

The Neurocognitive and Behavioral Profiles of 3 Brothers With Becker Muscular Dystrophy

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Abstract

Becker muscular dystrophy patients generally carry in-frame mutations in the dystrophin gene, allowing the production of partially functional dystrophin protein. The presence of cognitive and behavioral comorbidities and the relation with the location of mutations has been scarcely investigated in Becker. This case report describes the neurocognitive and behavioral profiles of 3 brothers with Becker carrying an in-frame deletion of exons 45-48. The 3 cases underwent 2 consecutive neuropsychological assessments of which one assessment took place when they completed their primary education (age range of the cases: 11.2 -12.1 years). Intellectual abilities were normal to high and all cases had difficulties with processing speed and math. The brothers differed in intellectual abilities, executive functions, working memory, attention and reading abilities. Variability in cognitive development was noted as well. This report suggests that cognitive and behavioral functions in Becker vary regardless of gene mutation and exposer to similar environmental factors.

Keywords

Becker muscular dystrophy, neurodevelopment, behavior, learning disabilities, mutations, dystrophin gene, dystrophin isoforms, epigenetics, cognition

Introduction

Becker muscular dystrophy (BMD) is one of the recessive x-linked dystrophinopathies, caused by mutations in the dystrophin (*DMD*) gene.¹ BMD mutations allow the production of internally deleted, but partially functional full-length dystrophin protein isoforms (Dp427) in various tissues including muscles (M) and the brain (B).^{1,2} The (*DMD*) gene produces in addition to the full-length isoform, shorter isoforms, Dp260, Dp140, Dp116 and Dp71/Dp40.¹⁻³ Dystrophin is a complex scaffold protein that modulates cellular homeostasis and multiple protein interactions.² It provides structural stability to muscle fibers during contraction.² The clinical severity of patients with BMD varies with some having a near normal functionality, whereas others lose the ability to walk during adolescence or early adulthood.¹ In addition to skeletal muscle and heart pathology, patients with BMD may have neurodevelopmental-, behavioral comorbidities, learning disabilities and epilepsy.^{1,4-7} For instance, autism features, inattention/hyperactivity features, language–speech delays and difficulties in reading, spelling and arithmetic are found in BMD.^{1,4,6,7} It has been suggested that these comorbidities are

related to a disturbed production of brain isoforms (i.e. Dp427_B, Dp140 and Dp71).^{8,9} However, this relation has been limitedly assessed in BMD. Only Bardoni and colleagues (2000) found intellectual disabilities in patients with BMD carrying mutations affecting Dp427_B and Dp140, but not in patients with only a disturbed expression of Dp427_B.⁸ A comparable association was assessed by Young et al.(2008), but in their BMD sample the intellectual abilities were not related to the mutation site.⁴ Additionally, the neurodevelopmental,

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behavioral and emotional problems in BMD are suggested to appear regardless of dystrophin gene mutation site.⁷ The current case report evaluates the neurocognitive and behavioral profiles of 3 brothers with BMD having a similar dystrophin mutation, to clarify whether a genotype-phenotype relation may exist in BMD. We expect that the profiles of the brothers are similar.

Case Report

The reported cases were 3 brothers with BMD referred to the outpatient clinic of the Centre for Neurological Learning Disabilities (CNL), Kempenhaeghe, Heeze, The Netherlands. The diagnosis of BMD was previously confirmed by genetic testing between December 2011 and February 2012, which revealed an in-frame deletion of exon 45-48 (information on Dp140 promoter was not available). As part of their clinical care, each case received 2 consecutive neuropsychological assessments between 2012 and 2018.

The parents of the boys completed high school education and had no neurodevelopmental-, behavioral comorbidities or learning difficulties. Written informed consents of patients and parents were obtained for current report.

Neuropsychological Assessment

See Table 1 for an overview of tested neurocognitive domains and behavioral questionnaires.

The Dutch version of the Wechsler Intelligence Scale for Children-Third edition (WISC-III-NL) measured 3 WISC-III indexes (1) Verbal Comprehension (subtests information, similarities, vocabulary, comprehension, digit span, arithmetic), (2) Perceptual Organization (subtests picture completion, picture arrangement, block design, object assembly and mazes) and (3) Processing Speed (subtests coding and symbol search). Verbal Intelligence Quotient was obtained by adding the scaled scores of Comprehension index without digit span. Performance Intelligence Quotient (PIQ) was based on Organization and Processing Speed indexes. The full-scale intelligence quotient (FSIQ) was obtained by adding scaled scores of all subtests. WISC-III subtest raw scores of the Digit span and Mazes were converted to age-related norm scores ($M = 10$, $SD = 3$).¹⁰ The Kaufmann Assessment Battery for Children-second edition (KABC-II) evaluated (1) sequential processing based on the subtests Number Recall and Word Order and (2) simultaneous processing using the subtests Rover and Block Counting.¹¹ Raw scores of the WISC-III (i.e. FSIQ, VIC, PIQ and Processing speed index) and KABC-II were converted to age-related norm scores ($M = 100$, $SD = 15$).^{10,11} Sustained attention was assessed using the speed and accuracy outcomes of the Bourdon Vos.¹² Technical reading was evaluated by the Continu Benoemen & Woordlezen (CB&WL) using the EMTB-T50 score subtest. Raw scores of this subtest reflect the total number of words read correctly.¹³ Scores of the CB&WL EMTB T50 and of the visuo-motor processing task i.e. Beery-VMI were transformed to age-related norm scores ($M = 10$, $SD = 3$).^{13,14} The Tempo

Table 1. Overview of Neurocognitive Tests and Behavioral Questionnaires.

Domains	Tests
<i>Intellectual functioning</i>	
– general	WISC-III
– verbal intelligence	
– performance intelligence	
<i>Cognitive functions</i>	
– working memory	KABC-II sequential scale
– executive functioning	Digit span of WISC-III
– attention	Mazes of WISC-III
– speed of information processing	Bourdon Vos (continuous performance task)
– visuospatial functioning	Processing speed index of WISC-III
– visuomotor processing	KABC-II simultaneous scale Beery VMI
<i>Academics</i>	
– reading	CB&WL EMB-T50 (word reading)
– mathematics	TTA (speeded arithmetic)
<i>Behavioral functioning</i>	CBCL TRF

NOTE: WISC-III = Wechsler Intelligence Scale for Children-third edition; KABC-II = Kaufmann Assessment Battery for Children-second edition; Beery VMI = Beery Visual-Motor Integration; TTA = Tempo Test Automatiseren; CB&WL = Continu Benoemen & Woordlezen, TTL = Tempo test Lezen; CBCL = Child Behavior Checklist, TRF = Teacher's Report Form.

Test Automatization (TTA) was used to evaluate the degree of automatization of mathematical facts.¹⁵ The TTA consists of 4 pages with 50 arithmetic problems including separate pages for addition, subtraction, multiplication and division problems.¹⁵ Raw scores are based on number of arithmetic problems answered correctly (range 0-50) and these were converted to age equivalent scores.¹⁵ The calculation of the age equivalent score is derived from a didactic (chronological) age score. This latest represents an expected score based on the number of months of arithmetic education a child has attended. At the end of primary regular education in the Netherlands, the didactic age score reach it ceiling score of 60.¹⁵ The age equivalent score of TTA estimates the level of arithmetic functioning according to a patients didactic age. Behavioral functioning was screened using the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF).^{16,17} Both instruments evaluate behavior based on 8 syndrome scales. The syndrome scales can be used to calculate 2 broadband scale scores (i.e. internalizing and externalizing symptoms) and a total problem score. Raw scores were converted to T-scores ($M = 50$, $SD = 10$). In line with the manual, a cut off-value of $T > 63$ was applied to indicate clinical ranges of the broadband scales and the total problem score.^{16,17}

Demographic and Disease-Related Characteristics

The 3 included brothers had a genetic mutation involving a deletion of exons 45-48 of the *DMD* gene (see Table 2 for the

Table 2. Neurocognitive and Behavioral Outcomes of the Cases.

Variables	Case 1		Case 2		Case 3	
	T0	T1	T0	T1	T0	T1
Age at assessment in years	7.7	11.8	11.3	14.5	9.3	12.1
<i>Intellectual functioning</i>						
– general	1.3	0.5	1.5	1.5	NA	0.2
– verbal index	1.5	1.4	1.5	1.1	NA	0.4
– performance index	0.7	-0.6	1.2	1.5	NA	-0.7
<i>Cognitive functions</i>						
– working memory						
sequential	0.4	-0.6	-0.2	0.2	0	0.2
digit span	-0.3	0.3	-0.3	1.0	NA	-1.0
– executive functioning	0.3	-0.7	2.0	1.0	NA	0.3
– attention						
speed	-2.0	-1.0	-1.0	-1.0	0.0	-1.0
accuracy	-1.0	0.0	0.0	1.0	-2.0	0.0
– speed of information processing	0.5	-0.7	-0.7	-0.7	0.1	-0.8
– visuospatial	1.5	NA	1.8	1.2	0.2	1.1
– visuomotor	0.0	NA	0.5	-0.6	0.5	-0.6
<i>Academics</i>						
– reading						
EMTB-T50	0.7	0.0	NA	-1.3	-1.7	-2.3
– speeded arithmetic ad/sub*	7	31	35	53	13	22
– speeded arithmetic ad/sub/mu/di*	–	29	28	45	<15	20
<i>Behavioral functioning</i>						
– CBCL						
Internalizing problems	-0.9	NA	1.7	0.4	1.1	0.9
Externalizing problems	-1.7	NA	0.0	-1.0	-0.4	-0.4
Total problems	-0.8	NA	0.4	-0.5	0.5	0.2
– TRF						
Internalizing problems	1.8	NA	0.6	NA	0.1	NA
Externalizing problems	0.9	NA	-0.9	NA	-0.9	NA
Total problems	0.6	NA	-0.1	NA	0.0	NA

NOTE: results are z-scores (mean = 0, SD = 1), except the speeded arithmetic scores

*Are didactic age equivalent scores.

NA = not available, EMTB-T50 = 1 minute reading test T50 score, speeded arithmetic ad/sub = speeded arithmetic additions and subtractions total score, speeded ad/sub/mu/di = speeded arithmetic total score based on additions, subtractions, multiplications and division problems, CBCL = Child Behavior Checklist, TRF = Teacher report Form, T0 = first neurocognitive testing, T1 = second neurocognitive testing.

Higher scores on the cognitive tests reflect better performances

Higher scores on the CBCL and TRF questionnaires reflect more behavioral problems.

age of the cases). None had hearing or vision problems, or used medication (i.e. steroids and stimulants) at time of neuropsychological testing. At first neuropsychological testing (T0), all cases followed regular education, were ambulant and had no formal neurodevelopmental or behavioral disorders. At second neuropsychological testing (T1; see Table 2), cases 1 and 2 continued with regular education, both remained ambulant and had no neurodevelopmental or behavioral disorders. Case 3 changed from special primary education for children with a physical handicap or learning disability to regular high school with a customized education plan. He was non-ambulant for long walking distances. Furthermore, based on the outcomes of his first assessment, case 3 was diagnosed with dyslexia by the neuropsychologist and child neurologist of the clinical team (JH, JV, SK).

Neurocognitive and Behavioral Assessment at the End of Primary Education

All cases underwent neuropsychological testing at a similar age (11.3–12.1 years), which was at the end of primary education. Norm scores of the cognitive tests and behavioral questionnaires were transformed to Z-scores (M = 0, SD = 1). Higher z-scores on the cognitive tests reflect better performances. Higher z-scores on the CBCL and TRF questionnaires reflect more behavioral problems. Results of cognitive testing showed that the 3 cases exhibited similar difficulties on speed (i.e. visual sustained attention speed and processing speed) and math (see Table 2; case 1 at T2, case 2 at T1 and case 3 at T2). The math outcomes of the 3 cases were lower than expected for their age, case 1 expected didactic score = 57

(at T2), case 2 expected didactic score = 51 (at T1) and the expected didactic score of case 3 (at T2) could not be calculated because the didactic scores are not applicable to special elementary education. We also found differences in cognition. Case 1 performed lower on executive functioning compared to case 2 and 3. Case 3 had dyslexia and attention deficits, and this latest deficit caused high distractibility throughout testing. Additionally, his general and verbal intellectual abilities and working memory scores were lower compared to cases 1 and 2.

Developmental Profiles of the Cases

Table 2 displays the outcomes of the first and second testing of each case. The time between their first and second testing ranged from 2.8 to 4.1 years. Z-scores of +2.0 SD or -2.0 SD were considered as clinical significant changes. At T1, case 1 improved (+1.0 SD) on accuracy and speed of visual sustained attention (see Table 2). Furthermore, case 1 had more difficulties on visuospatial abilities (-1.1 SD), executive functioning (-1.4 SD), processing speed (-1.2 SD) and sequential processing (-1.2 SD; see Table 2). Other cognitive outcomes of T1 were stable compared to T0. The behavioral outcomes of case 1 could not be evaluated as the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF) were not completed at T1 (see Table 2). Case 2 improved on working memory (+1.0 SD) and accuracy of visual sustained attention (1.0 SD) at T1. Additionally, case 2 performed less on executive functioning (-1.0 SD) and visuomotor processing (-1.0 SD; see Table 2). The other outcomes remained comparable to T0, although his math outcomes were not applicable because he followed high school education at T1. With respect to the behavioral outcomes of case 2, we found an elevated score (1.7 SD) on CBCL internalizing subscale (T-score >63) at T0, but no longer at T1 (0.4 SD; see Table 2). Finally, case 3, had more difficulties with speed of visual sustained attention (-1.0 SD) and visuomotor processing (-1.1 SD) at T1 compared to T0 (see Table 2). Other outcomes remained constant to T0 (see Table 2). No behavioral problems were noticed at both assessments of case 3 (see Table 2).

Discussion

The current study reports on a possible genotype-phenotype association in patients with BMD. This is the first case study on neurocognitive and behavioral profiles of 3 brothers with BMD with the same genetic dystrophin mutation, involving an in-frame deletion of exon 45-48. We retrospectively evaluated cognitive and behavioral performances cross-sectionally and longitudinally. Our results showed comparable difficulties in math and processing speed among the cases, but we also noted differences in cognitive abilities. The general intellectual abilities (FSIQ) of case 3 were 1.3 SD lower compared to case 2. A comparable difference in FSIQ has been described by a previous study of Chamova and colleagues, who found a difference of 18 points (1.2 SD) in IQ (83 versus 65) among 2 brothers with BMD sharing a similar mutation defect of exon 45 to 53.¹⁸ Additionally, in our report, case 3 exhibited severe reading

difficulties and attention problems, and this latest problem was expressed by high internal distractibility throughout testing. A higher incidence of attention problems has previously been described for BMD.⁴ The prefrontal cortex which is involved in attentional processes is a region that is rich in dystrophin, which may suggest that abnormal brain dystrophin production contributes to the attention problems of dystrophinopathy patients.^{4,19-22} With respect to the development profiles of the cases, we noted non-significant clinical changes and some variability in development. Improvements were noticed for case 1 and 2 on accuracy of visual sustained attention, but both also displayed decreased performances in executive functions and processing speed. Furthermore, case 2 and 3 displayed more difficulties with visuomotor processing, longitudinally.

It was striking that we observed variability in cognitive and behavioral difficulties cross-sectionally and longitudinally, despite the fact that the cases had an identical dystrophin mutation, were tested at a similar age, and grew up in the same environment. We in particular found differences within intellectual abilities, working memory, attention and reading abilities. This may suggest that not only genetic and environmental factors induce interindividual variability in phenotypes. Other factors may modulate brain development as well. There is growing evidence on the fundamental role of maternal health factors on neurodevelopment of new-borns.²³ Factors for instance as maternal stress, malnutrition, or prenatal exposure to toxic agents may also affect fetal brain development and induce altered brain structures and functions. However, the role of mechanism such as prenatal maternal stress on fetal brain development is not yet fully understood.²³ Our results highlight that further research on cognitive and behavioral comorbidities and its development in the BMD population is necessary.

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