Dundar BN, et al., J Neonatol Clin Pediatr 2014, 1: 003
DOI: 10.24966/NCP-878X/100003

HSOA Journal of Neonatology and Clinical Pediatrics

Research Article

Event-Related Potentials (P300 - MMN) and Neuropsychological Assessment in Duchenne Muscular Dystrophy Patients

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Abstract

Background: Mental retardation in children with Duchenne muscular dystrophy may be seen. This is related to the lack of dystrophin in different brain localizations, especially in the hippocampus. Dystrophin has a role in neurogenesis and plasticity during brain development and functioning of the hippocampus. Event related potentials are responsible for information processing in the hippocampus, as well as throughout the brain.

Methods: To examine the cognitive functions in Duchenne muscular dystrophy patients, P300, mismatch negativity potentials and neuropsychological tests were obtained from 10 Duchenne muscular dystrophy patients and 10 healthy control boys. In order to verify if data followed a normal distribution curve, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. Homogeneity of variance was evaluated with the Levene test. The two groups were compared with the Mann-Whitney U-test for independent samples. The linear associations between mismatch negativity quantitative parameters and full-scale IQ, performance IQ and verbal IQ were examined by using Pearson's correlations.

Results: Duchenne muscular dystrophy patients had lower IQ scores than the control group. However, they showed similar performance in Event related potentials that demonstrates no central auditory information processing and auditory deficit in these patients.

Conclusion: This is the first study that evaluates cognitive functions with mismatch negativity, P300 and neuropsychological tests together in Duchenne muscular dystrophy patients. In the future, it is appropriate to do larger studies in Duchenne muscular dystrophy patient groups with genetic defects that cause mental retardation.

Keywords: Cognition; Duchenne muscular dystrophy; Endogenous potentials; Mismatch negativity; P300

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Citation: Dundar NO, Kızılay F, Duman O, Fettahoglu C, Ozkaynak S, et al., (2014) Event-Related Potentials (P300 - MMN) and Neuropsychological Assessment in Duchenne Muscular Dystrophy Patients. J Neonatol Clin Pediatr 1: 003.

Received: July 15 2014; **Accepted:** October 06, 2014; **Published:** October 20, 2014

Introduction

Mental retardation in children with Duchenne Muscular Dystrophy (DMD) ranged from 20% to 50% in some studies [1,2]. Dubowitz first described cognitive dysfunctions in patients with DMD [3]. They especially decreased the verbal Intelligence Quotient (IQ) and its subgroups as language, memory, attention, and emotional skills [4-6]. Cognitive impairment may be explained by the lack of dystrophin in different brain localizations [7]. Dp140 and Dp71, which are the dystrophin isoforms, are found in the astroglial processes during development and the granule neurons of the dentate gyrus of the hippocampus (neurogenesis and synaptic plasticity), respectively [8]. Therefore, the absence of these isoforms may cause improper functioning of the brain and severe mental retardation [9,10].

Event Related Potentials (ERPs) are related to the basic aspects of brain mechanisms that are responsible for information processing. P300 and Mismatch Negativity (MMN) are well-known endogenous potentials that have been used extensively for the assessment of cognitive functions in different disorders including anemia, multiple sclerosis, stroke, Alzheimer's disease, myotonic dystrophy, and epilepsy [11-16]. Both P300 and MMN are recorded during irregular rare changes introduced during repetitive stimulation. The former is thought to represent a neurophysiologic index of auditory information processing that is dependent of attention, whereas the latter is considered to be the outcome of a pre-attentive system that is independent of attention [17].

Although studies on the cognitive functions in DMD patients with neuropsychological tests are many, there is only one neurophysiologic evaluation [18]. The aim of this study is to evaluate DMD patients with electrophysiological (MMN and P300) and neuropsychological tests to demonstrate neurocognitive impairment.

Material and Methods

Subjects

Ten boys with DMD, aged between 49 and 180 months (mean 103.8; SD 42.7 months), were enrolled in the study and compared to a control group consisting of 10 healthy boys, aged between 90 and 146 months (mean 113.4; SD 19.9 months). All of the participants had normal auditory tests and none of them were taking any medication. All children in the control group, from a routine outpatient service of the university, had no history of perinatal problems such as seizure, asphyxia, or premature birth. All patients were followed by the Pediatric Neurology Department. Written informed consent was obtained from the parents of all subjects studied. The study was approved by the local ethics committee.

Neuropsychological testing

As problems such as depression and anxiety affected the neurocognitive performance, and psychological mood examinations of all children who were enrolled into the study, and were examined by the same pediatric psychiatrist. Evaluation scales were used in order to evaluate the degree of depression and anxiety. Cognitive functions were assessed with the Turkish version of the revised Wechsler Intelligence Scale for Children (WISC-R) and Ankara Development Inventory Test for children who were aged under seven years [19,20]. Children were evaluated by the same qualified clinical psychologist who was single-blinded.

Neurophysiologic testing

Subjects were seated comfortably in an arm-chair in a quiet room and ERPs were studied using a Nihon Kohden Neuropack 8 4200K device.

P300: The oddball paradigm was used in the P300 recordings. This paradigm is based on distinguishing a target stimuli repeated randomly and less frequently from the non-target stimuli of frequent repetition, and the subject is asked to count the stimuli or to press a button when he or she encounters the stimuli. Binaural auditory stimuli were presented with earphones. Twenty percent of stimuli was in the rare (target) tones of 2000 Hz (90 dB) whereas the remainders were the frequent (non-target) tones of 1000 Hz (90 dB). The stimulus sequence was random. The recordings were made with Ag/AgCl electrodes. By using the 10-20 system, the reference electrodes were placed over the mastoid regions and the active electrodes over Fz and Cz. All the electrodes had a resistance of 5 kV or less and the frequency limits were set at 0.1-50 Hz. Thirty-two responses recorded by the target stimuli were averaged. Data from the two trials were obtained consecutively and stored. The latency and the amplitude of the N1, P2, N2, and P300 waves were taken into consideration.

MMN: Auditory stimulus sequences consisted of 1000 Hz standard tones and 900 Hz deviant tones (probability of occurrence: p = 0.20) delivered in random order, with the constraint that each deviant tone was preceded by at least three standard tones. All tones had an intensity of 70 dB Sound Pressure Level (SPL) and a duration of 50 ms (5 ms rise/fall). Stimuli were presented monaurally through headphones with a constant (onset to onset) interstimulus interval of 700 ms. A block of 1,000 stimuli was delivered to each ear; the order of the stimulated ear was counterbalanced across participants. The participants were reading the same storybook during the recording session. The MMN, elicited by the deviant stimulus, was calculated by taking the difference between the deviant and standard ERP.

Evaluation of data and statistical analysis

All statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) Windows 15.0 version (SPSS Inc., Chicago, IL, USA). P values less than 0.05 were considered "statistically significant". In order to verify if data followed a normal distribution curve, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. It was demonstrated that all variables had normal distribution with the Kolmogorov-Smirnov test but some variables had not normal distribution with the Shapiro-Wilk test. Levene test demonstrated variables had homogeneity of variance. The two groups were compared with the Mann-Whitney U-test for independent samples. The linear associations between MMN quantitative parameters and full-scale IQ, performance IQ, and verbal IQ were examined by using Pearson's correlations.

Results

The ages of patients were between 49 and 180 months (mean: 103.8; SD: 42.7 months) and that of control group were between 90 and 146 months (mean: 113.4; SD: 19.9 months). There was no statistically significant difference between the patient and control group with regard to age (p>0.05).

Neuropsychological testing

The psychological examination ruled out depression and anxiety disorders. The WISC-R test was applied to the six members of the patient group. It was found that these patients had significantly lower full-scale IQs, performance IQs, and verbal IQs when compared to the control group (p<0.05) (Table 1). The Ankara Development Inventory Test was administered to the remaining four patients because of age limitations and found mental retardation in only one patient.

	Patients (N=10)	Controls (N=10)	*P*
Verbal IQ	71.0 ± 13.2 *CI 57.1/84.9	101.4 ± 16.3 *CI 89.7/113.1	<0.05
Performance IQ	75.7 ± 19.1 *CI 55.6/95.8	107.2 ± 16.4 *CI 95.5/118.9	<0.05
Total IQ	72.3 ± 13.9 *CI 57.8/86.9	103.8 ± 17.6 *CI 91.2/116.4	<0.05

Table 1: IQ values comparison of the patients and the control group (mean ± SD).

SD: Standard deviation; IQ: Intelligence quotients

*CI: 95% Confidence Interval for Mean Lower/Upper.

Neurophysiologic testing

P300: The authors considered N100 and P300 quantitative parameters (latency and amplitude) in the controls and patients with DMD. In Fz and Cz recordings, N100, P2, N2, P300 latencies and N100, N1P2, P2N2, N2P3, and P3N4 amplitudes did not show any statistically significant differences among the groups (p>0.05) (Tables 2 and 3).

MMN: MMN quantitative parameters were recorded in Fz and Cz electrodes and considered among the groups. The parameters could not be recorded in one patient. In Fz and Cz recordings, MMN amplitude, peak, latency, and duration did not show any significant differences among the groups (p>0.05) (Tables 2 and 3). There was no correlation between MMN quantitative parameters and full-scale IQ, performance IQ, and verbal IQ.

Peak	EI	Patients (N=10)	Controls (N=10)	*P*
N100	Fz	134.6 ± 39.2 *CI 106.6/162.6	112.5 ± 22 *CI 96.7/128.3	> 0.05
	Cz	133.1 ± 41.3 *CI 103.6/162.6	102.4 ± 14.5 *CI 92.0/112.8	> 0.05
P300	Fz	340.9 ± 32.5 *CI 317.6/364.2	355.7 ± 30.4 *CI 333.9/377.5	> 0.05
	Cz	338.9 ± 33.5 *CI 315.0/362.8	346.4 ± 30.9 *CI 324.3/368.5	> 0.05
MMN	Fz	263.0 ± 39.5 *CI 232.7/293.3	189.7 ± 30.2 *CI 168.1/211.3	> 0.05
	Cz	256.1 ± 44.1 *CI 222.2/290.0	199.4 ± 39.1 *CI 171.4/227.4	> 0.05

Table 2: Peak latencies comparison of the patients and the control group (mean ± SD).

SD: Standard deviation; EI: Electrode placement; MMN: Mismatch negativity

*CI: 95% Confidence Interval for Mean Lower/Upper.

Amplitude	EI	Patients (N=10)	Controls (N=10)	*P*
N100	Fz Cz	12.9 ± 5.9 *CI 8.7/17.1 12.8 ± 5.6 *CI 8.8/16.8	14.3 ± 2.7 *CI 12.4/16.2 9.9 ± 3.8 *CI 7.2/12.6	> 0.05
N1P2	Fz Cz	9.1 ± 4.7 *CI 5.7/12.4 11.4 ± 6.9 *CI 6.5/16.3	8.4 ± 6.7 *CI 3.7/13.2 13 ± 6.3 *CI 8.4/17.1	> 0.05
P2N2	Fz Cz	10.4 ± 4 *CI 7.5/13.3 10.2 ± 4.6 *CI 7.0/13.5	12.2 ± 4.7 *CI 8.9/15.6 11.0 ± 6.0 *CI 6.7/15.2	> 0.05
N2P3	Fz Cz	15.2 ± 7.1 *CI 10.2/20.3 13.0 ± 4.6 *CI 9.7/16.2	17.2 ± 7.4 *CI 11.9/22.5 18.0 ± 8.0 *CI 12.3/23.8	> 0.05
P3N4	Fz Cz	14.5 ± 4.3 *CI 11.5/17.6 12.7 ± 4.4 *CI 9.6/15.9	17.1 ± 7.7 *CI 11.6/22.7 17.4 ± 10.5 *CI 9.9/24.9	> 0.05
MMN	Fz Cz	10.8 ± 3.1 *CI 8.3/13.2 10.8 ± 3.7 *CI 7.9/13.6	9.7 ± 3.5 *CI 7.2/12.2 10.9 ± 4.2 *CI 7.9/13.9	> 0.05

Table 3: Amplitudes comparison of the patients and the control group.

SD: Standard deviation; EI: Electrode placement; MMN: Mismatch negativity

*CI: 95% Confidence Interval for Mean Lower/Upper.

Discussion

Over the last decade, several studies have been published concerning cognitive impairment in neuromuscular disorders. DMD is caused, in most cases, by large out-of-frame deletions or duplications in the dystrophin gene [21]. The dystrophin gene is the largest gene that is expressed predominantly in skeletal and cardiac muscle with small amounts in the brain [22,23]. Three isoforms that have the same number of exons, but which are derived from three independent promoters in brain, muscle, and Purkinje cerebellar neurons, were recognized. The brain promoter drives expression primarily in cortical neurons and the hippocampus of the brain [24]. Different brain localizations of dystrophin isoforms may explain the role of the protein in cognitive development [7]. In particular, the severity and frequency of mental retardation increases with the successive loss of functional distal isoforms. Bardoni et al., [9], and Moizard et al., [10], found a statistically significant correlation between the absence of Dp140 and Dp71 promoters, respectively, and the presence of mental retardation in patients.

In a meta-analysis of patients reported by Emery and Muntoni, of 721 children studied in 14 reports, the mean IQ was 82, 202 children had an IQ below 70, and 32 had an IQ below 50 [25]. In the present study, the mean full-scale IQ was 72. In addition to the commonly reported delays in motor milestones, another study documented delays in the acquisition of language milestones as well [26]. Several studies compared performance with verbal IQs and most concluded that verbal IQ was more affected; the difference from performance IQ was approximately 5-8 points [27]. In the current study, the researchers found that mean verbal IQ was 71 and mean performance IQ was 75.7. Consequently, the difference was 4.7 points.

Event related potentials are related to the basic aspects of brain mechanisms. P300 represents the outcome of attention dependent systems and information processing. They have been used for a long time for the assessment of cognitive functions. The auditory P300 response has been studied in mentally retarded patients diagnosed with Fragile X syndrome, Down's syndrome, and Alzheimer's disease in Down's syndrome [28,29]. In all these studies, mentally retarded subjects were found, regardless of the etiology of their retardation, to have increased in latency and reduced in amplitude of the P300 response. In the literature, there is only one study that evaluated P300 in DMD patients. Della Coletta et al., [18] found poor performance in DMD patients as evaluated by P300 potential compared to the control group, although the difference was not statistically significant. In the present study, the researchers found no statistical difference in mean P300 values between the groups. The brain promoter of the dystrophin gene drives expression primarily in cortical neurons and the hippocampus of the brain [24]. On the other hand, P300 shows electrical activity in the entire brain. Consequently, it is possible to explain why the difference is not significant. Besides, the power for many variables is under eighty percent so it may be due to lack of power and small sample size.

MMN response reflects pre-attentive auditory information processing. Some studies evaluated the MMN test in children with autism, and attention deficit hyperactivity disorder in the literature [30,31]. The magnitudes of MMN were significantly lower than the controls. Holopainen et al., [32] showed that in both the mentally retarded and dysphasic groups, the peak amplitude of the frequency MMN was significantly attenuated when compared with the control group, but no significant difference was observed between the mentally retarded and dysphasic groups. In the current study, magnitudes of MMN were similar in the patient and control groups, which reflects no central auditory defects and information processing in this patient group.

To date, neurocognitive functions were not evaluated with MMN and correlations of ERPs through neuropsychological tests were rarely investigated in children with DMD. MMN and P300 are easy, safe, and inexpensive endogenous potentials that may reflect cognitive functions in such patients. Although the patients had low IQ, the researchers did not find any statistical difference in P300 and peak MMN values. The small number of patients may explain these results. However, the peak latencies of MMN were longer in DMD patients. It may be appropriate to do large-scale studies in DMD patient groups with specific genetic defects that cause to mental retardation.

We thank Bulent Ozkan, Ph.D., from Biostatistics & Medical Informatics Department, School of Medicine Izmir Katip Celebi University, for the statistical analysis.

References

1. Emery AE (1989) Clinical and molecular studies in Duchenne muscular dystrophy. Prog Clin Biol Res 306: 15-28.
2. Billard C, Gillet P, Signoret JL, Uicaut E, Bertrand P, et al., (1992) Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. Neuromuscul Disord 2: 371-378.
3. Dubowitz V (1965) Intellectual Impairment in Muscular Dystrophy. Arch Dis Child 40: 296-301.
4. Karagan NJ, Richman LC, Sorensen JP (1980) Analysis of verbal disability in Duchenne muscular dystrophy. J Nerv Ment Dis 168: 419-423.
5. Dorman C, Hurley AD, D'Avignon J (1988) Language and learning disorders of older boys with Duchenne muscular dystrophy. Dev Med Child Neurol 30: 316-327.
6. Leibowitz D, Dubowitz V (1981) Intellect and behaviour in Duchenne muscular dystrophy. Med Child Neurol 23: 577-590.

7. Tokarz SA, Duncan NM, Rash SM, Sadeghi A, Dewan AK, et al., (1998) Redefinition of dystrophin isoform distribution in mouse tissue by RT-PCR implies role in nonmuscle manifestations of duchenne muscular dystrophy. Mol Genet Metab 65: 272-281.

8. D'Angelo MG, Bresolin N (2006) Cognitive impairment in neuromuscular disorders. Muscle Nerve 34: 16-33.

9. Bardoni A, Sironi M, Felisari G, Comi GP, Bresolin N (1999) Absence of brain Dp140 isoform and cognitive impairment in Becker muscular dystrophy. Lancet 353: 897-898.

10. Moizard MP, Toutain A, Fournier D, Berret F, Raynaud M, et al., (2000) Severe cognitive impairment in DMD: obvious clinical indication for Dp71 isoform point mutation screening. Eur J Hum Genet 8: 552-556.

11. Weiskopf RB, Toy P, Hopf HW, Feiner J, Finlay HE, et al., (2005) Acute isovolemic anemia impairs central processing as determined by P300 latency. Clin Neurophysiol 116: 1028-1032.

12. Gil R, Zai L, Neau JP, Jonveaux T, Agbo C, et al., (1993) Event-related auditory evoked potentials and multiple sclerosis. Electroencephalogr Clin Neurophysiol 88: 182-187.

13. Korpelainen JT, Kauhanen ML, Tolonen U, Brusin E, Mononen H, et al., (2000) Auditory P300 event related potential in minor ischemic stroke. Acta Neurol Scand 101: 202-208.

14. Polich J, Ladish C, Bloom FE (1990) P300 assessment of early Alzheimer's disease. Electroencephalogr Clin Neurophysiol 77: 179-189.

15. Kazis A, Kimiskidis V, Georgiadis G, Kapinas K (1996) Cognitive event-related potentials and magnetic resonance imaging in myotonic dystrophy. Neurophysiol Clin 26: 75-84.

16. Duman O, Kizilay F, Fettahoglu C, Ozkaynak S, Haspolat S (2008) Electrophysiologic and neuropsychologic evaluation of patients with centrotemporal spikes. Int J Neurosci 118: 995-1008.

17. Näätänen R, Gaillard AW, Mäntysalo S (1978) Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst) 42: 313-329.

18. Della Coletta MV, Scola RH, Wiemes GR, Fonseca CN, Mäder MJ, et al., (2007) Event-related Potentials (P300) and neuropsychological assessment in boys exhibiting Duchenne muscular dystrophy. Arq Neuropsiquiatr 65: 59-62.

19. Wechsler D (1974) WISC-R Manual for the Wechsler Intelligence Scale for Children-Revised. Psychological Corporation, New York, USA.

20. Türk Psikologlar Dernegi (1994) WISC-R. Ankara: Türk Psikologlar Dernegi Yayinlari.

21. Koenig M, Beggs AH, Moyer M, Scherpf S, Heindrich K, et al., (1989) The molecular basis for Duchenne versus Becker muscular dystrophy: correlation of severity with type of deletion. Am J Hum Genet 45: 498-506.

22. Torelli S, Ferlini A, Obici L, Sewry C, Muntoni F (1999) Expression, regulation and localisation of dystrophin isoforms in human foetal skeletal and cardiac muscle. Neuromuscul Disord 9: 541-551.

23. Bies RD, Phelps SF, Cortez MD, Roberts R, Caskey CT, et al. (1992) Human and murine dystrophin mRNA transcripts are differentially expressed during skeletal muscle, heart, and brain development. Nucleic Acids Res 20: 1725-1731.

24. Górecki DC, Monaco AP, Derry JM, Walker AP, Barnard EA, et al., (1992) Expression of four alternative dystrophin transcripts in brain regions regulated by different promoters. Hum Mol Genet 1: 505-510.

25. Emery A, Muntoni F (2003) Duchenne Muscular Dystrophy. 3rd ed. Oxford: Oxford University Press.

26. Cyrulnik SE, Fee RJ, De Vivo DC, Goldstein E, Hinton VJ (2007) Delayed developmental language milestones in children with Duchenne's muscular dystrophy. J Pediatr 150: 474-478.

27. Bushby KM, Appleton R, Anderson LV, Welch JL, Kelly P, et al., (1995) Deletion status and intellectual impairment in Duchenne muscular dystrophy. Dev Med Child Neurol 37: 260-269.

28. St Clair DM, Blackwood DH, Oliver CJ, Dickens P (1987) P3 abnormality in fragile X syndrome. Biol Psychiatry 22: 303-312.

29. Muir WJ, Squire I, Blackwood DH, Speight MD, St Clair DM, et al., (1988) Auditory P300 response in the assessment of Alzheimer's disease in Down's syndrome: a 2-year follow-up study. J Ment Defic Res 32 : 455-463.

30. Dunn MA, Gomes H, Gravel J (2008) Mismatch negativity in children with autism and typical development. J Autism Dev Disord 38: 52-71.

31. Sawada M, Negoro H, Iida J, Kishimoto T (2008) Pervasive developmental disorder with attention deficit hyperactivity disorder-like symptoms and mismatch negativity. Psychiatry Clin Neurosci 62: 479-481.

32. Holopainen IE, Korpilahti P, Juottonen K, Lang H, Sillanpää M (1998) Abnormal frequency mismatch negativity in mentally retarded children and in children with developmental dysphasia. J Child Neurol 13: 178-183.