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Abstract We evaluated the course of cardiac involvement in 27 previously reported patients with Becker muscular dystrophy (BMD) originating from nine kindreds. Since almost all affected individuals of each kindred were included, intrafamilial variability could be studied. We also attempted to identify associations between cardiac involvement, functional ability and mutations at DNA level. The mean follow-up period was 12.5 years. The number of patients with electrocardiographic abnormalities progressed from 44% to 71%. Dilated cardiomyopathy (DCM) with or without congestive heart failure was now present in 33% as compared with 15% in the previous study. In addition, 22% developed borderline echocardiographic abnormalities. Six patients (22%) became symptomatic and four patients died of congestive heart failure. In all families cardiac abnormalities were found. There was no association between DCM and mutation type. Despite equal functional motor ability, there was a considerable intrafamilial variation in cardiac involvement, even in brother pairs. We conclude that cardiac abnormalities are the rule and not the exception in BMD and are progressive over time. Left ventricular dilatation may begin at any moment in the course of BMD and the rate of progression is unpredictable. A substantial proportion of patients will develop an incapacitating and life-threatening DCM.

Key words Becker muscular dystrophy · Cardiomyopathy · Dystrophinopathy · Cross-sectional study

Introduction

Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) are X-linked recessive disorders caused by mutations in the dystrophin gene. DMD shows a more or less uniform clinical picture, patients becoming wheelchair-bound before the age of 12 and mostly not surviving after 20 years of age, whereas BMD is a more heterogenous disease. The distribution of muscle weakness resembles DMD, but progression is usually much slower. In recent years, various other phenotypes have been described which are caused by mutations in the dystrophin gene [14, 21, 36, 46]. The clinical spectrum of these Xp21-dystrophinopathies also includes very mild phenotypes without apparent weakness such as myalgia, cramps after effort or episodes of myoglobinuria [1, 14] and intermediate types with clinical severity between DMD and BMD [26, 28].

Cardiac involvement is known to play a major role in the dystrophinopathies. In DMD many studies have revealed evidence of cardiac involvement (for a review see [15]). In BMD estimates of the prevalence of abnormal cardiac findings vary from 17% to 74% [1, 11, 12, 21, 23, 32, 45]. Dilated cardiomyopathy (DCM) in BMD is independent of age and severity of muscle weakness [1, 11, 12, 23, 41, 45]. It can even be the only clinical manifesta-

tion [25, 35, 39, 44, 49, 50], hence adding another phenotype of dystrophinopathy to the already known spectrum. Electrocardiographic (ECG) changes similar to those seen in DMD can be found in 41%–74% of BMD patients [7, 11, 12, 23, 45]. Echocardiographic abnormalities, including global hypokinesia [11, 23, 45], left ventricular dilatation or DCM [11, 12, 23, 45], right ventricular dilatation [23], hypertrophic cardiomyopathy [20, 32, 33] and other wall motion abnormalities [11, 23, 45] are seen in 17%–67% of patients [11, 12, 23, 32, 45]. Despite the high proportion of DCM in BMD, symptomatic patients are not common. The occasional patient with severe DCM necessitating cardiac transplantation or with a lethal outcome has been described [8, 13, 34, 39, 41, 50].

In recent years the correlation between cardiac involvement and the defect at the DNA level has been studied [11, 23, 25, 32, 40, 45]. To date, several mutations have been described which may give rise to DCM. Some investigators have found a possible correlation between cardiac impairment and deletions encompassing exon 49, deletions of exons 2–7, exons 45–46, exon 47 and exon 48 [19, 23, 32, 35, 40, 50]. Deletions in the promotor region of the dystrophin gene are presumed to cause DCM without musculoskeletal manifestations [5, 25, 27, 49, 50].

Most of the studies which evaluated cardiac impairment in BMD patients were cross-sectional or had a follow-up period of 4 years at the most, except for one [33]. Nigro et al. (1995) assessed diagnoses of cardiac involvement in a group of BMD patients on a yearly basis. They found an increase in clinically evident cardiomyopathy with increasing age during a mean follow-up period of 8 years [33]. We were able to evaluate the course of cardiac involvement in 29 previously reported individual patients with BMD originating from nine kindreds [12], with a mean follow-up period of 12.5 years. Since almost all affected individuals of each kindred were included, intrafamilial variability could be studied. We also attempted to identify associations between cardiac involvement, functional ability and mutations at the DNA level.

Patients and methods

Thirty-three patients with BMD in whom involvement of the heart was assessed previously in 1980 and 1981 were contacted again for participation in a follow-up study in 1994. Of the originally reported 33 patients, 28 were still alive. Twenty-four patients originating from nine kindreds agreed to be seen again. A clear X-linked recessive mode of inheritance was found in seven kindreds [12]. In five of these families and in one of the two remaining families, a mutation was found. The clinical pattern and laboratory data in one sporadic patient, in whom no mutation could be detected in the dystrophin gene, were consistent with BMD according to previously decribed diagnostic criteria, except that no muscle tissue was available for dystrophin analysis [22]. Nineteen patients were seen by one of us (WGdV). Five patients were seen by other cardiologists for various reasons.

All 24 patients underwent physical examination, ECG, and M-mode, two-dimensional, and colour-flow Doppler echocardiographic examination. Twenty-one patients were subjected to 24 -h ambulatory Holter monitoring. Most of the patients also had a chest radiograph. Of five patients who died during follow-up, we tried to establish the cause of death by studying the medical reports or autopsy data. When available, the ECG and echocardiographic findings of the last examination before death were also included in the evaluation.

Cardiac involvement on ECG examination was assessed according to the following criteria: (1) increased R-wave in lead V1 (> 4 mm), increased R/S ratio in V1 (> 1) in the absence of complete or incomplete right bundle branch block (RBBB), or (2) pathological Q-waves (> 0.2 mV) in lateral (I, AVL, V6) or inferior leads (II, III, AVF), or (3) complete or incomplete left or complete right bundle branch block.

The QT/PQs ratio was calculated as described by Nigro et al [30, 33] to establish its utility as a marker of early cardiac involvement.

Echocardiographic evidence for DCM consisted of an enlarged end-diastolic left ventricle corrected for the body surface area (BSA) [17] with impaired systolic function. If the BSA was not established, an end-diastolic diameter > 60 mm was considered pathological. Impaired systolic function was found if fractional shortening was less than 25% and/or global hypokinesia was seen at two-dimensional echocardiographic examination. Hypertrophic cardiomyopathy was diagnosed on the basis of thickening of the interventricular septum (IVS) and of the left ventricle posterior wall (LVPW) > 15 mm (symmetric), or an increased ratio of IVS and LVPW > 1.5 (asymmetric). Regurgitation abnormalities were established with colour-flow Doppler examination. We identified four groups of patients: (1) a group with no abnormalities as assessed by al the previously mentioned techniques, (2) a group with only ECG abnormalities, (3) a borderline group with abnormalities at echocardiographic examination of uncertain significance, (4) a group with DCM as defined before. The motor performance of all patients was scored using the Swinyard grading system of functional ability [47].

DNA analysis was performed in all families. DNA was isolated from peripheral blood cells by means of a salt precipitation protocol [24]. Screening for deletions in the dystrophin gene was performed by using two Multiplex PCR kits, according to previously described methods [3, 9]. Genomic DNA from all patients was also analysed by Southern blotting and cDNA hybridization utilizing cDNA probes across the dystrophin gene [2, 10].

To investigate possible associations between variables, Fischer exact tests were performed.

Results

One patient with a thorax deformity which hampered ECG interpretation and one patient who had suffered a myocardial infarction were omitted from analysis. None of the patients had a history of hypertension. Medical reports were obtained from four deceased patients. One patient was not seen again by a cardiologist prior to death. Because he had been diagnosed as having severe DCM in 1980 and he had died suddenly at home after an attack of dyspnoea in 1984, we included him in the study. Therefore, 22 living patients and five deceased patients, altogether 27 patients, were available for analysis.

Clinical characteristics

The mean age of the 27 patients who participated in our study was 37.5 years (range 17–60) at the time of the ex-

Table 1 Clinical characteristics and cardiac data from 27 patients with Becker muscular dystrophy (*ECG* electrocardiogram, *a* abnormal, *n* normal, *R* high R wave in V1, *LBBB* left bundle branch block, *ST* non-specific ST segment, *LV dil* left ventricular dilatation, *FS* ↓ diminished fractional shortening, *CHF* congestive heart failure, *GH* global hypokinesia, *DCM* dilated cardiomyopathy, *RS* R/S ratio >1 in V1, *Qlat* Q waves in lateral leads, *Qinf* Q waves in inferior leads, *NA* not available)

Family	Age[a] (year)	Functional ability[b]		Cardiac involvement						
		1980	1994	ECG 1980[c]	Echo 1980[d]	ECG 1994[e]	Echo 1994[f]	Diagnosis[g]	Progression	Death
A-1	43	2	5	a	n	R, Qlat	n	a ECG	No	
2	17	1	1	n	n	n	n	n	No	
3	53	1	5	n	n	n	n	n	No	
4	56	2	6	n	n	LBBB, ST	LV dil, FS ↓	CHF	Yes	1993
5	53	3	4	a	n	LBBB	LV dil, GH	CHF	Yes	1989
B-1	39	1	1	a	DCM	R, RS, Qlat, ST	LV dil, GH	DCM	No	
2	21	1	1	n	n	NA	LV dil, FS ↓	CHF	Yes	1991
3	36	1	2	a	DCM	R, RS, Qinf	LV dil, FS ↓	CHF	Yes	
4	44	1	6	n	n	n	GH	Borderline	Yes	
5	46	3	3	a	n	Qlat	n	a ECG	No	
6	47	1	5	a	n	R, RS, Qlat	LV dil, GH	DCM	Yes	
7	40	1	4	a	n	R, Qlat	LV dil, GH	DCM	Yes	
8	29	1	2	n	n	R, Qlat	LV dil	Borderline	Yes	
9	28	2	4	n	n	R, RS, Qlat, ST	LV dil	Borderline	Yes	
C-1	33	2	3	a	DCM	NA	NA	CHF	Yes	1984
2	26	2	5	a	n	Qlat	n	a ECG	No	
3	22	1	5	a	n	Qlat	n	a ECG	No	
D-1	60	4	6	a	DCM	LBBB	NA	CHF	Yes	1984
2	39	2	4	n	n	NA	n	n	No	
E-1	27	1	3	n	n	R	n	a ECG	Yes	
F-1	37	3	5	n	n	n	n	n	No	
2	40	1	5	a	n	R, RS	Inferolateral hypokinesia	Borderline	Yes	
G-1	32	1	2	n	n	LVH, ST	LV dil	Borderline	Yes	
2	35	1	1	n	n	ST	LV dil	Borderline	Yes	
3	37	1	1	n	n	n	n	n	No	
H-1	43	6	6	n	n	R, RS, Qinf	n	a ECG	Yes	
J-1	33	3	6	n	n	Qinf, LVH	n	a ECG	Yes	

[a] Age at time of examination or age prior to death
[b] Functional ability was scored by using a scale designed by Swyniard et al. [47] (grade 1: walks with waddling gait and marked lordosis and climbs stairs without assistance; grade 2: needs support for stairs; grade 3: cannot climb stairs, but can achieve erect posture from standard height chair; grade 4: unable to rise from a standard height chair; grade 5: wheelchair independence, good posture in the chair, and can perform all activities of daily living from chair; grade 6: wheelchair dependence, can roll chair but needs assistance in bed and wheelchair activities)
[c] ECG examination in 1980
[d] Echocardiographic examination in 1980
[e] ECG examination in 1994 or in the period preceding death
[f] Echocardiographic examination in 1994 or in the period preceding death
[g] Borderline abnormal echocardiographic examination

amination (22 patients), at the last examination before death (four patients) or at time of death (one patient). Mean follow-up period was 12.5 years, median 13.7 years (SD 3.0; range 2.7–14.0) (Table 1).

Fifteen patients (56%) were still able to walk (functional ability grades 1–4; mean age 34 years, range: 17–46). Twelve patients were wheelchair-bound (functional ability grades 5 and 6; mean age 42; range: 22–60 years). Eleven of those (41%) had been able to walk in 1980.

Physical examination and chest radiograph examination in 22 patients did not reveal additional information. One patient had shown symptoms of congestive heart failure prior to the present investigation, but he was now asymptomatic on medication. In four deceased patients physical examination and chest radiograph examination in the period preceding death, revealed signs of congestive heart failure (CHF).

Table 2 Distribution of electrocardiographic abnormalities in 27 Becker muscular dystrophy patients with and without echocardiographic abnormalities

Observed	Echocardiography				
	Normal	Borderline	Abnormal	Not performed	Total
ECG					
Normal	4	1	0	0	5
Non-specific abnormality	0	2	0	0	2
Specific abnormality	7 (3)[a]	3 (1)	6 (4)	1	17
Not performed	1	0	1	1	3
Total	12 (3)	6 (1)	7 (4)	2	27

[a] The number of patients with an increased QT/PQs ratio [30, 33] are given in parentheses

Table 3 Association between functional ability and cardiac abnormality in 27 Becker muscular dystrophy patients (*ECG* electrocardiogram, *DCM* dilated cardiomyopathy)

	Normal cardiac status	Only abnormal ECG	Borderline echocardiographic findings	DCM	Total
Ambulatory	3	2	4	6	15
Wheelchair-bound[a]	2	5	2	3	12
Total	5	7	6	9	27

[a] One patient developed DCM before he became wheelchair-bound

Electrocardiography

In 21 patients an ECG (Tables 1, 2) was performed and the most recent ECG data were obtained from three deceased patients. Seventeen patients had one or more abnormalities as defined in the methods section (71%) and two patients had non-specific ECG changes (8%). In half of these individuals, the abnormalities had not been present in 1980.

In three patients (11%) left bundle branch block (LBBB) was found, always concomitantly with severe congestive heart failure. Five patients (21%) had incomplete RBBB. An increased QT/PQs ratio was found in eight patients (33%). Twenty-one individuals underwent 24-h ECG monitoring. One of them had had periods of atrial fibrillation, otherwise no abnormalities were found.

Echocardiography

Twenty-two patients underwent an echocardiographic investigation and the most recent echocardiographic data were obtained from three deceased patients (Tables 1, 2). Seven of these patients (28%) had echocardiographic evidence of DCM and six patients (24%) showed borderline echocardiographic abnormalities, including left ventricular dilatation with normal systolic function (four patients), mild hypokinesia in the inferolateral part of the heart (one patient) and global hypokinesia without left ventricle dilatation (one patient). When regurgitation abnormalities were present, these were only mild. Hypertrophic cardiomyopathy was not found.

Evolution of cardiac abnormalities

Only five of the 27 patients (18.5%) had completely normal results of examination of the heart. In all families cardiac involvement was established. Seventeen individuals (63%) showed progression of cardiac abnormalities during follow-up [e.g. from normal to abnormal ECG, abnormal ECG to congestive heart failure (CHF), CHF to death; Table 1]. Seven patients had an abnormal ECG, but no echocardiographic abnormalities (26%). In nine patients (33%) DCM with or without congestive heart failure was present (Tables 1, 3).

Ten of 15 patients who were ambulatory at the second evaluation had developed borderline echocardiographic abnormalities or DCM and one patient who was wheelchair-bound developed DCM when he was still walking (Table 3; 69%). Four of 11 patients who were wheelchair-bound (36%) had DCM or borderline abnormalities. This difference was not significant ($P = 0.13$). Six patients (22%) had symptoms of congestive heart failure at the follow- up examination. In one, the symptoms had already been present at the first examination.

Five patients from four families (A, B, C, D) died during the follow-up period, one due to intestinal bleeding, four (15%) due to congestive heart failure. Three of these four were still able to walk at the time of death. The mean age of these four patients was 42 years (range 21–60). Mean survival after the first examination was 6.3 years (range 2.7–10.3; SD 3.5).

DNA-studies

A mutation was found in six of nine families. In five families a deletion was present (family A: exons 2–5; families

D and E: exons 45–47; family F: exons 3–6; family G: exons 45–55) and in one family a duplication (family B: exons 16–28).

Discussion

In a cross-sectional study we conducted in 1980 it was shown that nearly half of patients had ECG changes and 15% had DCM [12]. Our findings have been confirmed by others [11, 23, 32, 33, 45]. In the present study with a mean follow-up of 12.5 years, cardiac abnormalities had progressed in 63% of patients. Specific ECG abnormalities progressed from 44% to 71% and DCM was now present in 33% of patients. In addition, 22% of patients developed borderline echocardiographic abnormalities. These had not been present in 1980, but the significance of these findings is at yet uncertain. Fifteen percent of patients died during follow-up as a consequence of congestive heart failure. Cardiac involvement was established in all nine families.

We found a high proportion of ECG abnormalities, which is in accordance with others [23, 45]. The most frequently observed abnormalities consisted of high R-waves and pathological Q-waves. Studies in Duchenne muscular dystrophy have shown that these abnormalities most likely originate in the posterobasal and inferior wall of the left ventricle [18, 37, 38, 43]. Indeed in seven cases these ECG abnormalities were found in patients with either congestive heart failure, DCM, left ventricular dilatation or hypokinesia of the inferolateral part of the left ventricle wall. Twice however, left ventricular dilatation was found together with unspecific ECG findings, i.e. abnormal ST segments. In seven patients, high R-waves or deep Q-waves were present without involvement of the left ventricle on echocardiography, suggesting that in BMD this is the first sign of left ventricular involvement, as is also the case in DMD [37, 43]. Notwithstanding the fact that in four patients in whom these abnormalities were already present in 1980, no left ventricular dilatation has developed over a period of 15 years.

We found incomplete RBBB in five patients. It can be found in healthy persons as well, but its prevalence is higher than in the normal population (18.5% vs 2.4%). The origin of conduction disturbances might well be explained by multifocal areas of degenerative changes in the conduction system [42] and defective dystrophin localization at the membrane surface of the Purkinje fibre [6]. A severe conduction disorder such as LBBB was found only in the advanced cases. These patients all died of congestive heart failure. In the patients who underwent 24-h ECG monitoring, no rhythm disturbances were seen. We suppose that LBBB, and therefore the risk of developing lethal rhythmical disorders, only occurs in the end-stage cases of cardiac involvement where the dystrophic process has destroyed the whole heart.

Nigro et al. have used the QT/PQs ratio on ECG to detect early cardiac involvement [29–33]. We were not able to confirm this observation since this feature was only present in three of 12 patients with normal findings at echocardiography.

Nigro et al. also found an increase in clinically evident cardiomyopathy with increasing age during a mean follow-up period of 8 years [33]. Furthermore, they reported a high percentage of DCM (49%) in advanced cases of Becker muscular dystrophy designated as “walking patients not able to perform Gowers manoeuvre” as compared with the wheelchair-bound patients [33]. We also found that patients who could still walk (functional ability 1–4) more often had borderline echocardiographic abnormalities or DCM than the wheelchair-bound patients, but this did not reach statistical significance ($P = 0.13$), suggesting an unexplained association between mobility and occurrence of DCM. More follow-up is needed to further evaluate this observation.

Although the group of families is relatively small, we did not find an association between mutation type and DCM, confirming previous observations that muscle weakness in the presence of cardiac abnormalities might be due to mutations in every part of the dystrophin gene [11, 19, 23, 32, 40, 50]. Therefore we conclude that cardiac involvement, and especially DCM, is the rule and not the exception in BMD.

There is a remarkable interfamilial and intrafamilial variability regarding time at onset, severity and progression of cardiac abnormalities, as is also the case with muscular involvement [4, 11, 16]. Variability of cardiac and muscle involvement between families carrying the same mutations might in part be explained by different locations of deletion breakpoints relative to the intron–exon boundaries [11]. Intrafamilial variability of cardiac abnormalities, even in brother pairs with the same functional ability, may be very prominent. For example, in family A, in one 53-year-old wheelchair-bound patient (A-3) the heart appeared to be unaffected, whereas his 56-year-old brother, who is also wheelchair bound, developed congestive heart failure (A-4). In family B, the cardiac status of one individual (B-2) evolved from normal to a severe congestive heart failure. He died awaiting cardiac transplantation at age 21 years. In contrast, one of his two elder brothers (B-1), who had already been diagnosed as having DCM at the first examination, is still asymptomatic. The other brother (B-3) has been stable for several years on medication. All three had only mild musculoskeletal involvement. It remains enigmatic why DCM, once it has been established, can be stable and remains asymptomatic for many years or evolves rapidly to cardiac failure, sometimes leading to sudden death.

In BMD patients, therapeutic interventions as regards DCM are scarce. Over the past few years cardiac transplantation has been carried out in a number of patients with an end-stage congestive heart failure and relatively

mild muscle weakness [8, 13, 34, 39, 41]. Supportive measures and vasodilator therapy should be standard treatment in all BMD patients with congestive heart failure. Up to now, treatment of asymptomatic DCM has not received much attention. Among patients with asymptomatic left ventricular dysfunction from other causes, the angiotensin-converting enzyme inhibitor enalapril has proven to reduce the incidence of heart failure and the rate of related hospitalizations [48]. Only 9.5% of the patients in this study had an idiopathic DCM, but the favourable effect of therapy appeared to be independent of the cause of heart failure. There also was a non-significant reduction in cardiovascular mortality [48]. Since DCM in BMD is often progressive, early onset of therapy with enalapril could be considered in asymptomatic patients with DCM.

We conclude that cardiac involvement in BMD is progressive in the majority of patients. Left ventricular involvement may begin at any moment in the course of the disease and the rate of progression is unpredictable. A substantial part of patients will develop dilated, incapacitating and life-threatening DCM. In ambulatory patients timely heart transplantation should then be considered. Therefore, we advocate that BMD patients have an ECG at regular intervals. Cardiac involvement in BMD first becomes manifest as ECG abnormalities, which are usually characteristic, but sometimes only subtle changes can be found. If the ECG is normal, DCM is not very likely, but as soon as the ECG findings are abnormal, careful cardiologic follow-up is needed, for example in the form of yearly echocardiographic evaluation.

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