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Psychiatric and neurodevelopmental aspects of Becker muscular dystrophy

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Abstract

Little is known about the relationship between Becker Muscular Dystrophy (BMD) and mental disorders. This study aimed to clarify whether BMD is a risk factor for psychiatric diseases. We asked genetically or immunohistochemically confirmed BMD patients to participate in the study interview. Participants who consented to psychiatric tests underwent further assessments of intellectual, psychological, and neurodevelopmental disorders. In total, 76 (73%) of 105 BMD patients (median age, 37 years) completed the interview. Of these, 6 had developmental disorders (mental retardation, pervasive developmental disorder), 33/76 (43%) experienced bullying in school, 11 exhibited problematic behaviors such as cutting class and violent incidents, and 16 had psychiatric disorders (schizophrenia spectrum, 5; depressive spectrum, 4; stress-related disorders, 3; obsessive-compulsive and related disorders, 2; somatic symptom and related disorders, 2; bipolar and related disorders, 1). Mean IQ was normal, whereas 13/40 (32.5%) of participants were in a depressive state. High trait anxiety was found in 20/40 (50%) of patients, while 15/40 (38.5%) were in an anxious state. Review of MRI data from 14 participants revealed brain atrophy caused solely by BMD and unrelated to any other complication. Our findings suggest that BMD patients are at risk of developing psychiatric disorders. Physical handicap or bullying may influence their mental state, as many of them have high trait anxiety. Parents, teachers, and supporters should be mindful of the daily environment of BMD patients and provide support to help them cope with stress.

Keywords: Becker muscular dystrophy; Dystrophinopathy; Psychiatric diseases; Neurodevelopmental disorders; Bullying; Brain MRI.

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1. Introduction

Becker muscular dystrophy (BMD, OMIM 300376) is an X-linked recessive form of muscular dystrophy caused by mutations in the dystrophin gene (*DMD*), which is located on chromosome Xp21.2 [1]. The *DMD* gene is the largest gene identified in humans and contains 79 exons. Mutations in the gene result in a deficient dystrophin protein [2]. BMD is typically associated with mutations that maintain the open reading frame, producing an internally altered but partially functional dystrophin protein, with an intact C terminal domain [3],[4]. Patients with BMD have variable phenotypes, but are less severely affected than those with Duchenne muscular dystrophy (DMD), and have a much longer normal life expectancy [4].

Little is known about social and mental problems that accompany BMD. In a previous study, we found that BMD patients often experienced mental problems and difficulties in daily life (e.g., bullying) when they were attending school. Some patients also experienced mental stress at the workplace, which can lead to depression and neurosis [5]. However, we were unable to clarify the prevalence of psychotic disorders, difficulties in daily life, and other related factors among patients with BMD. This study aimed to clarify the prevalence not only of psychotic disorders but also of neurodevelopmental disorders and problematic behaviors, in addition to analyzing related factors among patients with BMD.

2. Methods

2.1. Aim and design

This study aimed to clarify the prevalence not only of psychotic disorders but also of neurodevelopmental disorders and problematic behavior, as well as analyze related factors in patients with BMD. We also assessed whether these disorders and/or problematic behaviors correlate with the genotype of patients with BMD.

2.2. Participants

This study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry (NCNP). We enlisted male patients with dystrophinopathy who visited the National Center Hospital of NCNP from July 1979 to September 2016. Among these patients, those with BMD aged $\geq$ 17 years were selected for this study. Patients who were ambulant at age 17 were defined as having BMD [6].

2.3. Interview

A neurologist (MMY) requested genetically- or immunohistochemically-confirmed BMD patients to participate in the study interview. Interview items included: (1) age at onset, first symptoms, past and present ambulatory performance, and wheelchair use, (2) information about developmental disorders (e.g., mental retardation, autism, Asperger syndrome, attention deficit hyperactivity disorder, epilepsy, and others), (3) information about bullying and problematic behavior (e.g., cutting class, domestic violence, suicide attempts and/or self-mutilation, and violent incidents), and (4) information about the history of psychiatric diseases and diagnoses. Ambulation status was also evaluated during the interview.

Since we assessed disease onset after participants became symptomatic, we asked about the age of onset when any symptoms arose, rather than the age at which test abnormalities were found. These interview reports were compared to medical records when there was a discrepancy between physical examination results and patient statements during the interview. We also collected information regarding history of psychiatric diseases from medical records.

2.4. Psychiatric and neurodevelopmental tests

Participants who consented to undergo psychiatric tests were assessed for intelligence (Wechsler Adult Intelligence Scale III (WAIS-III), Japanese Adult Reading Test (JART)), mental problems (Center for Epidemiologic Studies Depression Scale (CES-D), State-Trait Anxiety Inventory (STAI), Mini-International Neuropsychiatric Interview (MINI)), developmental problems (Autism-Spectrum Quotient (AQ), Conners' Adult ADHD Rating Scales (CAARS), Pervasive Developmental Disorders-Autism Society Japan Rating Scale (PARS)), and quality of life (MOS 36-Item Short-Form Health Survey: SF-36). Trained psychologists conducted all tests and assessments.

2.5. Genetic diagnosis

Information regarding genetic diagnosis was collected from medical records. We divided participants into two groups according to mutations that might alter Dp140 expression, with the aim to verify a possible association between the loss of Dp140 and developmental, social, or psychiatric problems in BMD patients. Specifically, deletion/duplication/small mutations in the region between the Dp140 promoter and the N-terminus, and frameshift/nonsense mutations involving intron 44 or downstream, were assumed to be Dp140 expression modifiers. Among these possible modifiers, we defined deleterious Dp140 mutations as deletion mutations which include the Dp140 start codon and/or coding region, or coding region nonsense or splice site variants, and discriminated these from other mutations (potentially deleterious: deletion mutations which include the Dp140 promoter and exon 1 of Dp140, partial deletion within 5′UTR which may influence Dp140 expression, No: mutations that did not affect Dp140 expression). We also defined deleterious Dp71 mutations as deletion mutations which include the Dp71 start codon and/or coding region, or coding region nonsense or splice site variants.

2.6. Radiological findings

MR examinations had been performed in 14 patients with BMD for the following reasons: incidental complications (falling, risk of cardiac embolism, tremor, deafness, amnesia, and loss of consciousness) in 6, no complication or psychological abnormalities but for a brain evaluation related to BMD in 4, severe psychiatric or developmental disorders (depression, schizophrenia, and/or mental retardation) in 3, and unknown in 1. Of these 14 participants, 9 had psychiatric diseases (schizophrenia, 4; depression, 2; neurosis, 2; bipolar disorder, 1), 4 had mental retardation, and 1 had pervasive development disorder. Two neuroradiologists (N.S. and E.M. with 20 and 14 years of experience in neuroradiology, respectively) independently assessed brain atrophy (severity, diffuse or focal, and location) and signal abnormalities on T1-weighted, T2-weighted and FLAIR images. Differences in evaluations were resolved by consensus. We also evaluated the relationships between these MR imaging and psychological findings.

2.7. Data analysis

Data are presented as mean ± standard deviation (SD), median, range, frequency, or percentage, as indicated. The one-sample or two-sample *t*-test was used for continuous data and Fisher's exact test for binary data. Pearson's correlation coefficients were estimated to evaluate the relationships between continuous variables. Logistic regression models were applied using developmental disorders and psychiatric diseases as the outcome variables and age at onset, ambulation, WAIS-III FIQ, JART, and deleterious Dp140 mutations as the explanation variables. Missing data were multiply imputed using the fully conditional specification (FCS) method [7],[8].

All statistical analyses were performed using SPSS for Macintosh (Version 24; SPSS Inc., Chicago, IL) and SAS (version 9.4; SAS Institute Japan, Tokyo).

3. Results

3.1. Participant characteristics at study entry (Fig. 1)

At the end of September 2016, a total of 104 BMD patients who fulfilled the inclusion criteria were considered candidates. Among them, 76 (74.1%) participated in this study. Mean age was 38.8 +/-13.3 (17-72, median 38), and mean age at BMD onset was 12.7 years; 73 were symptomatic and 3 were asymptomatic; 59 (77.6%) were ambulant, while 17 (22.4%) were not; and mean age at loss of ambulation was 33.9 years. None of the patients started steroids at age <17.

3.2. Developmental disorders, bullying, problematic behavior, and psychiatric diseases (Table 1)

Six participants were diagnosed with developmental disorders (mental retardation, 5; pervasive developmental disorders, 1). One had severe mental retardation. Five patients had epilepsy, and 2 had febrile seizures.

Up until graduation, 57 (45.6%) participants experienced bullying, 11 exhibited problematic behavior such as cutting class ($n=8$) and domestic violence ($n=3$), and 16 were diagnosed with psychiatric diseases. There were 5, 5, 3, and 1 participants with schizophrenia, neurosis, depression, and bipolar disorder, respectively. Among those with neurosis, 1, 1, 1, and 2 participants had panic disorder, obsessive-compulsive disorder, adjustment disorder, and an unknown disorder, respectively. One participant with neurosis also had depression.

Fisher's exact test revealed that developmental disorders ($p=0.04$) and problematic behavior ($p=0.05$) were significantly ($p=0.03$) correlated with psychiatric diseases.

3.3. Intelligence and psychological tests (Tables 2 and 3, Fig. 2)

Results of the psychiatric tests are shown in Table 2 and Fig. 2. The results of intelligence tests indicated that, on average, results were within the normal range (WAIS-III FIQ: 94.2 ± 18.9, $n=33$, 50–138); JART: 105.1 ± 9.9, $n=45$, 71.78–121.50), whereas 12.1% of participants were in the abnormal range. JART scores were significantly higher than WAIS-III FIQ ($p=0.004$) and PIQ ($p=0.003$) scores, but not significantly higher than the WAIS-III VIQ scores ($p=0.073$). One participant with severe mental retardation did not undergo the intelligence tests. PIQ was lower than VIQ, but not significantly ($p=0.211$). None of the participants had obvious hand weakness that would render writing or other test performance activity difficult.

Thirteen participants (32.5%) were deemed by the CES-D to be in a depressive state, although only 2 had been diagnosed with depression. Fifteen (38.5%) participants were in an anxious state, and 20 (50%) had high trait anxiety as noted by STAI.

The prevalence of disorders in 40 participants, as assessed by MINI, are shown in Table 3. Nineteen participants (25% of all participants, 46% of those assessed by MINI) met criteria for at least one lifetime MINI disorder (mood disorder, 8; anxiety disorder, 5; psychotic disorder, 2; substance use disorder, 2). Ten participants reported having attempted suicide. When MINI was used to rate current suicide risk, six participants were at one median risk, and 14 were at low risk.

Abnormalities of AQ, CAARS index in self-report and observer-report, and PARS for childhood and adolescence were 4 (11.4%), 8 (22.9%) and 3 (12.5%), and 3 (17.6%) and 0 (10.0%), respectively.

3.4. Relationship among clinical factors, developmental disorders, and psychological diseases

Logistic regression models revealed that none of the items were significant when the outcome variable was developmental disorders, but the JART score was found to be significantly associated with the existence of psychiatric

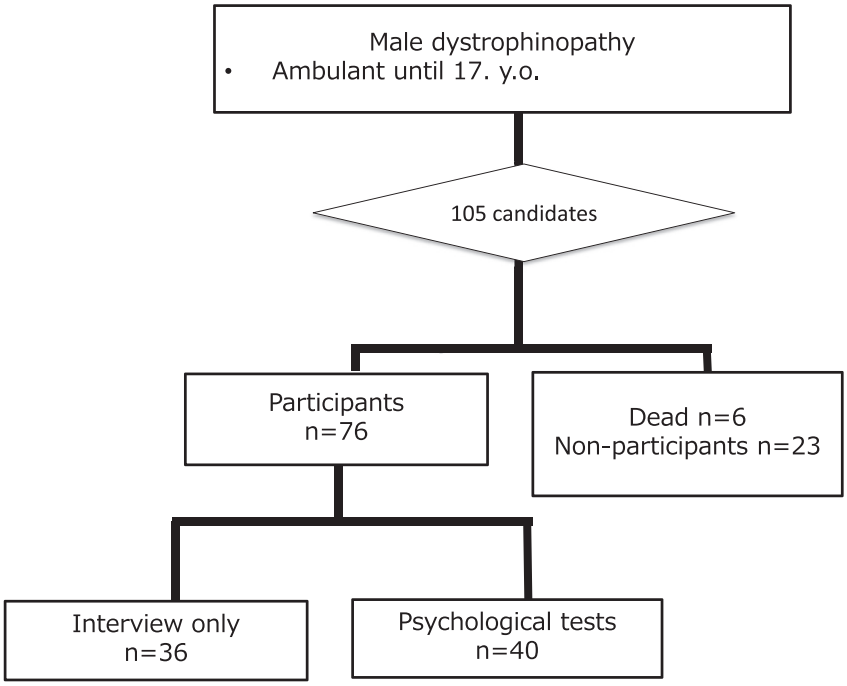

Fig. 1. Study participants. We recruited BMD patients who were ambulant age at 17. Among 105 candidates, 76 participated in this study. Six patients died and 23 could not be contacted during follow-up. Among the 76 participants, 40 underwent psychological and/or intellectual tests, whereas the remaining 36 participated only in the interview.

Table 1
Developmental disorders, education, and bullying.

				n	(%)	% among common Japanese population
Developmental disorders	Intellectural disorder			5	6.6	about 1% [15]
	Pervasive developmental disorders			1	1.3	
Epilepsy				5	6.6	0.5–1% [16]
Febrile seizures				2	2.6	3.4% [17]
Bullying experience	Yes			57	45.6	1.34 [18]
	No			63	50.4	
	no answer			5	4	
Problematic behavior	Yes			11	14.5	
	problematic behavior breakdown	Cutting class		8		1.17 [18]
		Domestic violence		3		
	No			65	85.5	
Psychiatric disease	Yes			16	21.1	
	Psychiatric breakdown	Schizophrenia Spectrum		5	6.6	prevalence 0.46%, lifetime incidence rate 0.7% [19]
		Neurosis	Adjustment disorder	1		lifetime prevalence 3∼7% [16]
			Panic disorder	1		lifetime prevalence 0.8% [16]
			Obsessive-compulsive disorder	1		prevalence 1∼2% [16]
			unknown	2	3.7	
		Depression		3	2.2	Lifetime prevalence 3∼7% [16]
		Pipolar disorder		1	0.7	Prevalence 0.7% [16]
		No answer		6	4.5	
	No			60	78.9	
	no answer			11	8.2	

Six participants had developmental disorders (mental retardation, pervasive developmental disorder), and nearly half suffered from bullying back when they were students; one with neurosis also had depression.
Fisher's exact test revealed that developmental disorders ($p = 0.04$) and problematic behavior ($p = 0.05$) were significantly ($p = 0.03$) correlated with psychiatric diseases.

Table 2
Results of intellectual, psychiatric, and developmental examination scores.

		n (%)	Mean	Median	SD	Minimum	Maximum	abnormal range (n, (%))	definition of abnormal range
WAIS-III	FIQ	33	94.2	92	18.9	50	138	3 (9.1)	<70
	PIQ	27	94.8	92	15.6	68	134	1 (2.2)	<70
	VIQ	27	99.6	95	17.6	72	142	0 (0.0)	<70
JART		45	105	107.1	9.9	71.78	121.5	0 (0.0)	<70
CES-D		40	14.7	13	9.6	0	42	13 (32.5)	≧16
STAI	state anxiety	40	41.3	41.5	13.1	21	78	15 (38.5)	≧44
	trait anxiety	39	45.8	43.5	11.9	28	78	20 (50.0)	≧44
MINI		40						19 (47.5)	having any items
AQ		45	24.3	23	7.9	7	42	4 (11.4)	≧33
CAARS self report	innatention	35	49.0	46	12.2	29	72	4 (11.4)	≧66
	hyperactivity	35	48.4	45	11.0	36	77	5 (13.4)	≧66
	impulsivity	35	51.8	50	14.3	33	87	8 (22.9)	≧66
	Self-Concept	35	52.3	51	11.9	33	78	6 (20.0)	≧66
	Index	35	50.8	47.0	14.6	30.0	79	8 (22.9)	≧66
CAARS observer	innatention	24	50.2	49.5	10.6	38	76	3 (12.5)	≧66
	hyperactivity	24	47.9	44	8.1	38	71	1 (4.2)	≧66
	impulsivity	24	53.9	51.5	11.1	40	78	2 (8.4)	≧66
	Self-Concept	24	50.6	47	10.1	40	78	4 (16.7)	≧66
	Index	24	51.3	50.5	10.4	39	74	3 (12.5)	≧66
PARS	childhood	24	5.1	5	5.6	0	21	3 (17.6)	≧9
	adolescent	17	5.9	3	6.2	0	18	0 (0.0)	≧9

One participant with severe mental retardation did not undergo the intelligence tests. None of the participants had obvious hand weakness that would render writing or other test performance activity difficult.
The results of intelligence tests indicated that, on average, results were within the normal range. JART scores were significantly higher than WAIS-III FIQ and PIQ scores, but not significantly higher than the WAIS-III VIQ scores. While 32.5% of participants had depressive tendencies, as assessed by CES-D, only two were diagnosed with depression, suggesting the existence of a subclinical population of depressive BMD patients who require intervention.

Table 3
Prevalence of disorders assessed by MINI.

		Total	Present	Past	Recurrent	Lifetime
With any disorders		19 (25%)				
Major depressive episode		8	3	5	2	0
Attempted suicide		10	6 (low 5, middle 1)	10 (low 5, middle 3, high 2)	0	0
Alcohol dependence		2	1	1	0	0
Anxiety disorder	Total	5	3	3	0	2
	Obsessive-compulsive disorder	3	3	1	0	0
	Social Phobia	2	2	1	0	0
	Panic disorder	2	2	0	0	2
	Agoraphobia	1	0	1	0	0
Psychotic disorder		2	2	1	0	0
Without disorders		21 (28%)				
Not examined		36 (47%)				

Nineteen participants (46% of those assessed by MINI) met criteria for at least one lifetime MINI disorder. Ten participants reported having attempted suicide. Six participants were at one median risk, and 14 were at low risk.

diseases (odds ratio: 0.92, $p=0.0143$). As the confidence intervals for the two variables were extremely wide due to the small sample size, these variables were excluded from the model for sensitivity analysis. The significance of the included two variables in the sensitivity analysis did not change ($p>0.7$ for both).

3.5. Radiological abnormalities (Fig. 3)

Previous MRI data of 14 participants were reviewed. Of the 14 participants, 10 had psychiatric diseases and/or developmental disorders. Nine participants had psychiatric diseases (schizophrenia, 4; depression, 2; neurosis, 2;

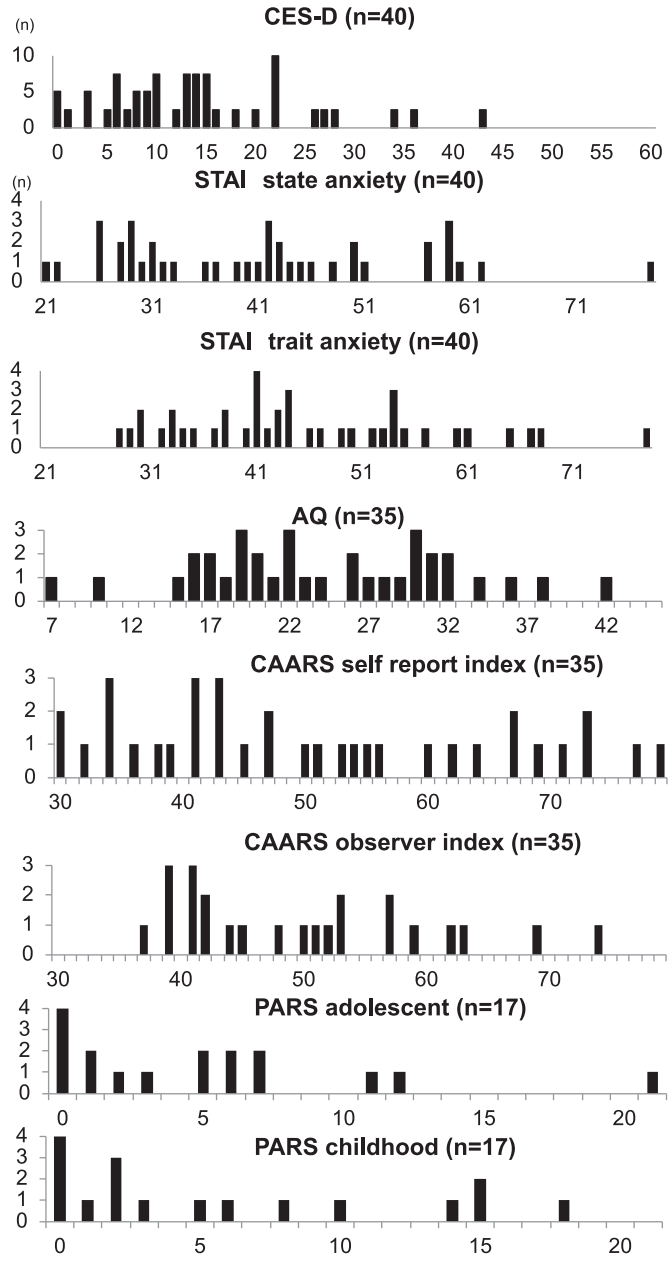

Fig. 2. Results of the psychological examination (CES-D, STAI state anxiety, STAI trait anxiety, AQ, CAARS self-report index, CAARS observer index, PARS adolescence, and PARS childhood). The CES-D found thirteen participants (32.5%) to be in a depressive state (>16), although only 2 had been diagnosed with depression. The STAI found that fifteen (38.5%) participants were in an anxious state (>44), and 20 (50%) had high trait anxiety (>44). Abnormalities of AQ (>33), CAARS index as self-reported and observer-reported (>66), and PARS for childhood and adolescence (>9) were 4 (11.4%), 8 (22.9%) and 3 (12.5%), and 3 (17.6%) and 0 (10.0%), respectively.

bipolar disorder, 1), 4 had mental retardation, and 1 had pervasive development disorder. Eleven participants had cerebral atrophy [Figs. 3A and C] that was mild in 7, marked in 4, diffuse in 6 and focal in 6 (frontal, 2; parietal, 2; frontotemporal, 1; and frontotemporoparietal, 1). Nine participants had mild atrophy in the corpus callosum [Figs. 3B and D], and 2 had mild cerebellar atrophy. One participant had right thalamic infarction and another had focal ischemic change in the left centrum hemiovale. No other abnormal MR findings were observed. There were no significant associations between brain atrophy and developmental disorders ($p=0.505$), psychological diseases ($p=0.505$), problematic behavior ($p=0.396$), age ($p=0.855$), ambulation ($p=0.473$), or any of the other psychological test results.

3.6. Quality of life and related indices (Table 4)

We obtained SF-36 national standard scores in order to evaluate quality of life (QOL) (Table 4). All assessed indices were significantly lower than the national standard index (score=50), except for body pain ($p=0.103$). CES-D, AQ, and both state and trait anxiety of STAI, while CAARS scores were significantly negatively correlated with role physical, social functioning, general health, and mental health status. In contrast, IQ in the JART and WAIS-III were not correlated with any QOL parameters.

3.7. Genetic analysis and dystrophin isoform expression (Tables 5 and 6)

Deletion mutations (52, 68.4%), duplication mutations (3, 3.9%), small mutations (8, 10.5%), and others (no mutation by MLPA and not examined but diagnosed by immunohistochemistry, 13, 17.1%) were identified (Table 5).

A total of 49 participants had deleterious Dp140 mutations. No significant differences were observed in developmental disorders, psychiatric disease, epilepsy, bullying, or problematic behavior between those with and without deleterious Dp140 expression modifiers (Supplementary Table 2). Moreover, no significant differences in these parameters were observed between those with and without Dp71 deleterious mutations, except for problematic behavior (Supplementary Table 2).

4. Discussion

This is a comprehensive report on various clinical aspects of central nervous system disorders associated with BMD, including developmental, intellectual, and psychological aspects, QOL, brain imaging, and disease background.

Of our study population, 21% had psychiatric diseases and 24% had mental problems. Schizophrenia (prevalence in Japan is 0.46% [9]) and neurosis were more frequent in our participants than in the general population in Japan. While 32.5% of participants had depressive tendencies, as assessed by CES-D, only 2 were diagnosed with depression, suggesting the existence of a subclinical population of depressive BMD patients who require intervention. In addition, participants exhibited high state and trait anxiety. Environmental factors such as bullying and other social difficulties may influence the mental health of BMD patients [5]. These tendencies were not correlated with their intelligence or ambulation

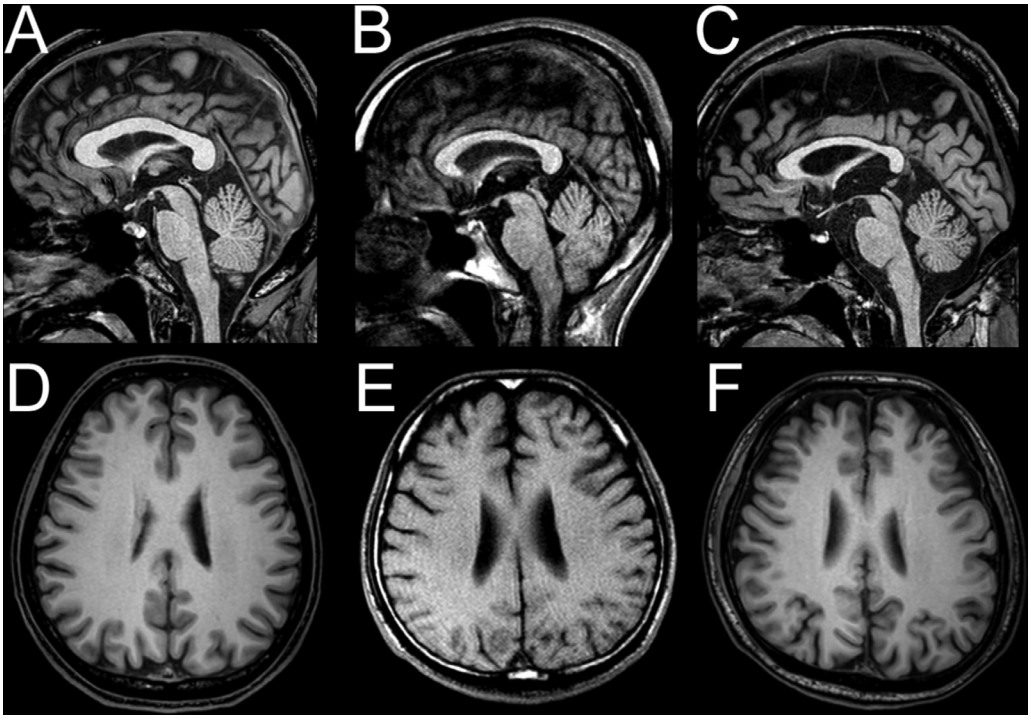

Fig. 3. Brain sagittal and axial magnetization prepared rapid gradient-echo (MP-RAGE) MR imaging (MPRAGE) of a 39-year-old healthy control [A, D] and Patient 1, a 33-year-old BMD participant with schizophrenia [C, F]. Sagittal and axial T1-weighted spin echo imaging of Patient 2, a 37-year-old BMD participant with schizophrenia and mild mental retardation [B, E]. Images of Patient 1 show mild atrophy especially in the frontal lobe (E) and the corpus callosum, except for the splenium (B). In the images of Patient 2, diffuse marked atrophy is detected in the callosum and the cerebrum (C, F). Apparent dilatation of the cerebral sulcus and volume loss of the white matter are evidence of cerebral atrophy.

Table 4
SF-36 national standard scores.

		Physical functioning	Role physical	Bodily pain	General health	Vitality	Social functioning	Role emotional	Mental health
Mean		16.541	37.068	46.8316	40.9478	42.9281	43.6379	42.6427	46.2476
Median		18.135	42.4286	44.7447	41.5217	43.4089	44.1335	43.5817	46.4541
SD		23.9595	15.7458	11.9771	12.5775	10.6156	13.4953	14.5456	11.2592
Minimum		−14.35	2.55	30.9	21.8	17.72	5.48	6.11	14.25
Maximum		57.84	55.72	61.71	65.5	62.68	57.02	56.07	65.24
Correlation (ρ)	age	−0.742**	−0.243	−0.26	−0.530**	−0.302	−0.327*	−0.109	−0.131
	WAIS-III FIQ	0.127	0.085	0.004	−0.239	0.069	0.04	0.069	0.278
	WAIS- III PIQ	0.226	−0.082	0.221	0.151	0.012	0.062	−0.03	0.133
	WAIS- III VIQ	0.121	−0.189	0.364	0.136	0.052	0.036	−0.064	0.022
	JART	0.327	0.103	0.113	0.148	−0.205	−0.012	−0.211	−0.005
	CES-D	−0.222	−0.425**	−0.372*	−0.382*	−0.608**	−0.376*	−0.650**	−0.804**
	STAI state anxiety	−0.066	−0.334*	−0.409**	−0.191	−0.489**	−0.111	−0.603**	−0.525**
	STAI trait anxiety	0.146	0.411**	0.327*	0.137	0.386*	0.223	0.567**	0.597**
	AQ	−0.15	−0.258	−0.318	−0.518**	−0.466**	−0.171	−0.437*	−0.519**
	CAARS index self report	−0.085	−0.031	−0.448*	−0.236	−0.410*	−0.302	−0.632**	−0.675**
	CAARS index observer	0.041	−0.119	−0.510*	−0.479*	−0.510*	−0.299	−0.717**	−0.707**
	PARS childhood	−0.075	−0.056	−0.305	−0.317	−0.500*	−0.212	−0.193	−0.421
	PARS adolescence	0.094	0.017	−0.243	−0.33	−0.238	−0.113	−0.268	−0.479

All assessed indices were significantly lower than the national standard index (score=50), except for body pain ($p=0.103$). CES-D, AQ, both state and trait anxiety of STAI, and CAARS scores were significantly negatively correlated with role physical, social functioning, general health, and mental health status.*: $p < 0.05$, **: $p < 0.01$.

Table 5
Molecular diagnosis of dystrophin gene.

	n	%		N	%	possible dp140 expression change	dp71	mutation	influences Dp140	influences Dp71
deletion	52	68.4	EX45_EX47del	16	21.1	probable	no	inframe	1)3)	
			EX45_EX48del	15	19.7	probable	no	inframe	1)3)	
			EX45_EX53del	5	6.6	definite	no	inframe	1)2)	
			EX45_EX55del	3	3.9	definite	no	inframe	1)2)	
			EX13del	2	2.6	no	no	inframe		
			EX48_EX51del	2	2.6	definite	no	inframe	2)3)	
			EX2_EX3del	1	1.3	no	no	frameshift		
			EX4del	1	1.3	no	no	inframe		
			EX5_EX9del	1	1.3	no	no	inframe		
			EX10del	1	1.3	no	no	inframe		
			EX17_EX19del	1	1.3	no	no	frameshift		
			EX26_EX44del	1	1.3	probable	no	inframe	1)	
			EX41_EX48del	1	1.3	definite	no	inframe	1)	
			EX48_EX49del	1	1.3	probable	no	inframe	3)	
			EX48_EX55del	1	1.3	definite	no	inframe	2)3)	
duplication	3	3.9	Ex3_Ex13dup	1	1.3	no	no	inframe		
			EX5dup	1	1.3	no	no	inframe		
			EX34_EX44dup	1	1.3	no	no	inframe		
small mutation	8	10.5	Exon 25 c.3295C>T	1	1.3	no	no	nonsense		
			Exon 22 >.2842A>G	1	1.3	no	no	missense		
			Exon 25 c.3337C>T (p.Gln1113*)	1	1.3	no	no	nonsense		
			Exon 25 c.3430C>T	1	1.3	no	no	nonsense		
			Exon 28 c.3882_3883insTT	1	1.3	no	no	frameshift		
			Exon 29-Intron 29 c.4070_4071+9del	1	1.3	no	no	splice-site deletion		
			Exon 68 c.9897A>G p.HIs3299Arg	1	1.3	definite	definite	missense	4)	4)
			Exon 74 c.10453_10454 delCT	1	1.3	definite	definite	frameshift	5)	5)
			Intron 73 c.10395-1 G>C	1	1.3	definite	definite	splice-site variant	6)	6)
others	13	17.1	no deletions/duplications	8	10.5					
			not examined	5	6.6					
total	76	100		103	100					

(1) Promoter and ex1 deletion, (2) Deletion of coding region including start codon, (3) Partial deletion inside 5′UTR (possibly influences DP140 expression), (4) Entire deletion, (5) Deletion of coding region, (6) Nonsense mutation in coding region.

status, indicating that depressive and anxiety states were not secondary phenomena induced by mental retardation or/and physical disability.

In the present study, we report on brain atrophy in BMD patients that is unrelated to other complications such as embolism or trauma. Since not all patients with brain atrophy exhibit mental retardation or psychiatric diseases, we could not conclude that the atrophy is related to psychiatric or intellectual problems. Brain MRI of DMD patients has revealed lower total brain volume and lower grey matter volume, and subgroup analyses found that DMD_Dp140 (-) subjects contributed the most to grey matter volume differences and performed worse on information processing [10]. Currently, we cannot conclude that Dp140 expression is related to brain atrophy, as a very small proportion of our participants underwent brain MRI. More comprehensive studies using MRI imaging in conjunction to mental, developmental, and intellectual evaluations are underway. A prospective MRI study of BMD patients combined with intellectual and psychiatric evaluations is warranted.

Consistent with a previous report, evaluation of intelligence revealed the average IQ of BMD patients to be in the normal range [11]. However, we found that JART scores were significantly higher than WAIS-III, especially in the PIQ. JART scores are the outcome of a standardized cognitive function test to estimate the premorbid IQ of examinees with cognitive impairments, indicating that intellectual disabilities are assumed to progress along with age. Based on the logistic regression model, JART scores significantly predicted the existence of psychiatric diseases, potentially indicating that IQ may be associated with the onset of psychiatric diseases. Therefore, these MRI findings indicate that BMD can cause progression in central nervous system disorders and may pose potential risks for psychiatric diseases.

Results of the intelligence test were not correlated with bullying, depressive states, anxiety, and QOL. On the other hand, depressive state and anxiety were significantly correlated with QOL scores, indicating the importance of mental health in maintaining the QOL of patients with BMD.

Mean QOL score of BMD patients was substantially lower than that of Japan's national standard. Within the items of the SF-36, general health, vitality, and mental health were significantly correlated with CES-D, AQ, CAARS, and STAI scores, highlighting the importance of appropriate approaches

to address depressive and anxiety states and developmental disorders when aiming to improve the QOL of BMD patients.

In a previous study, we found that BMD is a potential risk factor for social difficulty and/or mental stress and psychiatric disease [5]. Similar to results from that study, nearly half of the BMD patients (45.6%) in the present study also suffered from bullying back when they were students. This suggests that bullying may affect the mental status of BMD patients.

Epilepsy in BMD has been described in some patient populations in Japan. Reportedly, 8% of patients with dysrrophinopathy experience epilepsy [12]. As for patients with DMD, the prevalence of epilepsy has been reported to be 7.9% according to a questionnaire survey [13], or 6.3% based on medical records [14]. Our findings also suggested that some BMD patients are at risk of epilepsy, although the occurrence rate in the present study might have been underestimated due to study design (i.e., interview-based, no questions for parents) including mostly adult patients.

A significant difference was not detected in Dp140 or Dp71 expression based on most of the assessed parameters, including IQ, QOL, developmental disorders, problematic behavior, and psychiatric diseases. Therefore, unlike in patients with developmental disorders, problematic disorders, or epilepsy who had deleterious Dp140 or Dp71 mutations, we cannot conclude that differences in Dp140 or Dp71 expression caused the social issues. Only participants who had deleterious Dp140 mutations had developmental disorders, epilepsy, and problematic behavior, as well as more frequent psychiatric diseases and experiences being bullied, than those without deleterious mutations. Moreover, only problematic behavior was significantly correlated with deleterious mutations in Dp71, but not Dp140. While the significance is still unclear, these findings may reflect the causative nature of deleterious Dp140 or Dp71 mutations, which a larger sample size may help uncover.

This study has some limitations. First, the recruitment of participants from the NCNP Hospital is a potential source of selection bias, since the hospital has a specialized psychiatric department. However, the number of patients referred to our hospital due to psychiatric complications is not very high, and the hospital's psychiatrists are readily accessible to identify mental problems. Thus, we believe our study population is representative of the general BMD population. Second, some of the BMD patients at our hospital did not participate in the study, and some did not complete all psychological/psychiatric tests. Lack of time was the main reason for this. Many patients only took tests they could complete in a short time frame (e.g., JART). It is also possible that patients with psychological or behavioral problems tended to participate in the study and/or the psychological tests, which would overestimate the prevalence of these problems. Third, our study population was too small to reach a firm conclusion. In this regard, we are now collecting MRI data of dystrophinopathy patients to address questions relating to brain atrophy. Notwithstanding these potential limitations, we believe this study is the first to address central nervous system issues of BMD.

In conclusion, BMD patients are at risk of bullying and psychiatric diseases. Parents, teachers, and supporters should be mindful of the daily environment of these patients and provide support to help them cope with stress.

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CRediT authorship contribution statement

Madoka Mori-Yoshimura: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing - original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.09.006.

Abbreviations

BMD	Becker muscular dystrophy
DMD	Duchenne muscular dystrophy
NCNP	National Center of Neurology and Psychiatry
SD	standard deviation
WAIS-III	Wechsler Adult Intelligence Scale-III
JART	Japanese Adult Reading Test
CES-D	Center for Epidemiologic Studies Depression Scale
STAI	State-Trait Anxiety Inventory
MINI	Mini-International Neuropsychiatric Interview
AQ	Autism-Spectrum Quotient
CAARS	Conners' Adult ADHD Rating Scales
PARS	Pervasive Developmental Disorders-Autism Society Japan Rating Scale
SF-36	MOS 36-Item Short-Form Health Survey

References

[1] Davies KE, Smith TJ, Bundey S, Read AP, Flint T, Bell M, Speer A. Mild and severe muscular dystrophy associated with deletions in Xp21 of the human x chromosome. J Med Genet 1988;25:9–13.

[2] Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. Lancet Neurol 2003;2:731–40.
[3] Emery AE. The muscular dystrophies. Lancet 2002;359:687–95.
[4] Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. Genomics 1988;2:90–5.
[5] Mori-Yoshimura M, Mizuno Y, Yoshida S, Minami N, Yonemoto N, Takeuchi F, et al. Social involvement issues in patients with Becker muscular dystrophy: a questionnaire survey of subjects from a patient registry. Brain Dev 2018;40:268–77.
[6] Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK, et al. Diagnosis and management of Duchene muscular dystrophy, Part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2018;17:251–67.
[7] Brand J.P.L. Development, implementation and evaluation of multiple imputation [Ph.D. thesis] 1999 Erasmus University Rotterdam Holland.
[8] van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219–42.
[9] https://www.e-healthnet.mhlw.go.jp/information/heart/k-04-004.html (in Japanese. “e-healthnet”, supported by Ministry of Health and Welfare. [Accessed 10 April 2018].
[10] Doorenweerd N, Straathof CS, Dumas EM, Spitali P, Ginjaar IB, Wokke BH, et al. Reduced cerebral gray matter and altered white matter in boys with Duchene muscular dystrophy. Ann Neurol 2014;76:403–11.
[11] Young HK, Barton BA, Waisbren S, Portales Dale L, Ryan MM, Webster RI, et al. Cognitive and psychological profile of males with Becker muscular dystrophy. J Child Neurol 2008;23:155–62.
[12] Takeshita E. Dystrophinopathy and seizure. Brain Nerve 2016;68:128–36 (in Japanese)..
[13] Pane M, Messina S, Bruno C, D’Amico A, Villanova M, Brancalion B, et al. Duchenne muscular dystrophy and epilepsy. Neuromuscul Disord 2013;23:313–15.
[14] Hendriksen RGF, Vles JSH, Aalbers MW, Chin RFM, Hendriksen JGM. Brain-related comorbidities in boys and men with Duchene muscular dystrophy: a descriptive study. Eur J Paediatr Neurol 2018;22:488–97.
[15] https://www.e-healthnet.mhlw.go.jp/information/heart/k-04-004.html (e-healthnet.) “Intellectual disorder,” supported by Ministry of Health and Welfare. [Accessed 15 April 2019] (in Japanese)
[16] http://square.umin.ac.jp/∼jes/pdf/SEIJIN.pdf. Guideline of epilepsy. Japanese Society of Epilepsy. [Accessed 15 April 2019] (in Japanese.)
[17] Yamamoto N. Prolonged nonepileptic twilight state with convulsive manifestations after febrile convulsions: a clinical and electroencephalographic study. Epilepsia 1996;37:31–5.
[18] Elementary and Secondary Education Bureau. Severance of problems about pupil guidance such as problematic behavior in 2013. 22–55. http://www.mext.go.jp/b_menu/houdou/26/10/1351936.htm.
[19] http://www.mhlw.go.jp/kokoro/speciality/detail.html. (in Japanese. “Our mental health,” supported by Ministry of Health and Welfare. [Accessed 10 April 2018].