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ORIGINAL ARTICLES

Becker Muscular Dystrophy in the Pediatric Population: Diagnosis, Genetic Variability, and Disease Progression

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ABSTRACT

Introduction: Becker muscular dystrophy (BMD) is an X-linked neuromuscular disease caused by variants in the *DMD* gene that leads to progressive muscle weakness, dilated cardiomyopathy, and neurodevelopmental issues.

Objective: To characterize patients with BMD from a pediatric neuromuscular disease center.

Methods: Retrospective and descriptive study of BMD patients diagnosed between January 1995 and May 2024.

Results: A total of 22 male cases were identified, with 9/22 reporting family history of BMD. First symptoms appeared at a median age of 3.0 years (IQR 4.5) and included unstable gait (5/22), fatigue (5/22), myalgias (4/22), asymptomatic elevation of creatine kinase (3/22), delayed motor development (3/22), and myoglobinuria (2/22). Average age at diagnosis was 7.7 years (IQR 5.6). The most frequent genetic alteration was a deletion involving exon 48 of the DMD gene (8/22). The developmental issues identified were intellectual disability (5/22), attention-deficit/hyperactivity disorder (ADHD) (3/22), autism spectrum disorder (1/22), and specific language impairment (1/22). Dilated cardiomyopathy developed at pediatric age in 1 patient, and 3 started corticosteroid therapy owing to worsening motor symptoms. The average follow-up time was 8.7 years (SD 1.1).

Conclusion: The phenotypic variability of BMD complicates its diagnosis, but early recognition is crucial for conducting appropriate monitoring and genetic counseling as well as family studies. Our findings highlight the need for multidisciplinary follow-up, particularly due to the significant prevalence of neurodevelopmental problems.

Keywords: Becker muscular dystrophy; *DMD* gene; neuromuscular disorder

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INTRODUCTION

Becker muscular dystrophy (BMD) is an X-linked allelic disorder caused by deficiency of sarcolemmal dystrophin due to pathogenic variants in the *DMD* gene.[1] BMD is a rare disease, with an estimated worldwide prevalence ranging from 0.4 to 3.6 per 100,000.[2] The *DMD* gene, which encodes the dystrophin protein, consists of 79 exons and spans over 2,200 kb, roughly 0.1% of the whole genome.[3,4] Dystrophin plays a crucial role in maintaining the structural integrity of muscle cells, particularly skeletal and cardiac muscles. It forms part of the dystrophin-associated protein complex, which anchors the cytoskeleton of muscle cells to the extracellular matrix via the sarcolemma, protecting muscle fibers from damage during contraction and relaxation.[5] In addition to its mechanical role, dystrophin contributes to the stabilization of the sarcolemma and prevention of muscle cell degeneration. Its absence or dysfunction leads to increased membrane fragility, muscle fiber degeneration, inflammation, and subsequent fibrosis, which manifest as progressive muscle weakness and cardiomyopathy.[6,7]

The natural history of the disease can be variable, depending on when symptoms first present, but typically they are milder in progression compared to those of Duchenne muscular dystrophy (DMD).[8] DMD is primarily caused by out-of-frame variants, while BMD is generally due to in-frame variants. Typically, patients with DMD lack any detectable dystrophin expression in their skeletal muscles and present muscle weakness in early childhood. By contrast, patients with BMD present a wider range of symptoms, depending on their levels of functional dystrophin and how much of it is expressed.[9,10]

MATERIAL AND METHODS

Study design and setting

This was an observational, retrospective study of patients with BMD who were followed up at a tertiary pediatric neuromuscular disease center between January 1995 and May 2024. Informed consent was waived, as this is a retrospective study using data solely from clinical records. The STROBE statement for reporting observational studies was followed.

Participants, data collection, and variables

Inclusion criteria comprised all pediatric patients (aged 0–17 years, inclusive) with a G71. 01 diagnosis according to the International Classification of Diseases, 10th Revision (ICD-10). The predefined exclusion criterion was absence of electronic clinical records, which could hinder diagnosis classification.

The strategy employed to obtain a comprehensive list of patients meeting the inclusion criteria included a search of the clinical databases of the neuropediatrics department of the center. Data were extracted from the electronic clinical records by the research team.

Demographic and administrative data were retrieved, including age and gender and ICD-10 diagnosis. Additionally, data on the clinical presentation of the disease, diagnostic workup, and therapeutic interventions performed during follow-up were collected and analyzed. Cognitive function was assessed using the Wechsler Intelligence Scale for Children III (WISC-III).

Genetic analysis was performed using multiplex ligation-dependent probe amplification, comparative genomic hybridization and/or next-generation sequencing. Variants were classified based on the American College of Medical Genetics and Genomics guidelines and interpreted using the Leiden Open Variation Database.

Statistical analysis

Statistical analysis was performed using SPSS® version 30 (SPSS IBM, New York, NY, USA). The choice between mean (± SD) and median (IQR) reporting was based on the distribution of the data: parametric variables were described using means and standard deviations, while non-parametric variables were described using medians and interquartile ranges, after assessment of normality. Categorical variables were presented as absolute numbers and percentages.

Missing data were minimal and assumed to be missing completely at random; therefore, no imputation was performed.

RESULTS

A total of 20 families were represented in the study. Known family history of the disease was reported in 9/22 cases of male patients diagnosed with BMD at our center. Affected relatives included brothers (4/22) and maternal grandfathers (3/22), uncles (2/22), and cousins (2/22). All carrier mothers were asymptomatic, with no clinical signs of muscle weakness or cardiomyopathy.

The median age of symptom onset was 3.0 years (IQR 5.3). The earliest onset of symptoms occurred at 12 months, presenting as motor delay, while the latest onset occurred at 15 years, manifested as an increase in difficulty with running. The median age at diagnosis was 7.7 years (SD 3.9), with the earliest diagnosis made at 24 months, and the latest at 17 years of age. Patients had a mean follow-up of 8.7 years (SD 1.1), until they were transferred to the adult neurology department. Patient population characteristics are presented in **Table 1**.

The clinical presentations in this cohort were diverse, with the most frequently reported symptoms being gait abnormalities and exercise-induced fatigue, each observed in 5/22 patients. Myalgias occurred in 4/22 patients, asymptomatic creatine kinase elevation in 3/22, motor development delay in 3/22, and myoglobinuria in 2/22. In 3/22 patients, corticosteroid therapy was implemented temporarily due to early progressive motor symptoms.

The genetic analyses identified a range of pathogenic variants associated with BMD. Deletions were the most prevalent type of genetic variation (15/22), with exon 48 deletion being the most common (8/22). Additional deletions in the dystrophin gene included exons 45 to 47 (4/22), exons 45 to 51 (2/22), and exons 56 to 57 (2/22). Single nucleotide variants (SNVs) were also identified: 3/22 patients had variants affecting splicing (two with c.3603+3A>T in intron 26 and one with c.6290+5G>A in intron 43), and 1/22 patient exhibited a missense variant (c.9926A>G) in exon 68. Duplications were found in different regions, including exons 2 to 7 (1/22), exons 8 to 19 (1/22), and exons 50 to 57 (1/22). The mutational profile of the patients is detailed in **Table 2**.

A total of 5/22 patients had cognitive or behavioral manifestations. The main developmental disorder observed was intellectual disability (5/22); among these patients, the mean intelligence quotient (IQ) was 67. Other development disorders included attention-deficit/hyperactivity disorder (3/22), delayed onset of walking (3/22), autism spectrum disorder (1/22), and specific language impairment (1/22).

The main cardiac abnormalities identified comprised mild left ventricular dilation (5/22), dilated cardiomyopathy of the left ventricle with mild mitral regurgitation (1/22), and frequent polymorphic ventricular ectopic activity (1/22) (**Table 3**).

Cardiac involvement was associated with some specific mutations in this cohort. A total of 3/4 patients carrying a deletion of exons 45 to 47 exhibited cardiac abnormalities, including 1/4 case of dilated cardiomyopathy of the left ventricle with mild mitral regurgitation and 2/4 cases of mild left ventricular dilation. The most severe cardiac complication was observed in the patient carrying a duplication of exons 2 to 7. No cases of cardiomyopathy were observed in patients with the most frequent mutation, deletion of exon 48. We also analyzed the potential familial aggregation of the cardiac phenotype; among the patients with cardiac abnormalities, none belonged to the same family.

The proportion of patients experiencing muscle weakness progression at pediatric age (4/22) varied across mutation groups. No cases of early progression were observed in patients with deletion of exon 48. By contrast, early progression was identified in patients with the following variants: 2/22 patients with deletion of exons 45 to 47 and 2/22 patients with splicing variants c.6290+5A>G (intron 43), and c.3603+3A>T (intron 26).

The functional status of the patients currently followed by the pediatric neurology team (median age: 7.98 years, SD: 3.14) indicates that 6/8 showed no muscle weakness, 2/8 presented Gowers' sign, 2/8 had difficulty climbing stairs, 2/8 displayed scapular winging, and 1/8 reported myalgias. In comparison, at the time of transfer to the adult neurology department (age 18, 14/22 patients), 9/14 had difficulty climbing stairs, 8/14 exhibited calf pseudohypertrophy, 5/14 exhibited Gowers' sign, 4/14 had no muscle weakness, 4/14 experienced myalgias, and 1/14 displayed scapular winging.

Table 1 – Patient population characteristics

	Value	**Range**
Age at first appointment at the neuromuscular center (years)	Mean ± SD 7.3 ± 4.5	1.1–16.3
Follow-up duration (years)	Mean ± SD 8.7 ± 1.1	1.9–12.5
Age at diagnosis (years)	Mean ± SD 7.7 ± 3.9	2.0–17.0
Age at symptom onset (years)	Median (IQR) 3.0 (5.3)	1.0–15.0
Onset of independent walking (months)	Mean ± SD 14.2 ± 2.3	12.0–20.0
Serum creatinine kinase at initial survey (U/L)	Median (IQR) 6287 (11416)	928–31758

Table 2 - Mutational profile of the BMD patients identified in our cohort

Type of Variant	Variant Description	Number of Cases	Protein Effect Prediction* / RNA Effect (when available)	ACMG Classification
Copy Number Variants				
Large Deletions	exon 48 del.	8	In-frame deletion	P
	exons 45-47 del.	4	In-frame deletion	P
	exons 45-51 del.	2	In-frame deletion	P
	exons 56-57 del.	2	In-frame deletion	LP
Large Duplications	exons 2-7 dup.	1	In-frame duplication	P
	exons 8-19 dup	1	In-frame duplication	LP
	exons 50-57 dup	1	In-frame duplication	LP
Single Nucleotide Variants				
Splicing	c.3603+3A>T	2	Partial intronic retention of 116bp (recognition of cryptic donor splice site): r.[=, 3603_3604ins3603+1_3603+116; 3603+3a>u]. p.[=, Arg1202Valfs*25]	P
	c.6290+5G>A	1	Skipping of exon 43: r.6118_6290del; p.(Asn2040Alafs*3)	P
Missense	c.9926A>G	1	Aminoacid substitution p.(His3309Arg)	VUS

The table includes the type of variant, its predicted molecular effect, and classification of pathogenicity according to the American College of Medical Genetics and Genomics (ACMG) guidelines.[11] Additionally, the Leiden Open Variation Database status is reported, specifying whether the variant results in an in-frame or out-of-frame transcript.
LP - Likely Pathogenic / P - Pathogenic / VUS - variant of uncertain significance

Table 3 - Main cardiac abnormalities and age at diagnosis

Abnormal Findings	Age at Diagnosis	Variant Description
Mild left ventricular dilation	16 years old 16 years old 17 years old 15 years old 14 years old	Exons 45-47 deletion Exons 45-51 deletion Exons 45-47 deletion Exons 56-57 deletion Exons 50-57 duplication
Dilated cardiomyopathy of the left ventricle with mild mitral regurgitation	17 years old	Exons 45-47 deletion
Frequent polymorphic ventricular ectopic activity	16 years old	Exons 2-7 duplication

DISCUSSION

This retrospective study provides a comprehensive overview of the clinical presentation, genetic variants, and disease progression in pediatric patients diagnosed with BMD at a single neuromuscular disease center over nearly three decades. Our findings highlight the diverse phenotypic spectrum of BMD and the implications of genetic heterogeneity on clinical outcomes, as shown in previous studies.[11-13]

The median age of symptom onset in our cohort was 3.0 years, which is younger compared to previously reported ranges.[14,15] This difference may be explained by the referral pattern, as patients in our study were evaluated at a specialized pediatric neuromuscular center, potentially introducing a bias toward more severe cases that tend to present earlier. Early manifestations, such as motor development delays, highlight the need for vigilance and timely referral to specialized centers to facilitate early diagnosis and management.

Consistent with our findings, all the mothers in our cohort were asymptomatic, with no clinical signs of muscle weakness or cardiomyopathy. This aligns with the existing literature, which indicates that while most female carriers of BMD do not exhibit symptoms, a small proportion may develop mild muscle weakness or cardiomyopathy.[16]

Our genetic analysis underscores the predominance of exon deletions. This is in line with the existing literature reporting deletions as the most common genetic alteration in BMD.[16,17] Particularly, the isolated deletion of exon 48 was the most common mutation observed and appears to be associated with a better prognosis, as it correlates with a milder disease course. Notably, no cases of cardiomyopathy were identified in patients with this deletion, suggesting a potentially milder cardiac phenotype. Additionally, no cases of early disease progression were observed.[18,19] The absence of early progression in exon 48 deletions may reflect differences in dystrophin expression or residual protein function, whereas deletions involving more exons could disrupt essential domains more critically involved in maintaining muscle integrity.

The presence of single nucleotide variants and duplications further emphasizes the genetic heterogeneity of the disease. The identification of rarer variants, such as the splicing variants in intron 43 and intron 26, highlights the complexity of genotype-phenotype correlations. In the patient with the c.3603+3A>T variant, two types of transcripts were identified: one with partial intronic retention of 116 base pairs in intron 26, resulting in a prematurely truncated protein (p.Arg1202Valfs*25), and one normal transcript. The presence of the normal transcript may account for the BMD phenotype rather than a DMD phenotype. By contrast, the patient with the c.6290+5G>A variant exhibited, upon RNA analysis, a single transcript resulting in exon skipping (r.6118_6290del), predicted to cause a frameshift and potentially contribute to the early progression of muscle weakness observed in this case. Since all the deletions and duplications, as well as the missense variant, are predicted to be in-frame, they are compatible with a Becker phenotype. Understanding these genetic patterns is crucial for accurate diagnosis and genetic counseling.[19] In addition, to maximize the benefit of possible future exon-skipping therapies, it is crucial to have a precise genetic diagnosis and understand the link between genetic variants and clinical symptoms.[20]

The persistence of calf pseudohypertrophy in most patients further supports its role as a common clinical feature in BMD. Functionally, a significant proportion of our patients exhibited muscle impairment by the time they transitioned to adult care with a neurologist. While 66% of patients showed no muscle weakness during pediatric follow-up, only 36% retained this status into adulthood. There was a marked increase in difficulty climbing stairs and the presence of positive Gowers' signs. This progression highlights the degenerative nature of BMD and emphasizes the importance of ongoing monitoring to manage functional decline, as childhood-onset weakness typically leads to loss of ambulation in the third or fourth decade.[21,22]

Cardiac involvement, a critical aspect of BMD, was also observed in our cohort. Mild left ventricular dilation was the most common cardiac abnormality, occurring in 22.7% of cases; although, one patient exhibited severe cardiac manifestations with dilated cardiomyopathy (DCM). The association between genotype and DCM in patients with BMD has been widely investigated but remains inconclusive. Studies suggest that genotype influences the age of DCM onset. In our patient, who carries a deletion spanning exons 45 to 47, the diagnosis of BMD with DCM at age 17 aligns with previous findings indicating that deletions in this gene region may be associated with early cardiac manifestations, particularly when they disrupt the reading frame.[23,24] Cardiac involvement is often asymptomatic. While most patients remain symptom-free, up to one-third may develop dilated cardiomyopathy, potentially progressing to heart failure. Notably, cardiac involvement does not correlate with the severity of skeletal muscle symptoms or the location of exon deletions.[25,26] These findings highlight the need for regular cardiac monitoring and early cardioprotective treatment to reduce the risk of heart failure.[27] Although some patients in our cohort were members of the same family, none of the individuals with cardiac involvement were related, which suggests that there was no evidence of familial clustering of the cardiac phenotype.

Developmental disorders were prevalent, with intellectual disability being the most common, affecting 22.7% of the patients, which is consistent with existing literature.[28] In some patients, behavioral disorders may precede muscle weakness,[29] highlighting the neurodevelopmental impact of BMD and underscoring the necessity of a multidisciplinary approach to care, including neuropsychological assessment and support for educational and behavioral challenges. The presence of ADHD and other developmental disorders further complicates disease management and emphasizes the role of comprehensive pediatric care.

Our study has limitations, including its retrospective nature and single-center design, which may limit the generalizability of our findings. However, the long-term follow-up and detailed clinical and genetic characterization provide valuable insights into the natural history of BMD and highlight the need for continued research into genotype-phenotype relationships and novel therapeutic strategies.

CONCLUSION

In conclusion, this study reinforces the heterogeneity seen in BMD, both genetically and phenotypically, and emphasizes the progressive nature of the disease. Early diagnosis, regular multidisciplinary monitoring, and personalized management plans are essential to optimize patient outcomes and address both muscular and non-muscular manifestations. Future research should focus on understanding the mechanisms underlying phenotype variability and on exploring emerging therapies that target the underlying genetic defects.

AUTHORSHIP

Mário Ribeiro - Conceptualization; Methodology; Writing – original draft; Supervision

Joana Silva - Data curation; Formal analysis; Writing – original draft

Ana Gonçalves - Investigation; Writing – review & editing

Manuela Santos - Validation; Writing – review & editing

Cristina Garrido - Project administration; Visualization; Writing – review & editing

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