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Cognition of the mothers of patients with Duchenne muscular dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) has been found to be associated with cognitive impairment. However, few studies have addressed cognitive impairment among mothers of children with DMD. In the present study, the neuropsychological profiles of both carrier mothers (C-Ms) and noncarrier mothers (NC-Ms) were examined, and the findings were compared with healthy control mothers (HC-Ms). There were 90 participants, consisting of 31 C-Ms, 24 NC-Ms, and 35 HC-Ms, each of whom completed a neuropsychological test battery. C-Ms had poorer cognition performance in attention, working memory, immediate verbal memory, visuospatial skills, and executive functions than NC-Ms, and HC-Ms. This study provides evidence that there may be cognitive impairment in mothers of patients with DMD. The cognitive impairment of C-Ms has similarities to that seen in children with DMD.

KEYWORDS

carrier mothers, cognition, dystrophin gene, neuropsychological profile, noncarrier mothers

1 | INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare X-linked recessive hereditary muscle disorder with a frequency of approximately 1 in 5000 live male births, leading to progressive muscle weakness and wasting.[1-3] Mutations in the *DMD* gene, which is localized in the Xp21.2 region of the X chromosome, disrupts the production of dystrophin protein and causes dystrophin deficiency.[4,5] DMD is often associated with cognitive dysfunction.[6,7] Detailed neuropsychologic studies have shown that children with DMD have deficits in attention, memory, language, executive functions, and visuospatial processing.[8-10] Neuropathologic studies have shown that there is a lack of the dystrophin isoform in cells of the cerebellum and cerebral cortex of patients with DMD.[11] The lack of dystrophin isoforms in various brain regions is thought to be associated with the cognitive dysfunction seen in patients with DMD.[12]

Mild symptoms of dystrophinopathy can be seen in some carrier women.[13] Histologic changes have been found in the skeletal muscles of most clinically healthy carriers, and some will have muscle weakness later in life. Carrier females may have symptoms and findings, such as muscle pain due to exercise, myalgias, cramps, calf hypertrophy, elevated creatine kinase levels, and dilated cardiomyopathy.[14,15]

In the literature, there are few cognitive studies of the mothers of children diagnosed with DMD. In the present study we assessed the detailed cognitive performance of DMD carrier mothers (C-Ms) and noncarrier mothers (NC-Ms), and compared them with one another and with healthy control mothers (HC-Ms).

Abbreviations: BDI, Beck Depression Inventory; BNT, Boston Naming Test; C-M, carrier mother; DMD, Duchenne muscular dystrophy; HC-M, healthy control mother; MLPA, multiplex ligation-dependent probe amplication; NC-M, noncarrier mother; RCFT, Rey Complex Figure Test; ST; ToLT, Tower of London Test; VFT, verbal fluency test; VMPS, Verbal Memory Processes Scale.

2 | METHODS

2.1 | Participants

This study was conducted in conformity with the Declaration of Helsinki and was approved by the ethics committee of Istanbul

Faculty of Medicine, Istanbul University (2016/478). The investigation was performed with a group of mothers of children with DMD who were referred to the Neuromuscular Disease Unit in the Neurology Department of Istanbul University, Istanbul Faculty of Medicine. All participants provided informed consent.

The inclusion criteria for both the C-Ms and the NC-Ms were having a child with DMD, having had genetic tests, and having completed at least primary school education. The exclusion criteria were having a psychiatric or neurologic disorder and the presence of visual or hearing impairments that would interfere with the study. Individuals who had no children with chronic illness, at least one healthy son, and had no first- or second-degree relatives with DMD were included as the control group.

2.2 | Genetic analysis

Genetic tests of the mothers were performed at the Laboratory of Molecular Genetics, Department of Medical Genetics, Istanbul Faculty of Medicine, Istanbul University. Point mutations of patients with known DMD mutations were examined through exon-specific and Sanger sequencing, and large deletions and duplications were examined using multiplex ligation-dependent probe amplification (MLPA; P034 and P035 probes). All exons were first scanned using MLPA, and then using new-generation sequencing (Ion Torrent PGm and S5XL platform) to screen point mutations when the mutation in the patient with DMD was unknown or when the patient was deceased.

TABLE 1 Type of mutation and pedigree characteristics of the carriers

Patient no.	Family members with confirmed mutation	Location of mutation NM_004006.3	Mutation NM_004006.3; NP_003997.2
1	Index and carrier mother	Exon 61-74	Exon 61-74 duplication
2	Index and carrier mother	Exon 48-52	Exon 48-52 deletion
3	Index and carrier mother	Exon 45	Exon 45 deletion
4	Index and carrier mother	Exon 8-9	Exon 8-9 duplication
5	Index and carrier mother	Exon 43	c.4693_4694delCA;p.Gln1565Valfs*10
6	Index and carrier mother	Exon 64	c.9346C>T; p.Q3116*
7	Index, effected brother, and carrier mother	Exon 43	Exon 43 deletion
8	Index and carrier mother	Exon 56	c.8221_8221delC;p.L2741Sfs*23
9	Index, carrier sister, and carrier mother	Exon 47-48	Exon 47-48 deletion
10	Index, effected brother, and carrier mother	Exon 13-40	Exon 13-40 deletion
11	Index, carrier mother	Exon 46-52	Exon 46-52 deletion
12	Index and carrier mother	Exon 47-50	Exon 47-50 deletion
13	Index and carrier mother	Exon 20	c.2599A>T;p.K867*
14	Index, carrier sister and carrier mother	Exon 45-50	Exon 45-50 deletion
15	Index and carrier mother	Intron 36	c.5025 + 13G>T
16	Index and carrier mother	Intron 67	c.9808-2A>C
17	Index and carrier mother	Exon 46-51	Exon 46-51 deletion
18	Index and carrier mother	Exon 47-52	Exon 47-52 deletion
19	Index and carrier mother	Exon 45-47	Exon 45-47 deletion
20	Index and carrier mother	Exon 32	c.4486G>T;p.E1496*
21	Index and carrier mother	Exon 75	c.10782_10783insG; Q3595Afs*48
22	Index, effected brother, and carrier mother	Exon 48-50	Exon 48-50 deletion
23	Index and carrier mother	Exon 48	c.7054G>T;p.E2352*
24	Index, 2 effected brothers, and carrier mother	Exon 45-52	Exon 45-52 deletion
25	Index and carrier mother	Exon 45-52	Exon 45-52 deletion
26	Index, carrier sister, and carrier mother	Exon 51-52	Exon 51-52 deletion
27	Index and carrier mother	Exon 45-52	Exon 45-52 deletion
28	Index, effected brother, and carrier mother	Exon 54	c.7969A>T;p.R2657*
29	Index and carrier mother	Exon 17	c.2098C>T;p.Q700*
30	Index and carrier mother	Exon 48-50	Exon 48-50 deletion
31	Index and carrier mother	Exon 45-52	Exon 45-52 deletion

TABLE 2 Demographics of study subjects

Variables	C-Ms[a] (n = 31)	NC-Ms[a] (n = 24)	HC-Ms[a] (n = 35)	F	P
Age, years	38.7 ± 7.3[a]	40.9 ± 8.2	42.4 ± 7.6	1.877[b]	.159
Education, years	7.6 ± 3.2	8.0 ± 4.4	8.6 ± 4.4	0.449[c]	.799
Sleep duration, hours/day	6.6 ± 1.2	6.4 ± 1.3	6.9 ± 1.4	1.734[c]	.426
BDI scale scores	10.6 ± 6.8	11.0 ± 7.1	7.4 ± 6.4	5.851[c]	.054

Abbreviations: BDI, Beck Depression Inventory; C-M, carrier mother; HC-M, healthy control mother; NC-M, noncarrier mothers; η^2 = partial eta-squared.
[a]Data expressed as mean ± standard deviation.
[b]One-way analysis of variance.
[c]Kruskal-Wallis test.

TABLE 3 Neuropsychological tests for attention, language, verbal memory, visual memory, and visuospatial functions

Neuropsychological tests	C-Ms[a]	NC-Ms[a]	HC-Ms[a]	F	P	η^2
MMSE	29.5 ± 0.7	29.7 ± 0.6	29.9 ± 0.4	4.575[b]	.102	–
Attention						
DST—forward	5.1 ± 0.9	5.5 ± 1.0	5.8 ± 1.0	7.337[b]	.026	0.098
DST—backward	3.3 ± 1.0	3.7 ± 0.8	4.1 ± 1.0	8.317[b]	.016	0.120
Language						
BNT—total item (31 items)	26.2 ± 3.2	26.4 ± 2.4	28.3 ± 2.2	11.657[b]	.003	0.130
Verbal memory						
VMPS—immediate memory	5.2 ± 1.5	5.4 ± 1.6	6.3 ± 1.7	8.353[b]	.015	0.102
VMPS—total learning score	110.7 ± 14.2	115.9 ± 13.8	124.4 ± 10.9	16.259[b]	<.001	0.180
VMPS—learning wrong score	1.0 ± 1.1	1.1 ± 1.8	0.2 ± 0.5	16.543[b]	<.001	0.131
VMPS—perseveration	0.3 ± 0.6	0.2 ± 0.5	0.0 ± 0.0	8.306[b]	.016	0.083
VMPS—self-recall (delayed recall)	11.7 ± 2.1	12.3 ± 1.3	12.7 ± 1.4	3.181[b]	.204	–
VMPS—recognition	3.3 ± 2.1	2.6 ± 1.2	2.3 ± 1.4	3.056[b]	.217	–
VMPS—total recall	15.0 ± 0.0	14.9 ± 0.3	15.0 ± 0.0	5.563[b]	.062	–
Visual memory						
RCFT—immediate recall	18.5 ± 5.6	18.0 ± 4.7	21.7 ± 6.3	3.871[c]	.025	0.082
RCFT—delayed recall	17.6 ± 5.7	17.0 ± 4.9	22.1 ± 6.1	7.410[c]	.001	0.146
RCFT—recognition total correct	19.6 ± 2.0	19.3 ± 1.6	20.4 ± 1.6	3.094[c]	.050	0.066
Visuospatial functions						
BFRT	44.2 ± 4.8	44.3 ± 4.6	46.3 ± 3.1	2.993[b]	.137	–
BJLOT	16.8 ± 4.9	19.8 ± 4.9	22.2 ± 3.0	21.255[b]	<.001	0.232
RCFT—copy	33.6 ± 3.7	35.5 ± 1.1	35.4 ± 1.0	8.758[b]	.013	0.132

Abbreviations: BFRT, Benton Face Recognition Test; BJLOT, Benton Judgment of Line Orientation Test; BNT, Boston Naming Test; DST, digit span test; NC-M, noncarrier mother; RCFT, Rey Complex Figure Test; VMPS, Verbal Memory Processes Scale; C-M, carrier mother; HC-M, healthy control mother; MMSE, Mini-Mental State Examination; η^2 = partial eta-squared.
[a]Data expressed as mean ± standard deviation.
[b]Kruskal–Wallis test.
[c]One-way analysis of variance.

2.3 | Neuropsychologic assessment

The tests were administered in a quiet room in a single morning session and lasted approximately 2 hours. Each participant's cognitive status was quantified using the Mini-Mental State Examination.[16] In addition, the Beck Depression Inventory (BDI) was administered to all participants to exclude the possibility of depression. Participants with major depression were excluded from the study. A neuropsychological test battery was administered to all participants, covering cognitive domains of attention, language, visuospatial functions, memory, and executive functions (see Table S1 online).

2.4 | Statistical analysis

SPSS version 15.0 for Windows (SPSS, Inc, Chicago, Illinois) was used for statistical analysis. The demographic characteristics and neuropsychological test findings of the groups were analyzed as follows: normal distribution was checked using the Shapiro-Wilk test and homogeneity of variance was checked using the Levene test in measures from each group. If normality was justified, parametric one-way analysis of variance was performed using Bonferroni corrected pairwise group comparisons, and relationships between variables were analyzed using Pearson's correlation analysis. If normality was not justified, the nonparametric Kruskal-Wallis test was performed with Mann-Whitney *U* test corrected pairwise group comparisons, and relationships between variables were analyzed using Spearman's correlation analysis. The results were interpreted using the Bonferroni correction ($P < .017$) and $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Demographic features

There were 90 participants, including 55 mothers of children with DMD and 35 HC-Ms. Genetic analysis confirmed that 31 mothers of the children with DMD were carriers, and 24 were noncarriers. Neurologic examinations of the C-Ms, NC-Ms, and HC-Ms were normal. There was no history of alcohol and substance abuse among participants.

The mutation type and pedigree characteristics of the carriers are shown in Table 1. Study subject demographics are presented in Table 2. These differences were not significant between the three groups.

3.2 | Neuropsychological test findings

3.2.1 | C-Ms vs HC-Ms

The digit span test forward and backward scores for the C-Ms were lower than than those for HC-Ms ($P = .007$, Cohen's $d = -0.77$; and $P = .005$, Cohen's $d = -0.83$, respectively). C-Ms also performed worse than the HC-Ms on the Boston Naming Test (BNT) ($P = .006$, Cohen's $d = -0.80$). In the visuospatial domain, the C-Ms performed significantly worse on the Benton Judgment of Line Orientation Test ($P < .001$, Cohen's $d = -1.37$), but not on the Benton Face Recognition Test and copy portion of the Rey Complex Figure Test (RCFT), when compared with the HC-Ms.

Verbal memory function testing showed that the Verbal Memory Processes Scale (VMPS) immediate scores for the C-Ms were lower than those for the HC-Ms ($P = .005$, Cohen's $d = -0.73$). C-Ms had more difficulty learning word lists. Total learning scores on the VMPS were also lower ($P < .001$, Cohen's $d = -1.11$). VMPS learning wrong and preservation scores for C-Ms were higher than those for HC-Ms ($P < .001$, Cohen's $d = 1.06$; and $P = .003$, Cohen's $d = 0.73$,

TABLE 4 Neuropsychological tests for executive functions

Executive functions	C-Ms[a]	NC-Ms[a]	HC-Ms[a]	F	P	η^2
ST—interference time (seconds)	45.3 ± 12.8	45.2 ± 17.7	44.3 ± 14.3	0.129[b]	.938	–
VFT—semantic fluency—animal names	19.9 ± 5.3	19.8 ± 4.4	23.7 ± 5.6	5.816[c]	.004	0.118
VFT—phonetic fluency: K-A-S	29.7 ± 11.8	33.2 ± 11.4	38.8 ± 12.7	7.435[b]	.024	0.098
TMT—B-A (seconds)	57.7 ± 21.0	53.7 ± 22.1	43.6 ± 19.9	7.236[b]	.027	0.084
WCST—completed category	4.0 ± 1.7	5.2 ± 2.3	6.0 ± 2.1	13.251[b]	.001	0.155
WCST—perseverative error percentage	21.8 ± 8.1	19.6 ± 6.9	17.5 ± 7.9	5.339[b]	.069	–
WCST—trials to complete first category	25.2 ± 17.5	19.8 ± 11.6	19.2 ± 11.9	4.088[b]	.130	–
WCST—failures to maintain set	1.3 ± 1.3	1.3 ± 1.1	0.8 ± 0.9	4.272[b]	.118	–
WCST—conceptual level response	49.0 ± 13.4	55.9 ± 15.3	59.7 ± 15.7	4.319[c]	.016	0.090
ToLT—total correct score	3.7 ± 2.0	4.3 ± 1.8	4.0 ± 2.0	0.687[c]	.506	–
ToLT—total move score	32.2 ± 14.9	25.3 ± 11.8	29.4 ± 13.6	1.729[c]	.183	–
ToLT—total initiation time	31.9 ± 18.0	34.0 ± 13.4	25.3 ± 9.8	8.073[b]	.018	0.069
ToLT—total application time	203.8 ± 67.0	177.2 ± 70.0	158.3 ± 39.1	8.710[b]	.013	0.102
ToLT—total complete time	235.7 ± 73.8	210.8 ± 75.3	183.4 ± 42.0	10.854[b]	.004	0.113
ToLT—total time violations	0.4 ± 0.7	0.2 ± 0.7	0.0 ± 0.0	11.658[b]	.003	0.083
ToLT—total rule violation	1.0 ± 1.5	0.4 ± 0.8	0.3 ± 0.6	10.734[b]	.005	0.101

Abbreviations: C-Ms, carrier mothers; HC-Ms, healthy control mothers; NC-Ms, noncarrier mothers; ST, Stroop test; TMT, Trail-Making Test; ToLT, Tower of London Test; VFT, Verbal Fluency Test; WCST, Wisconsin Card Sorting Test.

[a]Data expressed as mean ± standard deviation.

[b]Kruskal-Wallis test.

[c]One-way analysis of variance (η^2 = partial eta–squared).

respectively). In contrast, long-term verbal memory performance was similar for C-Ms and HC-Ms. For visual memory, delayed recall scores on the RCFT for C-Ms were lower than those for HC-Ms (P = .006, Cohen's d = −0.76) (Table 3).

Semantic and phonetic fluency scores on the Verbal Fluency Test (VFT) for the C-Ms were lower than those for HC-Ms (P = .013, Cohen's d = −0.70; and P = .011, Cohen's d = −0.75, respectively). C-Ms performed worse on the trail-making test's B-A portion than HC-Ms (P = .009, Cohen's d = 0.70). On the Wisconsin Card Sorting Test, the completed category and conceptual level response scores of C-Ms were lower than those for HC-Ms (P < .001, Cohen's d = −1.05; and P = .013, Cohen's d = −0.74, respectively). The Tower of London Test (ToLT) total application times, total complete times, total time violations, and total rule violations scores were significantly higher for the C-Ms compared with the HC-Ms (P = .003, Cohen's d = 0.86; P = .001, Cohen's d = 0.90; P = .001, Cohen's d = 0.79; and P = .003, Cohen's d = 0.69, respectively) (Table 4).

3.2.2 | NC-Ms vs HC-Ms

NC-Ms performed worse than the HC-Ms on the BNT (P = .002, Cohen's d = −0.86), and VMPS learning wrong score and perseveration scores for NC-Ms were higher than those for HC-Ms (P = .001, Cohen's d = 0.84; and P = .013 Cohen's d = 0.66, respectively). For visual memory, NC-Ms performed worse than HC-Ms on RCFT immediate recall and delayed recall scores (P = .048, Cohen's d = −0.66; and P = 0.004, Cohen's d = −0.91, respectively) (Table 3). ToLT total initiation time was better for NC-Ms when compared with HC-Ms (P = .007, Cohen's d = 0.78) (Table 4). No differences were found between the NC-Ms and HC-Ms on any of the other tests.

3.2.3 | C-Ms vs NC-Ms

Comparisons between the C-Ms and NC-Ms show that the RCFT copy scores were poorer for the C-Ms (P = .009, Cohen's d = 0.69) (Table 3). No differences were found between C-Ms and NC-Ms on any of the other tests.

4 | DISCUSSION

The neuropsychological profile of the C-Ms demonstrated a number of cognitive impairments including attention, working memory, naming, immediate verbal memory, delayed visual memory, visuospatial skills, and executive functions, when compared with the HC-Ms. The NC-Ms were found to have fewer cognitive impairments (naming and visual memory) compared with HC-Ms.

Thangarajh et al studied 25 mothers of boys with DMD using the National Institutes of Health Toolbox Cognition Battery and reported that C-Ms performed worse overall compared with NC-Ms. C-Ms scored lower than average on executive function, as measured using the Flanker Inhibitory Control and Attention Test. On population-normed data, the C-Ms had lower scores on the task of attention and working memory compared with NC-Ms.[17] Similarly, we found that C-Ms performed worse on the attention, working memory, and executive function components. However, we found these findings between the C-Ms and the control group.

In another study of *DMD* gene mutation carriers (6 girls, including 5 DMD carriers and 1 Becker muscular dystrophy [BMD] carrier; mean age, 13 years), all patients were found to have motor and speech delays with learning difficulties. They had delays in speech between 17 and 24 months, and delays in unsupported walking. All patients had mutations in the distal part of the *DMD* gene.[18]

Some studies performed with manifesting carriers showed DMD-like disease symptoms. In their case series, Mieko et al described a 22-year-old manifesting carrier with a mental score of 76 (borderline intellectual functioning), and another, aged 32 years, with an intellectual disability score of 37 (moderate intellectual disability).[19] Similarly, in another case series, Song et al described a 32-year-old manifesting carrier who had two children with DMD and was found to have borderline intellectual functioning. They also found borderline intellectual functioning in another manifesting carrier, aged 34 years, who had two children with DMD.[20] Seemann et al reported on nine manifesting carrier patients and identified learning problems in five and speech delays in three. The researchers suggested that manifesting carrier women had similar comorbidities to men with DMD.[21] Mercier et al reported learning difficulties in five manifesting carriers, and intellectual disability in two manifesting carriers in their study of 26 manifesting carriers. They further suggested that the cognitive impairment detected in manifesting carriers was associated with mutations in the distal part of the *DMD* gene.[22]

Dystrophin isoforms in the brain areas are as abundant as the dystrophin protein in muscle.[23] Therefore, the lack of dystrophin isoforms in the brain may also affect brain function.[24] Cognitive impairment seen in DMD has been postulated to be the result of a deficiency of dystrophin isoforms expressed in the brain.[11,12,25] Dystrophin deficiency has been documented in cerebral and cerebellar tissues in patients with DMD.[24] Autopsy studies showed that children with DMD had no dystrophin in the postsynaptic densities of the cerebral cortex.[26] One of the dystrophin Dp427 isoform is mainly found in the cerebral neocortex, hippocampal regions, Purkinje cells of the cerebellum, and postsynaptic densities.[11,25] These regions are parts of a large network that plays an important role in learning and memory, and are connected with the frontal lobe.[27] This network also is responsible for executive functions such as planning, problem-solving, decisionmaking, judging, and maintaining attention.[28] Therefore, Dp427 dysfunction causes impaired brain function with muscle degeneration in patients with DMD.[25] Deletions between exons 45 and 52, which affect Dp427 and Dp140 isoforms, were associated with a higher incidence of cognitive impairment.[29] The lack or absence of Dp140 and Dp71 isoforms may lead to an increase in the severity of cognitive impairment in DMD.[30] In our study, mutations in C-Ms were mostly (20 patients) exons 45-52 and 62. The mutations detected in C-Ms in the Dp140 and Dp71 isoforms localized here may be the cause of cognitive impairment.

On many of the tests, there was no significant difference between NC-Ms and C-Ms. Thus, in addition to the DMD gene mutation, other genes may play a role in the pathophysiology of DMD. *Anxa6*, LTBP4, and SPP1 are known as genetic modifiers.[31-33] These modifiers may affect the onset age of the disease, the affected muscle groups, and the severity and prognosis of the disease in muscular dystrophies.[31-42] These modifiers may also explain the cognitive impairment seen in NC-Ms.

One limitation of this study is the relatively small number of participants. Another limitation is that the mothers in the control group did not have children with chronic disease. We believe it will be important to compare the cognitive profiles of mothers of children with DMD to those of mothers of children with other chronic diseases. Taking care of a child with a chronic disease can be extremely stressful and may have a negative effect on cognition.[43-45] Another reason for the cognitive impairment in C-Ms in our study may be related to effects of stress and sleep deprivation.

In conclusion, in this study we found that mothers carrying *DMD* gene mutations had cognitive impairment. We suggest that the cognitive impairment seen in C-Ms has similarities to cognitive impairment seen in patients with DMD, and that the cognitive impairment detected in C-Ms may be due to the same etiology as the cognitive impairment in patients with DMD. There is a need to further investigate this relationship with cognitive impairment through functional imaging, autopsy studies, and genotyping.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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