± 5.24	6.03 ± 3.41	0.11
Latency, msec	312.97± 32.79	318.30 ± 16.92	0.89
Pz			
Amplitude, μV	10.07 ± 7.26	10.49 ± 7.58	0.83
Latency, msec	320.81 ± 31.06	314.57 ± 23.41	0.37

DISCUSSION

Currently, the P300 is one of the best-known and studied evoked potentials providing information about the neural basis of cognition [12]. Its expression is associated with conscious cognitive processes, attention in particular [13], and storing of information coded in short-term memory [14].

The P300 is a positive wave whose peak occurs around 300 milliseconds after the significant (informative) stimulus. It appears when a focused subject is discriminating an important stimulus from another; the amplitude of this wave correlates with the amount of "attentional" sources in immediate memory processes and reflects the brain work linked to the tasks required for the memory maintenance. The P300 amplitude is proportional to the amount of attention used in a particular task and is associated with the memory performance [15, 16].

The P300 amplitude expresses the attention degree to input information when memory is participating; it increases with the interhemispheric communication and decreases at dysfunction of the *corpus callosum* [17]. The P300 latency measures the stimulus-qualifying velocity, but not the response selection; it expresses the pre-response processing time, or cognitive processing velocity. It also reflects the time required to allocate resources and to upgrade memory in a given task.

A correlation between the P300 latency and mental performance has been described. Abnormalities of this parameter are linked to normal aging [18] and diseases affecting cognition [19].

The DMD patients often have cognitive impairments. Cyrulnik et al. [20] and Hinton [21] found cognitive abnormalities in children with DMD detected by their parents. These authors described weak verbal skills and memory deficits in these children. Other studies have shown deterioration of the cognitive functions in children with DMD using different tools, such as the Denver Developmental Screening Test, Griffith Mental Development Scale, Stanford and Binet intelligence test, and Bayley III evaluation [22–27] among others. It has been convincingly documented that children with DMD have a non-progressing cognitive deficit, usually of one standard deviation. Cotton et al. [5] in their meta-analysis of 1224 DMD patients (age from 2 months to 27 years) found that younger children have deficits in verbal reasoning and processing, while children over 14 years were less likely to have these problems. Other researchers have found that children with DMD have below-normal scores in global intelligence evaluations, especially in verbal processing assessment [20, 23, 28]; language, memory, attention, and emotional skills also demonstrated some abnormalities in patients with DMD.

In our study, DMD patients and control children were of a comparable school age. The IQ estimated in both groups was within "normal" limits, but noticeably higher among controls. This difference was significant in conceptual thinking, reasoning, and numerical reasoning where there were lower scores among patients with DMD. In the social intelligence assessment, we found a noticeable trend towards lower scores between DMD patients, although statistically insignificant. Several researchers have found differences in the cognitive status according to age; however, in our study the subjects were 5 to 14 years old; so, we do not consider age stratification appropriate.

Veiga et al. [29] found a great variability in normal subjects during the procedure standardization; the authors also noted that this was a consistent neurophysiological marker in various neurological diseases, and this peculiarity has been verified by many studies.

The IQ, although being within the normal range (90.77 ± 12.62 vs. 106.77 ± 9.62), was lower in DMD-affected children vs. controls with a statistically significant difference. When the cognitive level was evaluated, there was also a significant difference with a lower performance in the DMD group. Della Coletta et al. [7] studied 16 patients with DMD vs. 20 controls; in their sampling, the mean IQ was 64.35 vs. 82.68 ($P < 0.01$). It is noteworthy that the differences between the groups also do exist in our study. The DMD children reached the levels of "normality" unlike what Della Coletta et al. found. This is probably due to the type of population, as our patients were monitored in a national reference center and usually had better socioeconomic conditions than a national average. Other possibility could be that they were too young to detect changes that dramaticaly modified the IQ. This opens the necessity of further studies. Della Coletta et al. [7] did not find significant differences in the values of both P300 latency and amplitude between DMD patients and their controls; three conventional electrodes were used. Nevertheless, we found that some parameters differ in DMD patients; especially this was related to the amplitude in the center electrode (Cz).

No satisfactory explanation for the lack of correlation between cognitive impairment and changes in P300 is yet established. One possibility is the great variability within normal values of this potential in both groups. A larger group of patients is probably desirable. On the other hand, there are distractors in pediatric evaluations that could affect the proper execution of the test instructions. However, it is obvious that this would affect both groups randomly. It should also be considered that the examined potential is not sensitive enough for the type of cognitive disorders that occur in patients with DMD. Further studies are needed to define the role of the P300 in cognitive assessment in DMD-affected individuals.

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Informed consent was obtained from all participants; written consent was obtained from all patient parents. All procedures performed were in accordance with the ethical standards of the Helsinki declaration and were approved by the respective Ethics Committees.

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КОГНІТИВНІ ПОТЕНЦІАЛИ, ПОВ'ЯЗАНІ З ПОДІЄЮ (P300), ТА РОЗЛАДИ КОГНІТИВНОЇ СФЕРИ У ПАЦІЄНТІВ ІЗ М'ЯЗОВОЮ ДИСТРОФІЄЮ ДЮШЕНА

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Р е з ю м е

М'язова дистрофія Дюшена (Duchenne muscular dystrophy – DMD) є прогресуючим розладом із втратою м'язової маси та послабленням м'язів; патологія розвивається через відсутність або альтерацію функцій білка дистрофіну. Останній захищає м'язові клітини від механічного стресу, індукованого скороченнями м'язів. Функції ізоформ дистрофіну, експресованих у головному мозку, з'ясовані не до кінця, але наявність непрогресуючого ушкодження когнітивних функцій (включаючи розлади навчання та пам'яті) є загальною особливістю пацієнтів із DMD. Намагаючись оцінити кореляцію між параметрами когнітивних потенціалів, пов'язаних із подією (P300), та психологічними оцінками рівня інтелекту (IQ, тест-система Стенфорда та Біне) у пацієнтів із DMD і осіб групи контролю, ми піддали відповідному тестуванню 31 пацієнта та 30 контрольних суб'єктів. Середній вік дітей у групі DMD та групі контролю складав 9.35 ± 2.88 та 9.43 ± 2.69 року відповідно (P = 0.89). Середні значення IQ у цих групах дорівнювали 90.77 ± 12.62 та 106.77 ± 9.62 відповідно ($P < 0.001$). Середні значення амплітуд та латентних періодів когнітивного потенціалу P300 у відведеннях Fz, Cz та Pz не продемонстрували істотних міжгрупових відмінностей. Отже, параметри когнітивного потенціалу P300 у пацієнтів із DMD та контрольних осіб не мали істотних розбіжностей, тоді як певна різниця спостерігалася в оцінках IQ.

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