

Muscular and cardiac manifestations in a Duchenne-carrier harboring a *dystrophin* deletion of exons 12-29

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Summary

Female carriers of mutations in the dystrophin gene (DMD-carriers) may manifest clinically in the skeletal muscle, the heart, or both. Cardiac involvement may manifest before, after, or together with the muscle manifestations. A 46y female developed slowly progressive weakness of the lower and upper limbs with left-sided predominance since age 26y. Muscle enzymes were repeatedly elevated and muscle biopsy showed absence of dystrophin. MLPA analysis revealed a deletion of exons 12-29. After starting steroids at age 39y, she developed palpitations and exertional dyspnoea. Cardiac MRI at age 41y revealed mildly reduced systolic function, a slightly enlarged left ventricle, mild hypokinesia of the entire myocardium, and focal, transmural late gadolinium enhancement (LGE) of the midventricular lateral wall. She did not tolerate beta-blockers but profited from ivabradine and lisinopril. In conclusion, muscle manifestations in DMD-carriers with deletions of exons 12-29 may start years before cardiac involvement becomes clinically apparent. Progressive worsening of systolic function in DMD-carriers is attributable to progressive myocardial fibrosis, as demonstrated by LGE. Steroids may trigger the development of cardiac disease in DMD-carriers.

Keywords: Duchenne muscular dystrophy, cardiac involvement, heart failure, dystrophin, X-chromosomal, carrier, myopathy

1. Introduction

Due to skewed X-chromosome inactivation of one of the two X-chromosomes, female carriers of X-chromosomal gene mutations may present with variable clinical manifestations, ranging from normal to a phenotype like in males (1). This is also the case for carriers of deletions or point mutations in the *dystrophin* gene causing Duchenne muscular dystrophy (DMD) (DMD-carriers) (1). DMD-carriers are usually asymptomatic. However, some of the DMD-carriers become symptomatic and develop a progressive DMD-like phenotype. This is the case if the majority of the X-chromosomes carrying

the wild-type allele is inactivated, The higher the percentage of inactivated wild-type *dystrophin* genes, the more severe will the phenotype of manifesting DMD-carriers be. Some of the DMD-carriers may even resemble male patients with DMD (1). Since *dystrophin* mutations not only manifest in the skeletal muscles but also in the myocardium, DMD males and DMD-carriers may develop variable degrees of cardiac disease (2). Cardiac involvement in DMD usually starts with ECG abnormalities until patients develop dilated cardiomyopathy. In DMD-carriers dilated cardiomyopathy may be the initial manifestation of the skewed X-inactivation. Here we present a DMD-carrier with muscle and myocardial manifestations since adulthood and compare them with clinical and genetic findings of previous reports.

2. Case Report

The patient is a 46y female, height 172 cm, weight

Released online in J-STAGE as advance publication April 15, 2018.

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64 kg, with an uneventful history until age 25y, when she developed difficulties climbing stairs. Muscle enzymes were repeatedly elevated (Table 1). During the further course she developed slowly progressive proximal muscle weakness with left-sided predominance and experienced recurrent falls without losing consciousness. The patient was first admitted to the authors' institution at age 29y. Work-up for the above mentioned abnormalities at age 29y with informed consent of the patient revealed scapula alata, weakness (M4-) and wasting of the shoulder girdle and proximal upper limb muscles, and proximal weakness and reduced tendon reflexes of the lower limbs. Muscle biopsy at age 29y from the right deltoid muscle revealed myopathic features with atrophic and hypertrophic muscle fibres, necrotic fibres, proliferation of endomysial connective tissue (Figure 1A), absence of dystrophin on the sarcolemma of some fibres (mosaic pattern) (Figure 1B), and upregulation of utrophin (Figure 1C). At age 37y genetic testing of blood lymphocyte DNA by means of multiplex ligation-dependent probe amplification (MLPA) revealed a heterozygote deletion of exons 12-29 in the dystrophin gene (NM_004006.2:c.(1331+1_1332-1)_ (4071+1_4072-1)del). According to the Leiden DMD reading frame checker this mutation leads to an out-of-frame deletion (<http://www.dmd.nl/>). At age 39y she had experienced a right-sided tibial shatter fracture after a fall when going down a stair. At age 43y she underwent surgery for left-sided clubfoot. She was

regularly smoking 20 cigarettes/d since age 18y. The family history was positive for death from DMD at age 15y (nephew), myocardial infarction (mother), lung carcinoma (father), and uterus carcinoma (sister) (Figure 2). She had been taking aprednisolon (initially 25mg/d after some weeks 5mg/d) between age 39y and age 43y.

Clinical neurologic examination at age 46y revealed slow and slightly dysarthric voice, scapula alata, bilateral diffuse weakness (M4- to M5-) with distal and left-sided predominance on both upper limbs, diffuse wasting of the shoulder girdle and upper limb muscles with proximal and left-sided predominance, bilaterally reduced tendon reflexes, hypotonia, a fixed flexion contracture of the left elbow, diffuse weakness (M3 to M5-) with proximal, flexor, and left-sided predominance of the pelvic girdle and lower limb muscles, diffuse wasting with proximal predominance, and reduced freedom of motion of the left ankle joint, reduced tendon reflexes, and hypotonia. The Gower sign was positive.

Routine cardiologic investigation for cardiac involvement at age 26y showed a normal electrocardiogram (ECG) but slightly enlarged left atrium on echocardiography. ECG at age 29y was normal again. Since initiation of steroids at age 39y, she experienced exertional dyspnoea and palpitations, manifesting as sinustachycardia on ECG. Upon administration of beta-blockers at age 41y she developed vertigo and low blood pressure, which is why they were replaced by ivabradine (7.5 mg/d), which was well tolerated and effective.

Table 1. Blood chemical investigations indicating affection of the skeletal muscle

Parameter	RL	10/97	11/00	05/04	05/04	03/07	05/16	08/16
CK	0 - 70 U/L	562	625	2101*	1365*	1968 [#]	371%	nd
GOT	0 - 35 U/L	nd	nd	76	60	58 ^{&}	nd	26
GPT	0 - 35 U/L	nd	nd	68	61	50 ^{&}	20	28
LDH	120 - 240 U/L	198	nd	286 [§]	267 [§]	324 [§]	nd	200
Aldolase	0 - 7.6 U/L	7.4	nd	nd	nd	13.9	nd	nd
Myoglobin	0 - 70 µg/L	nd	nd	331	234	nd	nd	nd

CK: creatine-kinase, GOT: glutamate-oxalate transaminase, GPT: glutamate-pyruvate transaminase, *: Reference limit 26-145 U/L, #: reference limit: < 170 U/L, &: reference limit GOT: < 31 U/L, reference limit GPT: < 34 U/L, §: reference limit 135-235 U/L, §: reference limit < 247 U/L, %: reference limit 20-180 U/L, nd: not done.

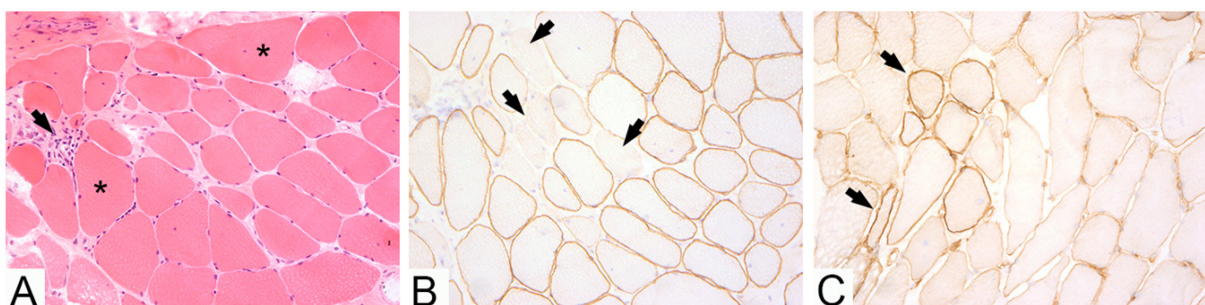


Figure 1. Muscle biopsy from the deltoid muscle shows myopathic features with variation in fibre size and phagocytes invading necrotic fibres. (A, H&E; arrow: phagocytes; asterisks: hypertrophic fibres), some fibres lacking dystrophin next to fibres with normal dystrophin expression (mosaic pattern) (B, dystrophin; arrows: fibres lacking dystrophin expression), and upregulation of utrophin on the sarcolemma (C, utrophin; arrows). ×200

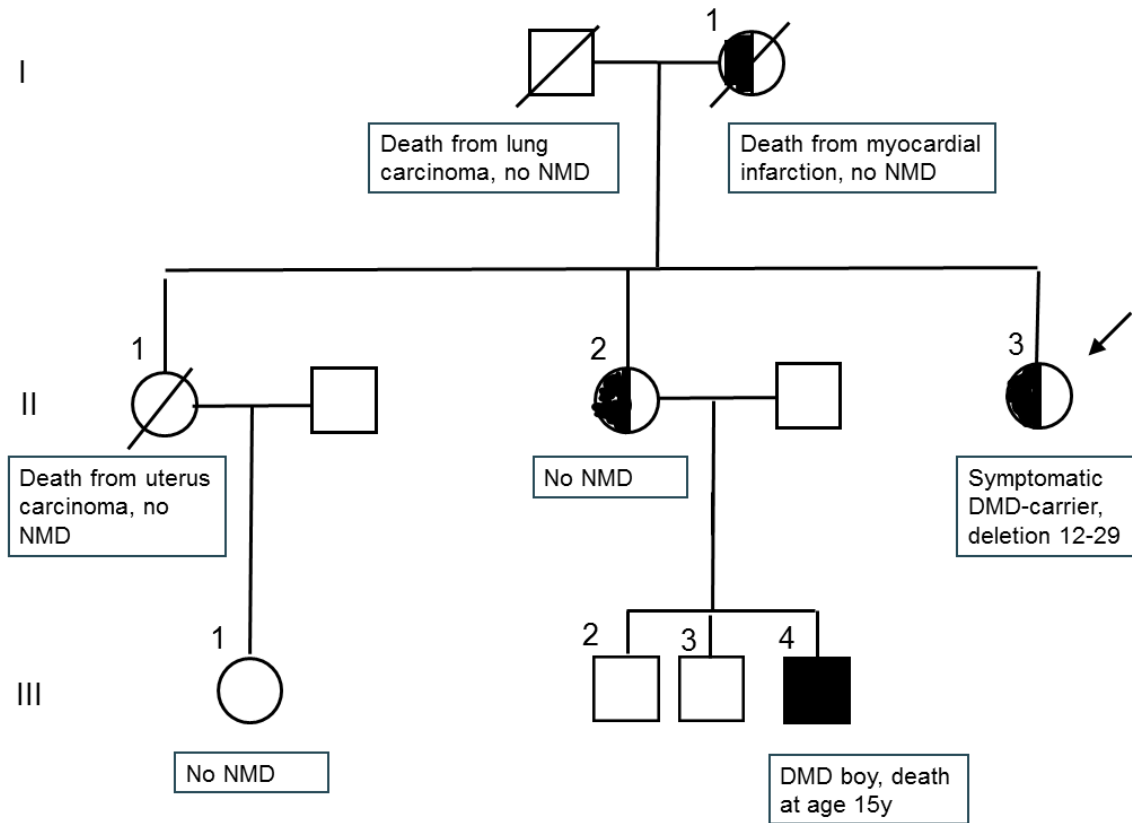


Figure 2. Pedigree of the presented patient. NMD: neuromuscular disorder.

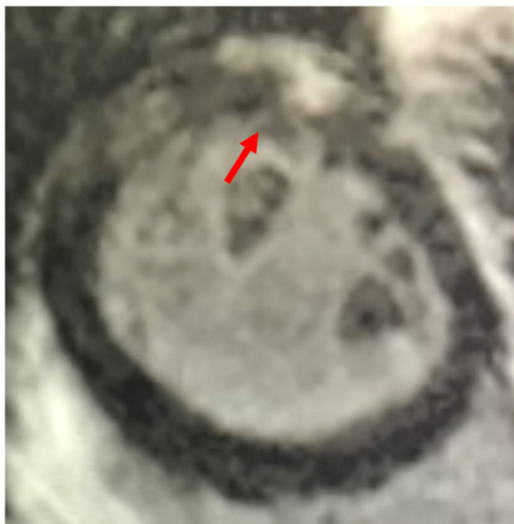


Figure 3. Cardiac MRI (cMRI) at age 41y shows a slightly enlarged left ventricle, mild hypokinesia of the entire myocardium with a left ventricular ejection fraction (EF) of 50%, and focal, transmural late gadolinium enhancement (LGE) of the midventricular lateral wall (arrow).

Cardiac MRI (cMRI) at age 41y revealed mildly reduced systolic function, a slightly enlarged left ventricle, mild hypokinesia of the entire myocardium with a left ventricular ejection fraction (EF) of 50%, and focal, transmural late gadolinium enhancement (LGE) of the midventricular lateral wall (Figure 3). Lisinopril (5 mg/

d) was added. At age 45y she consulted a cardiologist because of recurrent chest pain. ECG showed left anterior hemiblock (LAH) and right bundle branch block (RBBB). Echocardiography showed a borderline systolic function (EF 50%), slightly enlarged left atrium, and minimal mitral insufficiency. Since chest pain resolved under non-steroidal analgesics, it was interpreted as vertebrogenic. At follow-up, one month later, she again complained about chest pain and exertional dyspnoea. ECG was unchanged since the previous recording. Echocardiography showed borderline systolic function (EF 50%), mildly enlarged atria, diastolic dysfunction, abnormal mobility of the interventricular septum, and mitral insufficiency. Serum N-terminal pro-brain-natriuretic peptide (NT-pro-BNP) levels were measured several times between age 42y until 46y and were always slightly elevated ranging between 206-244 ng/L (normal < 169 ng/L). Her last medication included lisinopril (2.5 mg/d) and ivabradine (7.5 mg/d).

3. Discussion

DMD-carriers have been previously reported to predominantly manifest phenotypically in the skeletal muscle or myocardium (Table 2) (2). Muscle disease in DMD-carriers may have a broad range of manifestations. Muscle disease can be quite variable and may manifest with only creatine-kinase (CK)-elevation (3,17,22,25,29), with exercise intolerance (14), muscle cramps (20), or

Table 2. Phenotypic and genotypic characteristics of published DMD-carriers with or without skeletal muscle involvement and with or without cardiac disease

NOP	Mutation	MM	MB	Myocardium	Ref.
15	del (<i>n</i> = 10),	Weakness (<i>n</i> = 7) CK ↑ (<i>n</i> = 15)	Dystrophin ↓ (<i>n</i> = 9)	Normal (<i>n</i> = 15)	(14)
20	del (<i>n</i> = 13), dup (<i>n</i> = 7)	Symptoms (<i>n</i> = 2)	nm	cMRI ab (<i>n</i> = 13)	(8)
22	nm	nm	nm	LGE (<i>n</i> = 7)	(9)
1	nm	Weakness	nm	dilation, HF	(15)
1	nm	Normal	nm	HF	(13)
1	nm	lipid ↑ on MRI	nm	nm	(16)
1	nm	CK ↑	nm	ECG, echo an, TnT ↑	(17)
5	dup 2	nm	nm	LGE (<i>n</i> = 5), HF (<i>n</i> = 1)	(18)
1	Not detected	Weakness, CK ↑	Dystrophin ↓	LGE	(19)
15	del 45-52, 50, 46-49, 51-57, 8-13, dup 43, 17-18, 45-59, PM 14, 15 47, ins 8	Weakness (<i>n</i> = 14) Cramps (<i>n</i> = 6)	nm	ECG, echo an	(20)
7	nm	Weakness (<i>n</i> = 5)	nm	LGE (<i>n</i> = 4)	(10)
1	dup 2	Normal	nm	HF, dystrophin ↓	(21)
1	dup 1-6	CK ↑	Dystrophin ↓	HF	(22)
38	del 48-50, 3-7, dup 8-9 dup 45, del 6-7	Weakness (<i>n</i> = 13) Cramps (<i>n</i> = 3)	an (<i>n</i> = 2)	dCMP (<i>n</i> = 5)	(23)
1	ins 43	Weakness	nm	HF	(24)
1	nm	CK ↑	nm	Arrhythmias	(25)*
1	nm	nm	nm	HF, HTX	(26)
1	nm	Normal	nm	dCMP, dystrophin ↓	(27)
1	del 50-52	Normal	Dystrophin ↓	dCMP, HTX	(28)
2	nm	CK ↑	nm	Dystrophin ↓, HF	(29)
16	nm	CK ↑	nm	ECG, echo an	(3)
1	nm	Normal	Dystrophin ↓	dCMP	(30)
1	nm	Normal	nm	HF	(31)
1	Not detected	Normal	nm	Dystrophin ↓	(32)

MM: muscle manifestations, MB: muscle biopsy, LGE: late gadolinium enhancement, HF: heart failure, dCMP: dilated cardiomyopathy, PM: point mutation, nm: not mentioned, an: abnormal, *: during general anesthesia

with muscle weakness and wasting (14,15,19,20). Other DMD-carriers may develop wasting without muscle weakness and the more severely affected patients may develop slowly progressive weakness, which may be asymptomatic at onset, as in the presented case. In a study of 16 DMD-carriers, 87% had CK-elevation in the absence of muscle symptoms or signs (3). Occasionally, muscle involvement may histologically mimic myositis (4). In accordance with these previously described manifestations (Table 2), the currently presented patient manifested with muscle weakness and wasting and CK-elevation.

Concerning cardiac disease in DMD-carriers, frequency, type, degree, and onset can be quite variable. In a study of 210 DMD-carriers 60% had cardiac involvement (2). In a Japanese study of 16 DMD-carriers 31% had cardiac symptoms, ECG abnormalities were found in 56%, and 75% had echocardiographic abnormalities (3). One of these carriers underwent endomyocardial biopsy showing absence of dystrophin in 75% of the fibers (3). Cardiac disease in DMD-carriers includes myocardial fibrosis, ECG abnormalities, systolic dysfunction, or heart failure. Rarely, DMD-carriers may develop dilated cardiomyopathy (Table 2) (5,6), even as the initial cardiac manifestation (5). In a single DMD-carrier sudden cardiac death was reported (7). In a study of 20 DMD-carriers of whom only 2 had

muscle symptoms, 13 had at least one cMRI abnormality, 4 (20%) had reduced systolic function, and 13 (65%) had LGE (8). All LGE-positive patients had non-ischemic LGE with subepicardial involvement of the lateral free wall being the most frequent pattern (8). In another study of 20 DMD-carriers one third had LGE (9). Muscle and cardiac symptoms were not different between those with and without LGE (9). In a cMRI study of 7 DMD-carriers, LGE was found in four of them (10). LGE was subendocardial but two patients had focal LGE in the left inferolateral wall (10). In the majority of the cases, cardiac involvement in DMD-carriers does not develop before adulthood. In a study of 23 DMD-carriers under age 16y, none had any abnormality on extensive cardiologic work-up (11). However, in some patients cardiac disease may already develop in childhood. In a 10yo DMD-carrier, systolic dysfunction was recognised already at age 10y in the absence of muscle manifestations (12). Frequently, cardiac involvement may precede muscular abnormalities (3,10,13). Cardiac dysfunction in DMD-carriers may be triggered by pregnancy (13) or steroids, as shown in our case. In accordance with previous reports (Table 2), the currently presented patient manifested cardiologically with heart failure, reduced systolic function, LGE, and ECG abnormalities.

Whether the degree of muscle and cardiac involvement

only depends on the degree of X-chromosome inactivation or additionally depends on the location and size of the dystrophin deletion has been only poorly investigated. Exons most frequently deleted in DMD-carriers include numbers > 45 (Table 2). Though there have been reports according to which deletions in the N-terminal domains are predominantly associated with cardiac involvement, these reports have not been confirmed in later studies. From Table 2 it is not possible to draw a strong correlation between the location of the mutation within the dystrophin gene and the type and degree of muscle or cardiac involvement.

In conclusion, this case shows that muscle manifestations in DMD-carriers may start years before cardiac involvement becomes apparent. Muscle and cardiac manifestations may slowly progress over years. Systolic dysfunction, heart failure, and conduction defects are attributable to myocardial fibrosis, manifesting as LGE. Application of steroids may trigger cardiac involvement, and this is why they should be given with caution in DMD-carriers.

Note: Informed consent: Informed consent was obtained from the described participant

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- (Received January 6, 2018; Revised February 25, 2018; Accepted March 21, 2018)*