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Cognitive function in DMD carriers: personal case series and literature review

Laura Carraro[1], Arianna Iosca[1], Maria Irene Dainesi[1], Sara Fusco[1], Daniela Pia Rosaria Chieffo[2,3], Federica Moriconi[2], Giulia d'Amario[4], Marika Pane[4,5], Eugenio Mercuri[4,5], Angela Berardinelli[6]

[1] Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; [2] Clinical Psychology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [3] Departement of Life Sciences and Public Health Department, Catholic University of Sacred Heart, Rome, Italy; [4] Department of Life Science and Public Health, Pediatric Neurology, Catholic University of Sacred Heart, Rome, Italy; [5] The NEMO Center in Rome, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [6] Casimiro Mondino Foundation, IRCCS, Pavia, Italy

Improvement in clinical conditions allowed physicians to pay more attention to the cognitive function in DMD patients, leading to description of a cognitive impairment not only in affected males, but in female carriers as well.
This study aimed to investigate the cognitive involvement in a cohort of DMD carriers and to summarize the current knowledge about the intellectual involvement and neuropsychological profile in DMD/BMD carriers.
Our case series consisted of 22 carrier patients from two different centers (IRCCS Mondino, Pavia and Policlinico Gemelli, Rome), for whom we retrospectively collected cognitive, clinical and genetic data. For literature review, we selected 9 studies published in English language from 2011 to 2023 and cited in PubMed.
We found that the average IQ of DMD carriers was lower (74; very low) than the average score on normal curve (100 as average standard score). Furthermore, about 50% of them fell in the "extremely low IQ" range, compared with 2-3% of general population. A higher incidence of intellectual disability was confirmed in symptomatic DMD carriers (mean IQ 66; extremely low) from IRCCS Mondino, but not in the asymptomatic ones (mean IQ 99; average), when compared to the general population.
Current literature, albeit limited, seems to confirm the presence of a cognitive impairment in carriers, although milder than in affected males but with a similar neuropsychological profile. However, further studies are necessary to delve deeper into this issue and provide adequate educational support.

Key words: DMD, Duchenne, carriers, cognition, isoform, Dp140

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Correspondence
Angela Berardinelli
Casimiro Mondino Foundation, IRCCS, Pavia, Italy; Department of Life Science and Public Health, Pediatric Neurology, Università Cattolica del Sacro Cuore, Rome, Italy
E-mail: angela.berardinelli@mondino.it

Laura Carraro
Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy
E-mail: laura.carraro02@universitadipavia.it

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Introduction

Duchenne muscular dystrophy (DMD) and its milder form, Becker muscular dystrophy (BMD), are the most common childhood muscular dystrophies. They are caused by mutations in the dystrophin gene, at Xp-21 locus [1-4].

Being X-linked recessive diseases, they affect males, whereas female carriers usually remain asymptomatic [1,4-8].

Carrier females can however present symptoms and findings with different impacts on their quality of life (e.g. elevated creatine kinase levels, myalgia, cramps, progressive weakness, calf hypertrophy, dilated cardiomyopathy) [1,3-5,7-9].

The improvement in clinical conditions and survival of DMD patients achieved in the last 20 years, has driven the need to improve their social participation, shedding light on the

cognitive impairment described in this condition. Neuropsychological studies have confirmed deficits in attention, memory, language, executive functions, and visuospatial processing. Furthermore, the incidence of neurodevelopmental disorders (obsessive-compulsive disorder, attention-deficit hyperactivity disorder, autism spectrum disorder) and language delay appear higher in these children [2,3,10].
In most recent years, greater attention was paid to female carriers as well, considering not only their muscular and cardiac phenotypes but also their cognitive involvement and neuropsychological profile.
Cognitive dysfunction in DMD patients seems to be associated with a lack of dystrophin isoforms in various brain regions (e.g. cerebellum and cerebral cortex) [3,10,11].
Dystrophin is a 427 KDa cytoplasmic protein, responsible for connecting the muscular contractile apparatus to the extracellular matrix, stabilizing the sarcolemma during contraction [12]. The encoding gene contains 79 exons, 78 introns and multiple tissue-specific promoters producing different isoforms [11].
Dp140 (exon 45 as N-terminal domain) and Dp71 (exon 63 as N-terminal domain) isoforms are expressed only in the brain, so they may play a significant role in fetal brain development. Patients and carriers with distal DMD gene deletions resulting in disruption of Dp140 and Dp71 isoforms are more likely to experience significant neurocognitive impairment [10,11].

Patients and methods

Aim of this work was to investigate cognitive involvement in our cohort of subjects and to summarize current knowledge about intellectual involvement and neuropsychological profile of DMD/BMD carriers.
Our case series consisted of 22 carrier patients who were referred to IRCCS Mondino in Pavia (11 subjects) or to Policlinico Gemelli in Rome (11 subjects).
The data were collected retrospectively, with cognitive assessments dating back from 1994 to 2023. Due to the wide timeframe considered, different Wechsler scales were used (Tab. I). At least one cognitive evaluation through a Wechsler Intelligence assessment Scale (WISC or WAIS) was performed in 15 subjects.
The genetic data were retrospectively collected to evaluate the possible genotype-phenotype correlation suggesting a more frequent cognitive involvement in subjects with disruption of Dp140 and Dp71 isoforms.
Additionally, we collected some social data (educational level, occupation) about a small population of carrier mothers of our affected patients. Lacking their cognitive evaluations, we looked for some relation between their occupation (although not indicative of their intellectual level, due to significant interference from social factors), genotype and cognition of their DMD/BMD children.
The search of scientific literature was conducted through PubMed selecting papers published in English from 2011 to 2023. The keywords for the search were DMD, DMD carriers, cognitive profile, CNS involvement.

Table I. Wechsler Intelligence Scales.

Wechsler Scale	First publication	Publication in Italy	Italian curator
WISC-R	1974	1986	Rubini, V.; Padovani, F.
WISC-III	1991	2006	Orsini, A.; Picone, L.
WISC IV	2003	2012	Orsini, A.; Pezzuti, L.
WAIS-R	1981	1997	Orsini, A.; Laicardi, C.
WAIS IV	2008	2013	Orsini, A.; Pezzuti, L.

Statistical evaluation

Because of reduced sample size, the nonparametric statistics was applied to the study, when possible.

Results

Personal cohort

The mean age of the carrier patients at first cognitive evaluation was 13 years (range 8-22). A total of 15 patients was investigated. Four patients were evaluated through WISC-R, one through WAIS-R, two through WISC-III, seven through WISC-IV and one through WAIS-IV. The mean IQ score was 73.8 (median 75), with a maximum value of 126 and a minimum of 42 (Tab. II).
Scores on the Wechsler intelligence scales approximate a normal curve with a mean of 100 and a standard deviation of 15, representing situation in the general population (Fig. 1). To compare the cognitive outcomes of our carriers to the expected scores, we referred to that normal curve and divided our subjects in the following Intelligence Quotient (IQ) ranges: Extremely low: < 70; Very Low: 70-79; Low Average: 80-89; Average: 90-109; High average: 110-119; Very High: 120-129; Extremely High ≥ 130. Results confirmed that the majority of our subjects (46.7%) had an extremely low IQ (< 70), unlike the general population, where only 2.2% of individuals fall into this category (Fig. 1, Fig. 3).
Furthermore, we divided our subjects based on their intellectual level in: severe intellectual disability: ≤ 20; moderate intellectual disability: 21-35; mild intellectual disability: 36-49; borderline intellectual functioning: 50-69; normal intellectual level: 70-89; high potential: 90-119; gifted: 120-129; exceptionally gifted: ≥ 130. Based on this classification The results showed that our population was homogeneously distributed between a normal cognitive level (IQ 70-89) and a moderate intellectual disability (IQ 21-35), with only one subject showing high potential IQ (90-119) (Fig. 2).
Focusing on the phenotype, in Pavia cohort 6 patients were asymptomatic and reached specialist evaluation due to family history or casual finding of elevated creatine kinase (CK) levels, while 5 patients were symptomatic (cramps, myalgia, weakness) or had motor (± language) delay. We noticed a different behaviour between the two groups: asyntomatic carriers showed a mean IQ of 99 (average) while symptomatic carriers had a mean IQ of 66 (extremely low) (Tab III). Using one-tailed Mann-Whitney independent samples T-Test we found that IQ score at presentation in symptomatic carriers was significantly lower (p-value 0.008) than IQ score in asymptomatic group (Fig. 4). All tested asymptomatic carriers had normal or higher

Table II. Cognitive evaluation data in our case series.

Pt-ID	Year of Eval.	Age at Eval.	Test	IQ	IQ Level	IQ Distribution
1P	2013	14	WISC-III	90	Normal	Average
2P	2009	18	WAIS-R	75	Borderline	Very low
3P	1999	13	WISC-R	91	Normal	Average
4P	2003	16	WISC-R	51	Mild ID	Extremely Low
5P	1994	18	WISC-R	79	Borderline	Very low
6P	2006	6	WISC-R	89	Normal	Low-Average
7P	2009	10	WISC-III	66	Mild ID	Extremely Low
8P	2022	11	WISC-IV	126	High Potential	Very High
9P	2015	8	WISC-IV	60	Mild ID	Extremely Low
1R	2023	8	WISC IV	103	Normal	Average
2R	2017	14	WISC IV	57	Mild ID	Extremely Low
3R	2015	12	WISC IV	42	Moderate ID	Extremely Low
4R	2019	8	WISC IV	46	Moderate ID	Extremely Low
5R	2022	22	WAIS IV	49	Moderate ID	Extremely Low
6R	2021	13	WISC IV	83	Borderline	Low-Average

Abbreviations: Pt-ID: Patient identifier; Eval: evaluation; IQ: Intelligence quotient; ID: Intellective deficit.

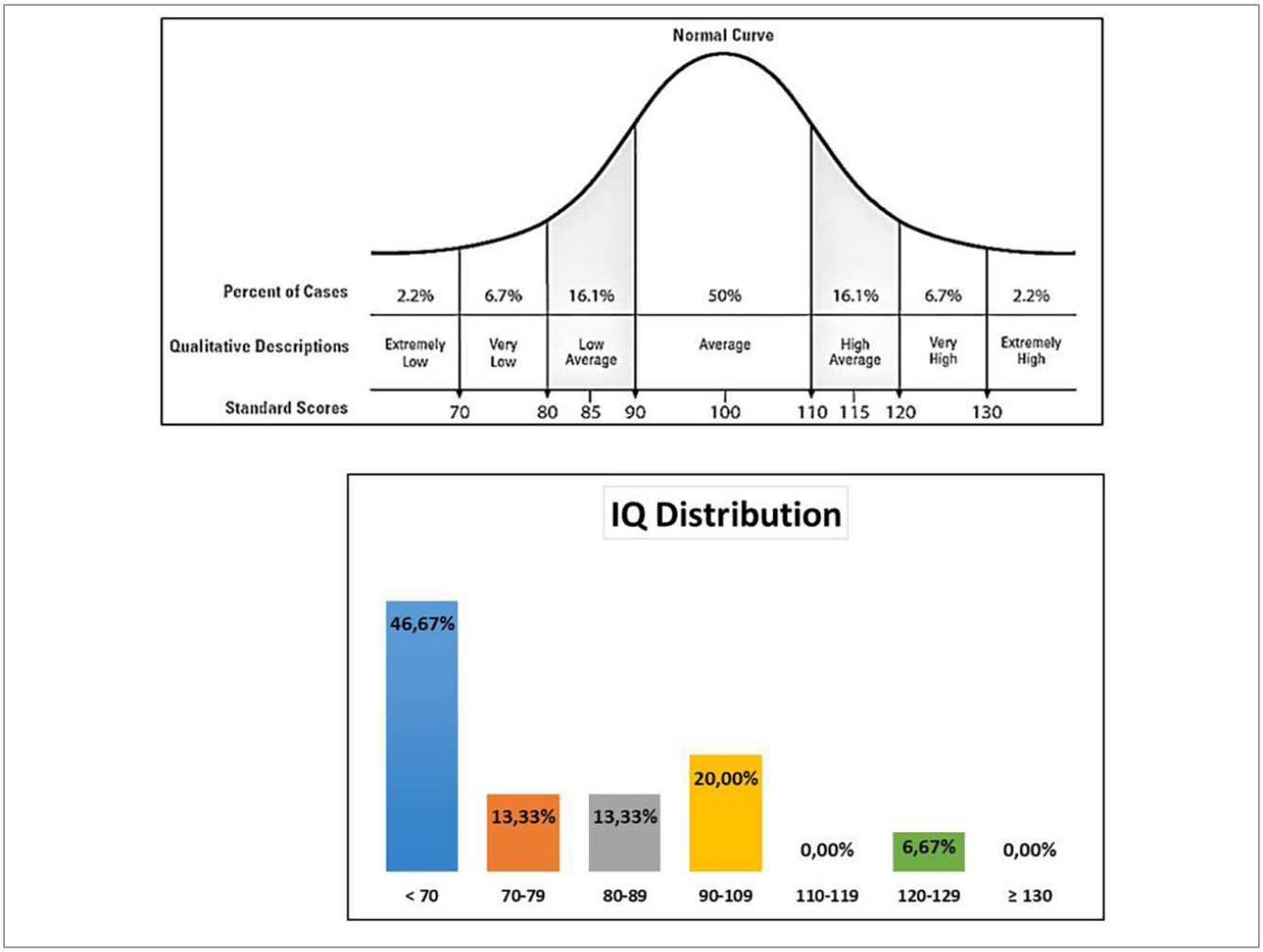

Figure 1. Comparison between general population normal Intelligence Quotient (IQ) curve (above) and IQ distribution in our cohort (*below*). IQ ranges: Extremely low: < 70; Very Low: 70-79; Low Average: 80-89; Average: 90-109; High average: 110-119; Very High: 120-129; Extremely High ≥ 130.

Table III. Cognitive evaluation in relation to reason for accessing care (Pavia cohort).

Pt-ID	Test	IQ	IQ Level	Symptoms at Access to Care - (*)
1P	WISC-III	90	Normal	IperCKemia, Family History - (0)
2P	WAIS-R	75	Borderline	IperCKemia, Weekness, Motor Delay - (1)
3P	WISC-R	91	Normal	Family History - (0)
4P	WISC-R	51	Mild ID	IperCKemia, Motor Delay, Language Delay, Cognitive Delay - (1)
5P	WISC-R	79	Borderline	IperCKemia, Myalgia, Cramps - (1)
6P	WISC-R	89	Normal	IperCKemia - (0)
7P	WISC-III	66	Mild ID	IperCKemia, Motor Delay, Language Delay - (1)
8P	WISC-IV	126	High Potential	IperCKemia - (0)
9P	WISC-IV	60	Mild ID	IperCKemia, Motor Delay, Falling, Tenderness - (1)
10P	NT	NT	NT	IperCKemia - (0)
11P	NT	NT	NT	IperCKemia - (0)

Abbreviations: Pt-ID: Patient identifier; IQ: Intelligence quotient; ID: Intellective deficit.
* Symptoms Coding: 0: absence; 1: presence.

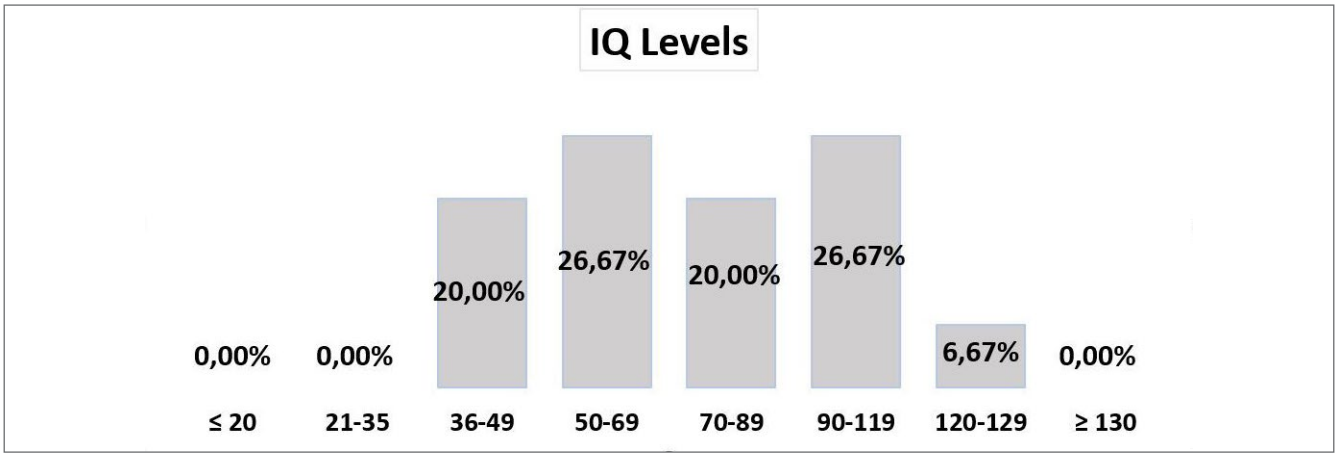

Figure 2. Distribution of Intelligence Quotient (IQ) levels in our cohort. Severe intellectual disability: ≤ 20; moderate intellectual disability: 21-35; mild intellectual disability: 36-49; borderline intellectual functioning: 50-69; normal intellectual level: 70-89; high potential: 90-119; gifted: 120-129; exceptionally gifted: ≥ 130.

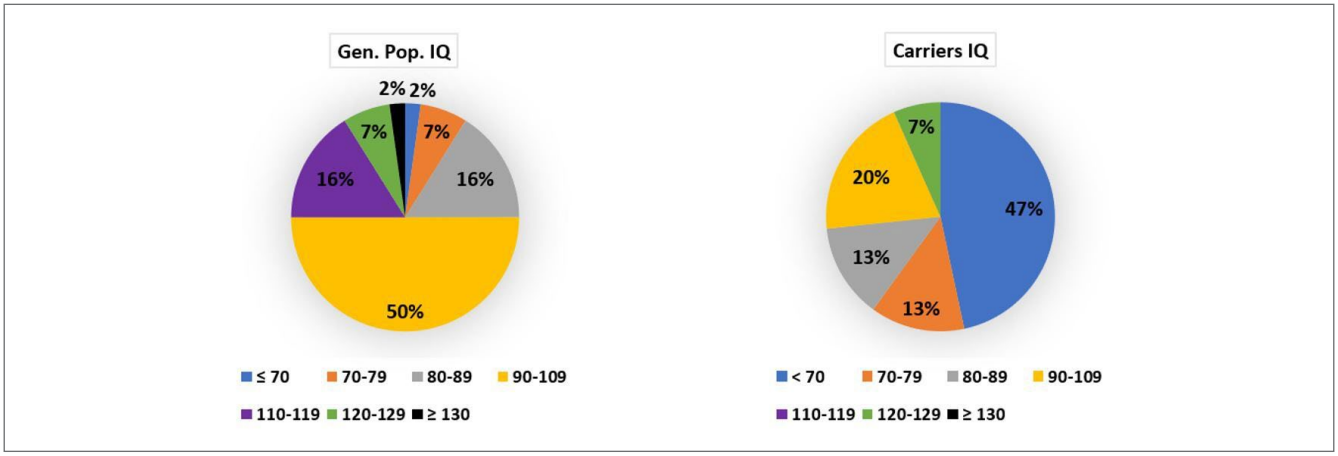

Figure 3. Pie Chart representing Intelligence Quotient (IQ) in general population (Gen. Pop.) (*on the left*) *vs* our cohort of carriers (*on the right*). IQ ranges: Extremely low: < 70; Very Low: 70-79; Low Average: 80-89; Average: 90-109; High average: 110-119; Very High: 120-129; Extremely High ≥ 130.

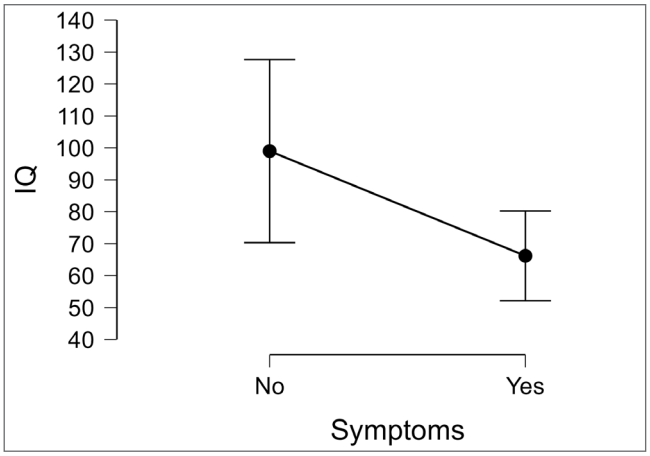

Figure 4. Descriptive plot: Intelligence Quotient (IQ) in symptomatic (= Yes) vs asymptomatic (= No) carriers of our cohort.

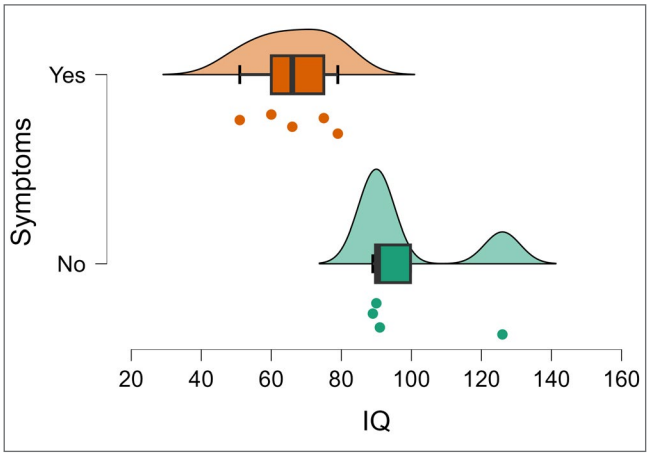

Figure 5. Raincloud plot: Intelligence Quotient (IQ) distribution in symptomatic (= Yes) vs asymptomatic (= No) carriers of our cohort.

IQ (the only 2 untested patients were clinically unimpaired), while all symptomatic carriers had borderline or deficient IQ.

Furthermore, observing the distribution of the IQ scores in the two subgroups (Fig. 5), the higher score in the asymptomatic carriers (IQ = 126) could be considered an anomalous value; however, repeating the one-tailed Mann-Whitney independent samples T-Test after elimination of this value, still confirmed a statistically significant difference (p-value = 0.018) between the two groups.

The genetic characterization was available for only 7/15 who had undergone at least one cognitive assessment. A Dp71 isoform involvement wasn't present in any, while the Dp140 isoform was involved in 3 subjects. The average IQ in Dp140+ subjects was 60.8, while the average IQ in Dp140- subjects was 106.3; this finding is apparently in contrast with the scientific literature, probably due to the small sample size and the limited molecular data available (Tab. IV). Moreover, one-tailed Mann-Whitney independent samples T-Test did not show any statistically significant difference (p-value 0.114).

Regarding the social data, all adult carrier had jobs that could be classified at level 1-3 out of 9 of the *Hollingshead Index of Socioeconomic Status* (SES) [*Hollingshead, A. B. (1975). Four-factor index of social status. Unpublished manuscript, Yale University, New Haven, CT*]. Therefore, no comparison with genotype or with cognitive abilities of their affected children was possible.

Review of scientific literature

We were able to find and review 9 studies, published from 2011 to 2023, six of them were case series, one a case report, one a literature review and one a workshop report.

Seven studies referred to the carriers' intellectual involvement within a broader phenotypic description, while two focused on the similarities and differences between the neuropsychological profile of DMD/BMD patients compared to their healthy or carrier mothers.

In most of the studies a lower cognitive level was described among DMD/BMD carriers compared to the general population, with a neu-

Table IV. Cognitive evaluation in relation to the genotype in our cohort.

Pt-ID	Test	IQ	Genotype	Dp 140 *
1P	WISC-III	90	del exons 48-50	X
2P	WAIS-R	75	Xp21	NK
3P	WISC-R	91	del exon 44	0
4P	WISC-R	51	NK	NK
5P	WISC-R	79	NK	NK
6P	WISC-R	89	NK	NK
7P	WISC-III	66	NK	NK
8P	WISC-IV	126	del exons 50-52	X
9P	WISC-IV	60	NK	NK
1R	WISC IV	103	nonsense mutation exon 59	X
2R	WISC IV	57	del exons 3-25	0
3R	WISC IV	42	del in c.11058+22 3UTR	NK
4R	WISC IV	46	dupl exons 45-51	0
5R	WAIS IV	49	out-of-frame del exons 45-51	0
6R	WISC IV	83	del intron 15	NK

Abbreviations: Pt-ID: Patient identifier; IQ: Intelligence quotient; del: deletion; dupl: duplication; NK: not known.
* Coding Dp140 involvement: NK: not known; X: Dp140 involved; 0: Dp140 not involved.

rocognitive profile similar to the affected males. The average IQ in symptomatic carriers compared with the general population was normal in only one study [4]. Behavioral problems, learning anomalies, delayed language and autism were also described [1,6,7].

The literature examined seems to confirm a phenotype-genotype correlation for cognitive impairment, especially when the mutation involves the Dp140 and Dp71 isoforms (Tab. V) [10,11]. It has also been shown that carrier mothers (C-Ms) of affected patients had poorer cognition performance in terms of attention, working memory, immediate verbal memory, visuospatial skills, and executive functions than non-carrier mothers (NC-Ms) and healthy controls (HC-Ms), thus demonstrating the similarities in neurocognitive profile between the carriers and affected individuals [2,3]. In particular, one of these studies showed that carrier mothers scored lower in Total, Crystalized, and Fluid composite scores in comparison to non-carriers, and they performed better in crystallized cognitive domains then in fluid cognitive domains [2] (Tab. V).

Table V. Summary of current literature on carriers' cognition and neuropsychological profile.

Literature	Cognitive and NP profile	Genetic background
Tae-Jin Song et al. 2011 [8] Case report	3 Pts: - 1:3 N (IQ NA) - **2:3 ID (IQ 70; 78)**	
Giliberto F. et al. 2013 [1] Case Series	8 Pts: **- 4:8 BP + mild LD (1:4 ASD)** - 2:8 no elementary school (1:2 ASD) - 1:8 incomplete school - 5:8 finished elementary school - 3:5 went to high school - 1:3 went to university	
Mercier S. et al. 2013 [9] Case Series	26 Pts - **7:26 (27%) CI → (2:7 ID) + (5:7 LD)** - 2:26 N - 17:26 NA	**6:7 CI (86%) Inv. Dp 140 ± Inv. Dp71** 2:7 CI Duplication exons 61-66 1:7 CI Triplication exons 60-63
Papa R. et al. 2016 [5] Case Series (Prospective)	15 Pts - **4:15 (29%) minor LD or BP**	7:15 Deletion exons 45-50 (0:7 LD or BP)
Ishikazi M. et al. 2018 [6]. Review	93 subjects (10 studies) **22:93 ID or LD or BP or SD or AD or SLD**	
Jingzi Zhong et al. 2019 [4] Case Series (Prospective)	78 carriers (4:78 symptomatic) **All N**	
Sarkozy A. et al. 2023 [7]	Dutch cohort: 12 Pts - **3:12 (25%) ASD +/- LD**	
Thangarajh M. et al. 2019 [2] Case Series (Cross-sectional)	**C-Ms** < NC-Ms in: - **Total cognition** - **Crystalized cognition** - **Fluid cognition** (worst: **Executive Function**) **Fluid** < Crystalized	
Demirci et al. 2020 [3] Case Series	90 Mothers: - 31 C-Ms - 24 NC-Ms - 35 HC-Ms **C-Ms** < (NC-Ms and HC-Ms) in: - **Attention** - **Working Memory** - **Immediate Verbal Memory** - **Visuospatial Skills** - **Executive Functions**	

Abbreviations: NP: Neuropsychological; Pt: Patient; IQ: Intelligence quotient; ID: Intellectual disability; CI: Cognitive impairment; LD: Learning disabilities; ASD: Autism spectrum disorder; BP: Behavioural problems; SD: Speech delay; SLD: Specific learning disorder; AD: Attention deficit; N: Normal; NA: Not available; Inv: Involvement; C-Ms: Carrier mothers; NC-Ms: Non carrier mothers; HC-Ms: Healthy control mothers.

Discussion

A cognitive involvement in DMD carriers, with a neuropsychological profile similar to that of male patients, have been recently described. However, the analyzed studies appear inconsistent and should be complemented by further cognitive and neuropsychological data, collected through standardized and validated tests and scales in order to make them comparable. It would also be important to know the pathogenic mutation of every subject analyzed, to carry out genotype-phenotype correlations.

In this report we found that the average IQ of our carrier subjects was lower (74, falling in "very low IQ" range) than the average score on the Wechsler intelligence scales normal curve (100, "average IQ" by definition). Furthermore, about 50% of the group fell in the "extremely low IQ" range, compared with 2-3% of general population (Fig. 3). Thus, our results confirm a higher incidence of intellectual disability in the carrier group if compared with the general population. Further analysis of the Pavia cohort showed intellectual involvement in the subgroup of symptomatic carriers, but not for the asymptomatic carriers.

Analyzing the genotype-phenotype correlation, our results seem in contrast with current literature: in particular, a higher average IQ was observed in the group of Dp140- carriers compared to the Dp 140+ carriers. However, they are most likely due to the small size of our sample.

Alongside the small size of our sample, we are aware that our study has other limitations such as the inhomogeneity and lack of cognitive and genetic data for the entire patients group, and the large period retrospective collection of the data with differences in type of cognitive evaluations (Tab. I). However, our study confirms that DMD female carriers, especially if symptomatic at time of first evaluation, may present intellectual disability beside muscle and cardiac involvement. Further studies on larger study populations are necessary to better investigate the neuropsychological profile of these subjects and the possible genotype-phenotype correlation in order to provide better social and educational support. This will be important especially for the girl carriers who, more than the adults female carriers, could benefit, through a thorough cognitive and neuropsychological evaluation, of implementation of tailored educational support.

Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

LC, AB, EM: conception and design of the work; LC, MID, AI, SF, DPRC, FM, GdA, AB: execution of tests and acquisition of data: AB, LC, EM: analysis and interpretation of data; LC, AI, MID, MP, AB: writing the paper; LC, MID, AI, MP, EM, AB: reviewing the paper. Final approval: all authors.

Ethical consideration

Data was collected retrospectively and analysed. Testing was performed for clinical purposes only. Data cannot be traced back to specific patients. Ethical approval is not required.

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