Arq Neuropsiquiatr 2007;65(1):59-62

EVENT-RELATED POTENTIALS (P300) AND NEUROPSYCHOLOGICAL ASSESSMENT IN BOYS EXHIBITING DUCHENNE MUSCULAR DYSTROPHY

Marcus Vinicius Della Coletta[1], Rosana Herminia Scola[1], Gislaine Richter Minhoto Wiemes[2], Cláudia Nasser Fonseca[3], Maria Joana Mäder[3], Aline Andrade Freund[4], Lineu César Werneck[1]

ABSTRACT - *Objective:* To examine auditory cognitive evoked potentials (P300 potentials) and neuropsychological dysfunction in patients with Duchenne muscular dystrophy (DMD). *Method:* P300 potentials and neuropsychological test results were obtained from 16 healthy control boys and 20 DMD patients. Full Intelligence Quotients (IQ) were estimated for patients and control group. Mean age was 9.5 years in the DMD patient group, and 10 years in the control group (p>0.05). *Results:* The mean IQ values were 64.35 in the DMD patients and 82.68 in the control group (p=0.01). Mean P300 values were 347.6 in the DMD group and 337.4 in the control group (p=0.14). There was no significant correlation between parameters in each group. *Conclusion:* DMD patients showed a poor performance as evaluated by P300 potential compared to the control group, although the difference was not statistically significant. Systematic alterations in neuropsychological test results were found, the differences paralleling those detected in IQ.

KEY WORDS: P300, Duchenne muscular dystrophy, neuropsychologic dysfunction.

Potencial evocado cognitivo (P300) e testagem neuropsicológica em pacientes com distrofia muscular de Duchenne

RESUMO - *Objetivo:* Avaliar potenciais evocados cognitivos auditivos (P300) e disfunções neuropsicológicas em pacientes com distrofia muscular de Duchenne (DMD). *Método:* Potenciais auditivos P300 e testes neuropsicológicos foram obtidos de 16 controles e 20 pacientes com DMD. Valores de quociente de inteligência (QI) foram estimados para os dois grupos. A media de idade foi de 9.5 anos no grupo DMD e 10 anos no grupo controle (p>0.05). *Resultados:* Os valores médios de QI foram 64.35 no grupo DMD e 82.68 no grupo controle (p=0.01). A média de valores de P300 foi 347.6 no grupo DMD e 337.4 no grupo controle (p=0.14). Não houve correlação significativa entre os parâmetros em cada grupo. *Conclusão:* Os pacientes com DMD mostraram um pior desempenho nas testagens de P300 quando comparados com o grupo controle, embora a diferença não tenha apresentado diferença significativa. Alterações sistemáticas foram encontradas nos testes neuropsicológicos, correspondendo às alterações significativas vistas nos valores de QI.

PALAVRAS-CHAVE: P300, distrofia muscular de Duchenne, disfunção neuropsicológica.

It is widely accepted that patients afflicted with Duchenne muscular dystrophy (DMD) present cognitive deficits, generally manifested as a reduced full intelligence quotient (IQ) when compared to that of the general population[1]. A complex profile of cognitive disorders has been disclosed, particularly as regards verbal IQ; however, language, memory, attention and emotional skills are also altered in DMD patients[2-5]. The most recent studies of the neuropsychological profile associated with DMD demonstrate deficits related to currently known genetic alterations[6,7].

In 2004, Veiga et al. developed a brazilian database study for P300 using a visual discrimination task[8]. The values found showed high variability in normal subjects. P300 potentials have been used as a reliable neurophysiological marker for various neurological conditions. Multiple sclerosis, stroke, Alzheimer's disease and myotonic dystrophy are illnesses that have been analyzed employing this test[9-12]. Visioli-Melo and Rotta[13], analyzing epileptic brazilian children, did not found differences in P300 when compared with non epileptic children. In a study evaluating

[1]Neuromuscular/Neurology Division, Internal Medicine Department, Hospital de Clínicas. Universidade Federal do Paraná, Curitiba PR, Brazil (UFPR); [2]Otorrinolaringology Service, Surgery Department, Hospital de Clínicas, UFPR; [3]Psychology Service, Hospital de Clínicas, UFPR; [4]Neuromuscular and Genetic Laboratory, Hospital de Clínicas, UFPR.

Received 19 May 2006, received in final form 4 August 2006. Accepted 6 October 2006.

Dr. Marcus Vinicius Della Coletta - Serviço de Neuromuscular - Rua General Carneiro 181 / 3º andar - 80060-900 Curitiba PR - Brasil. E-mail: neurocoletta@hotmail.com

myotonic dystrophy patients, P300 values were altered in 57% of patients, with a significant difference compared to the control group when separated by age[12].

The aim of this study is to obtain P300 potentials and perform neuropsychological tests to evaluate the P300 findings with respect to cognitive impairment in DMD patients.

METHOD

Local Institutional Review Board approved the methodology and ethics issues of the study. Written, informed consent was obtained previously from each patient's parents in accordance with local Institutional Review Board policy.

Subjects – Twenty children, ages between 6 and 15 years (mean 9,5; SD 2.3 years), with diagnosis of DMD through clinical and DNA analysis, or biopsy and immunohistochemistry, participated of the study. The patients were from the neuromuscular division of neurology service of Hospital de Clínicas, Universidade Federal do Paraná. All patients were able to perform motor skills with their hands. Sixteen boys with similar economical and cultural profile, from a routine outpatient service of the university, were the control group. Their mean age was not significantly different from that of the DMD patient group (mean 10 years; SD 2.6 years, p=0.16). The same recording methods were used in the DMD patient and control groups.

Cognitive measurement – The Weschler Intelligence Scale for Children – third edition (WISC III)[14] was administered to all boys, and a full intelligence quotient (IQ) was established. The WISC-III sub-tests used were information, similarities, vocabulary, digit span, picture completion and block design. An expert neuropsychologist applied all tests.

P300 – The P300 potentials were elicited using a standard oddball paradigm. Measurements were performed using a Nihon Koden - Neuropack 2 device. Subjects were presented with a series of binaural tones at 70-db intensity, with a 10 ms rise/fall and 100 ms plateau duration. The tones were presented in a random sequence with a 2000 Hz tone (target) constituting 20% of the period, and a 1000 Hz tone (standard) comprising the remaining 80% of the period, at a rate of 0.5 tones per second. DMD patients and control boys were instructed to perform a silent count of the target tones and to report the number at the end of the series. All electrode impedance was maintained at 5 KW or less throughout the recording.

Electroencephalographic activity was recorded from scalp AgCl electrodes at the Fz, Cz and Pz sites, according to the international 10 to 20 system, employing linked earlobe electrodes with a forehead ground electrode. Responses to target and standard tones were averaged separately. Stimuli were presented until 30 artifact-free, target trials were obtained. Each patient was tested twice to ensure reproducibility of waveform components.

Statistical analysis – To compare the P300 values, and the IQ between the DMD patient group and the control group, a student t-test using a 95% confidence interval was applied. Pearson's correlation coefficient was calculated for parameters within each group. The Mann-Whitney, non-parametric analysis was used when data distribution was not normal. The data were analized with Epi Info v6.0 software.

RESULTS

The IQ values for the DMD patients ranged from 45 to 95 (mean 64.35; SD 14.12), and those for the control group were between 71 and 99 (mean 82.68; SD 8.92) (Fig 1). These mean IQ values are significantly different (p=0.01).

The P300 values in the DMD group varied from 300 to 402 (mean 347.60; SD 28.23); P300 values in the control group ranged from 303 to 409 (mean 337.4; SD 28.3) (Fig 2). There was no statistical difference in mean P300 values between the two groups

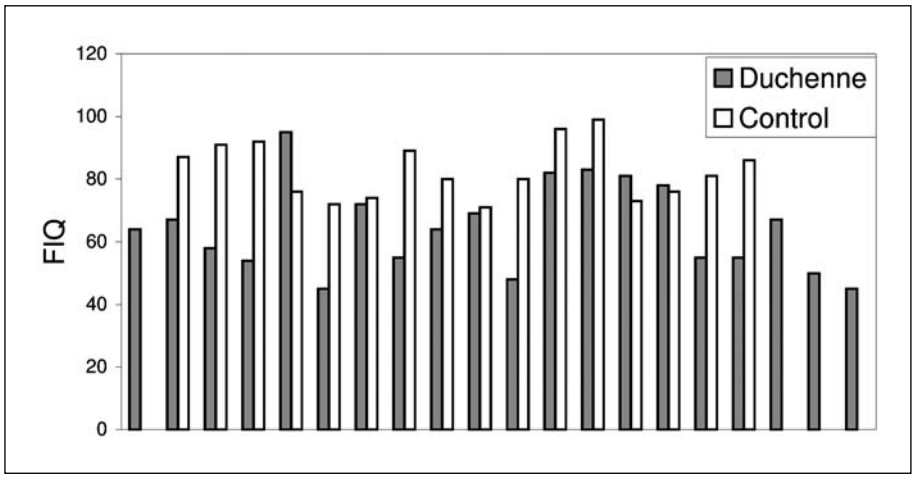

Fig 1. Distribution of full intelligence quotient values in DMD afflicted and control subjects.

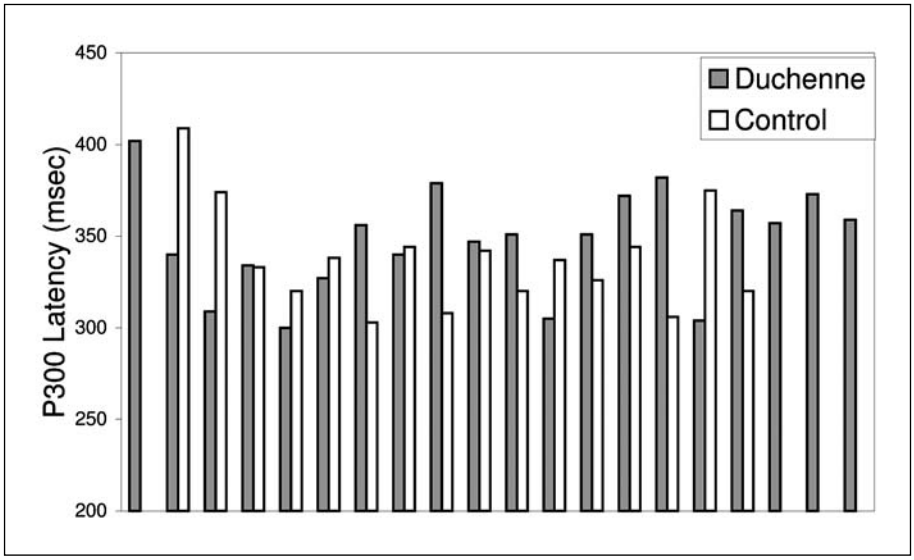

Fig 2. Distribution of P300 latencies from DMD afflicted and matched control subjects.

Table 1. Summary of neuropsychological test findings, P300 latency and amplitude data in DMD patients and control group.

DMD				Control			
Age	P300	Amp	IQ	Age	P300	Amp	IQ
6	402	2.16	64	5	337	4.78	80
6	340	5.04	67	7	374	7.73	91
7	309	7.25	58	7	320	5.16	86
8	334	3.57	54	9	333	1.64	92
8	300	3.86	95	9	344	17.6	74
8	327	7.66	45	9	326	6.3	96
8	356	6.7	72	9	306	8.85	73
8	340	4.02	55	10	409	6.47	87
9	379	12.8	64	10	320	1.39	71
9	347	12.4	69	11	303	8.54	72
9	351	5.24	48	12	338	5.84	76
9	305	7.97	82	12	375	5.31	81
10	351	5.57	83	13	308	7.03	89
10	372	8.06	81	13	342	6.73	80
11	382	7.02	78	14	320	1.71	76
11	304	16.9	55	16	344	3.96	99
12	364	5.26	55				
13	357	6.54	67				
13	373	4.64	50				
15	359	16.1	45				

DMD, Duchenne muscular dystrophy; IQ, full intelligence quotient; Amp, amplitude.

Table 2. Statistical findings for parameters evaluated in DMD afflicted and paired, control subjects.

	DMD			Control			p value
	Range	Mean	SD	Range	Mean	SD	
IQ	45 - 95	64.35	14.12	71 - 99	82.68	8.92	0.01
P300	300 - 402	347.60	28.23	303 - 409	337.43	28.3	0.14

IQ, intelligence quotient; DMD, Duchenne muscular dystrophy.

(p=0.14).

Amplitude measurements were performed but no correlation was found: DMD group mean, 7.56 μV and SD 4.13 μV; Control group mean, 6.19 μV and SD 3.8 μV (p=0.17).

WISC-III sub-tests showing statistical differences were "information" (p=0.001), "digit spam" (p= 0.004), "vocabulary" (p=0.0003), "picture completion" (p=0.001) and "block design" (p=0,006). "Similarities" showed no significant difference (p=0,08).

The P300 values and the neuropsychological findings for the two groups are summarized in Table 1. The statistical findings for parameters (IQ and P300) in DMD and controls are in Table 2.

DISCUSSION

In 1965, Dubowitz described cognitive dysfunctions in boys afflicted with DMD[15]. It is now established that affected individuals exhibit specific, cognitive abnormalities[16]. The core profiles of neuropsychological abnormalities lie in the areas of attention modulation, verbal short-term memory and phonological language processing[16-17]. Our findings for cognitive functions show notable, significant differences (p<0.01) in digit span, block design and vocabulary tests, with poor performance in information and picture completion in the DMD group (p<0,001), the latter being justified by motor deficits. Bardoni et al. reported important differences in IQ with respect to genetic subtype[17]. We found a marked difference in IQ values (p=0.01), however there were no correlation with P300 data.

The P300 differ between the two groups, although statistical significance was not reached. Previous results for P300 potentials and dystrophinopathies come from myotonic dystrophy patients. Kazis et al. showed that the P300 values differed only in patients older than 36 years of age[12]. Our findings differ from this view, with no differences of P300 values corresponding to older patients.

There was no correlation between any of the parameters showing that older DMD patients did not perform more poorly than younger patients. This finding agrees with the current notion that age does not affect cognition in DMD patients[18].

In conclusion, this study finds no statistical differences in P300 values in DMD patients compared to a control group. The neuropsychological test findings show marked variation between the two groups with regard to cognitive analysis.

REFERENCES

1. Karagan NJ. Intellectual functioning in Duchenne muscular dystrophy: a review. Psychol Bull 1979;86:250-259.
2. Bushby KM. Genetic and clinical correlations of Xp21 muscular dystrophy. J Inherited Metab Dis 1992;15:551-564.
3. Fitzpatrick C, Barry C, Garvey C. Psychiatric disorder among boys with Duchenne muscular dystrophy. Dev Med Child Neurol 1986;28:589-595.
4. Natori N. A case of atypical Duchenne type muscular dystrophy with fragile X. Jpn J Hum Genet 1992;37:235-239.
5. Smith RA, Sibert JR, Harper PS. Early development of boys with Duchenne muscular dystrophy. Dev Med Child Neurol 1990;32:519-527
6. Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. Neurology 2000;54:2127-2132.
7. Felisari G, Martinelli B, Bardoni A, et al. Loss of Dp140 dystrophin isoform and intelectual impairment in Duchenne dystrophy. Neurology 2000;55:559-564.
8. Veiga H, Deslandes A, Cagy M, et al. Visual event-related potential (P300) - A normative study. Arq Neuropsiquiatr 2004;62:575-581.
9. Gil R, Zai L, Neau JP, et al. Event-related auditory evoked potentials and multiple sclerosis. Electroenceph Clin Neurophysiol 1993;88: 182-187.
10. Korpelainen JT, Kauhanen ML, Tolonen U, et al. Auditory P300 event related potential in minor ischemic stroke. Acta Neurol Scand 2000; 101:202-208.
11. Polich J, Ladish C, Bloom FE. P300 assessment of early Alzheimer's disease. Electroenceph Clin Neurophysiol 1990;77:179-189.
12. Kazis A, Kimiskidis V, Georgiadis G, Kapinas K. Cognitive event-related potentials and magnetic resonance imaging in myotonic dystrophy. Neurophysiol Clin 1996;26:75-84.
13. Visioli-Melo JF, Rotta NT. Avaliação pelo P300 de crianças com e sem epilepsia e rendimento escolar. Arq Neuropsiquiatr 2000;58:476-484.
14. Weschler D. Weschler Intelligence Scale for Children - Third Edition (WISC-III). San Antonio, TX : Psychological Corporation, 1991.
15. Dubowitz V. Intellectual impairment in muscular dystrophy. Arch Dis Child 1965;40:296-301.
16. Mehler MF. Brain dystrophin, neurogenetics and mental retardation. Brain Res Rev 2000;32:277-307.
17. Bardoni A, Felisari G, Sironi M, et al. Loss of Dp 140 regulatory sequences is associated with cognitive impairment in dystrophinopathies. Neuromusc Disord 2000;10:194-199.
18. D'Angelo MG, Bresolin N. Report of the 95th European Neuromuscular Centre (ENMC) sponsored International Workshop Cognitive Impairment in Neuromuscular Disorders, Naarden, The Netherlands, 13-15