Spontaneous Left Ventricular Hypertrabeculation in Dystrophin Duplication Based Becker's Muscular Dystrophy

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Background: Left ventricular hypertrabeculation is frequently associated with neuromuscular disorders. Whether left ventricular hypertrabeculation in these patients is congenital or develops during lifetime, is unknown.
Case Report: In a 65-year-old man with Becker's muscular dystrophy, due to a duplication in the dystrophin gene on chromosome Xq21 (dystrophin molecular weight: 500 kD), left ventricular hypertrabeculation was detected on transthoracic echocardiography although being absent in repeated previous echocardiographic examinations. Additionally, there was thickening of the left ventricular myocardium. The spontaneous occurrence of left ventricular hypertrabeculation was interpreted as progression of cardiac involvement in Becker's muscular dystrophy.
Conclusion: Left ventricular hypertrabeculation may not exclusively be congenital, but may occasionally develop spontaneously during lifetime, being interpreted as progression of cardiac involvement in Becker's muscular dystrophy.

Key Words: Neuromuscular disorder · Myopathy · Myocardial thickening · Cardiac abnormality · Cardiomyopathy · Non-compaction

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Spontane linksventrikuläre Hypertrabekulierung bei Dystrophin-Duplikation-bedingter Becker'scher Muskeldystrophie

Hintergrund: Linksventrikuläre Hypertrabekulierung ist häufig mit neuromuskulären Erkrankungen assoziiert. Ob die linksventrikuläre Hypertrabekulierung bei diesen Erkrankungen bereits bei der Geburt besteht oder erst im Laufe des Lebens auftritt, ist nicht bekannt.
Fallbericht: Bei einem 65-jährigen Mann mit Becker'scher Muskaldystrophie, bedingt durch eine Duplikation im Dystrophin-Gen auf Chromosom Xq21 (Dystrophin-Molekulargewicht 500 kDa), zeigt die transthorakale Echokardiographie eine linksventrikuläre Hypertrabekulierung und eine Verdickung des linksventrikulären Myokards. Die linksventrikuläre Hypertrabekulierung war bei wiederholten, früheren echokardiographischen Untersuchungen nicht nachweisbar. Das spontane Auftreten der linksventrikulären Hypertrabekulierung wurde als Progression der Herzbeteiligung bei Becker'scher Muskeldystrophie interpretiert.
Schlussfolgerung: Linksventrikuläre Hypertrabekulierung tritt nicht nur kongenital, sondern gelegentlich auch spontan im Laufe des Erwachsenenlebens auf. Die spontan auftretende linksventrikuläre Hypertrabekulierung kann als Progression der Herzbeteiligung bei neuromuskulären Erkrankungen interpretiert werden.

Key Words: Neuromuskuläre Erkrankung · Herzwandverdickung · Kardiale Abnormität · Kardiomyopathie · Non-compaction

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Introduction

Left ventricular hypertrabeculation has been shown to be associated with neuromuscular disorders in the majority of the cases so far described [1–8]. Whether left ventricular hypertrabeculation develops during life or is present already at birth is yet unknown. The following case report describes a patient with Becker's muscular dystrophy, in whom left ventricular hypertrabeculation developed between two echocardiographic investigations within 4 years.

Case Report

The patient was a 65-year-old man (June 2000), who noticed lower limb weakness and proximal wasting since 1980, leading to recurrent falls, particularly during exercise. Neurologic examination in 1983 revealed reduced deep tendon reflexes, proximal wasting of the lower limbs and pseudohypertrophy of the calves. The creatinekinase (CK) was maximally increased to 1 900 U/l (normal: 0–70 U/l). Electromyography from the right gastrocnemius muscle was neurogenic. Muscle biopsy in 1983 showed features of a "dying-back" neuropathy. Based on these findings, spinal muscular atrophy was suspected.

Re-evaluation in 1994 revealed symmetrical, proximal weakness and wasting of the upper and lower limbs, a positive Trendelenburg's sign, pseudohypertrophy of the calves, and reduced brachial biceps and patella tendon reflexes. No ankle contractures were found. Motor and sensory nerve conduction studies, including F-wave studies (retrograde stimulation of anterior horn cells), from various upper and lower limb nerves were normal. CK was maximally increased to 1 115 U/l. Electromyograms from proximal and distal limb muscles were neuropathic.

A second muscle biopsy in 1995 from the right lateral vastus muscle showed typical myopathic features, occasionally necrotic muscle fibers, patchy staining for dystrophin, moderate glycogen accumulation, and a slight moderate diffuse reduction of the cytochrome-c oxidase staining. All other stainings were normal, and mitochondria were morphologically normal on electron microscopy. Repeated immunoblot analysis (SDS-PAGE 4–12% gradient gel electrophoresis) of dystrophin revealed a molecular weight of 500 kD (normal: 427 kD) each time. Biopsy of the right femoral nerve showed marked variation of the myelin thickness, hypomyelination, remyelination and regenerating fibers. Multiplex PCR screening for deletions in the dystrophin gene was negative.

Based on these findings, Becker's muscular dystrophy with subclinical neuropathy due to a dystrophin gene duplication was diagnosed. Repeated intensive screening for causes of polyneuropathy was uninformative each time. The family history for neuromuscular disorders was negative. There was only a slight progression of the neurologic abnormalities between 1994 and 2000.

The patient was cardiologically examined in 1995, 1996, 1997 and 2000. Some of these results have been reported earlier [9]. His cardiac history was noteworthy for arterial hypertension and exertional dyspnea long before neuromuscular symptoms had developed. Clinical cardiologic examinations were normal at each of these consultations. The ECG was indicative of myocardial thickening each time. 24-hour ambulatory ECG was normal at each visit. Transthoracic echocardiography (TTE) in 1995 and 1996 showed an E-wave/A-wave (E/A) ratio < 1 exclusively. TTE in 1997 revealed thickening of the left ventricular wall and septum in addition to the reduced E/A ratio. TTE in June 2000 showed thickening of the left ventricular myocardium, and most surprisingly, left ventricular hypertrabeculation. Left ventricular hypertrabeculation was not seen at any of the previous examinations, even after repeated re-evaluation of the corresponding videotapes by different investigators (Figure 1). The fractional shortening was normal, and there was no restrictive filling pattern (normal systolic function and deceleration time of the E-wave < 150 ms), no valve abnormality, regional wall motion abnormality or abnormal myocardial texture. The patient was not taking any medication since years.

Discussion

Usually, the diagnosis of Becker's muscular dystrophy is based on clinical findings (pelvic and shoulder girdle weakness and wasting with pseudohypertrophy of the calves), the electromyogram (myopathic alterations), muscle biopsy (patchy staining for antibodies against various portions of dystrophin), immunoblot (reduced molecular weight of dystrophin), and genetic findings (deletions, duplications, and point mutations in the dystrophin gene on chromosome Xp21) [1]. In the presented patient, the diagnosis of Becker's muscular dystrophy was based on clinical findings, and the muscle biopsy. Most surprisingly, electromyograms from various muscles were neurogenic without any indication for neuropathy on clinical neurologic examination or nerve conduction studies. The discrepancy between the neuro-

pathic electromyogram, the histological nerve abnormalities, and the normal nerve conduction studies could be explained with the fact that nerve conduction studies were carried out on distal nerves, whereas biopsies were taken from a proximal nerve and muscle, respectively. Theoretically, there may be also muscle fiber hypertrophy in the absence of denervation or reinnervation, although the later could not be confirmed by the histological findings.

The association of Becker's muscular dystrophy and neuropathy is not unusual and has been described earlier [10]. Increased molecular weight of dystrophin was interpreted as duplication, though not confirmed by DNA analysis. Duplications in the dystrophin gene have been described earlier to be associated with a Becker's muscular dystrophy phenotype [11]. The generally reduced staining for cytochrome-c oxidase was interpreted as a secondary effect following dystrophin deficiency. A primary mitochondriopathy was excluded according to the normal mitochondrial ultrastructure [1].

Atypical for Becker's muscular dystrophy is that the patient became symptomatic not earlier than the age of 45 years and that there was only slight progression.

Left ventricular hypertrabeculation is defined as more than three coarse and prominent trabeculations apically to the papillary muscles on transthoracic echocardiography [5]. The trabeculations are surrounded by intertrabecular spaces which are perfused from the ventricular cavity, have the same echogenicity as the myocardium, move synchronously with the myocardium, and are not connected to the papillary muscles or the left ventricular wall [2, 5, 12]. Trabeculations can be delineated from false tendons and aberrant bands by taking atypical views [5, 12]. Besides echocardiography, left ventricular hypertrabeculation may be visualized by cardiac MRI and ventriculography [3]. Positron emission tomography studies have shown that there is restricted perfusion inside the trabeculations compared to the normal myocardium [13]. Left ventricular hypertrabeculation is more frequent in male than female patients. In adults, left ventricular hypertrabeculation has a prevalence of 0.08% [6, 14], a figure which presumably is too low, since an autopsy study showed more than three trabeculations in almost 4% of the normal human hearts [6, 13]. The low prevalence of left ventricular hypertrabeculation may be due to the assumption that left ventricular hypertrabeculation is frequently overlooked when performing routine echocardiographic examinations by unexperienced examiners. Left ventricular hypertrabeculation occurs in normally sized and well contracting left ventricles, as well as in dilated left ventricles with depressed systolic function [15]. Left ventricular hypertrabeculation may be associated with congenital cardiac malformations, thickening of the left ventricular myocardium, and neuromuscular disorders [6, 13] in particular Becker's muscular dystrophy [4], Barth's syndrome (neutropenia, growth retardation, elevated urine organic acids, low carnithine levels, mitochondrial abnormalities) [2], respiratory chain disorders [3, 5, 7], Roifman syndrome and myotonic

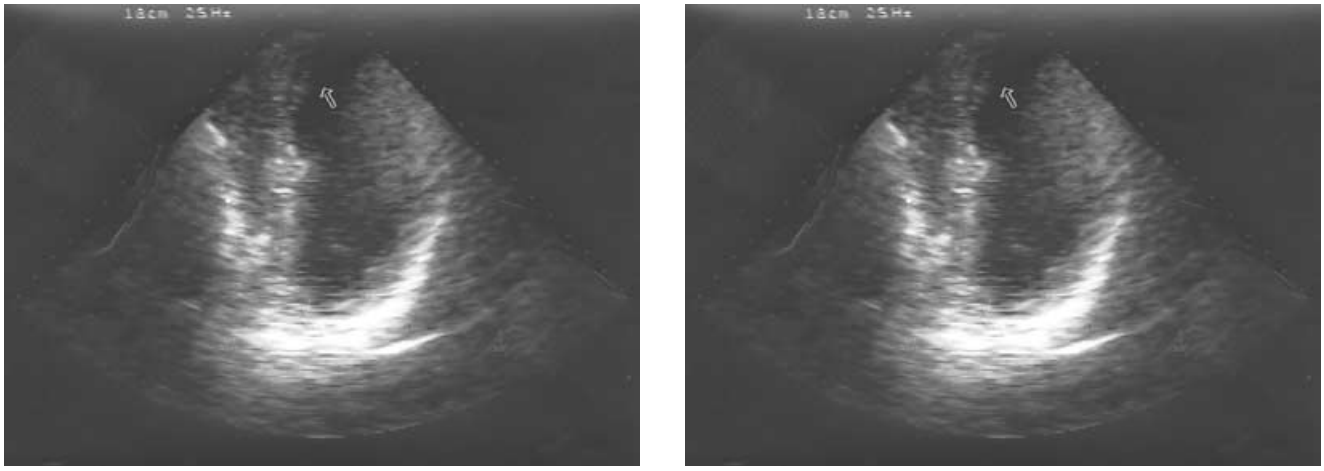

Figure 1. Transthoracic echocardiography of the described patient in 1996 shows left ventricular myocardial thickening exclusively (left panel). 4 years later (2000), transthoracic echocardiography additionally shows apical, left ventricular hypertrabeculation (right panel).

Abbildung 1. Die transthorakale Echokardiographie des präsentierten Patienten aus dem Jahre 1996 zeigt eine Verdickung des linksventrikulären Myokards (links). Die transthorakale Echokardiographie aus dem Jahre 2000 (rechts) zeigt zusätzlich die links-apikale Hypertrabekulierung.

dystrophy [16]. Because of the strong association between left ventricular hypertrabeculation and neuromuscular disorders, patients with left ventricular hypertrabeculation should routinely undergo a neurologic investigation [5, 6, 13].

The pathogenesis of left ventricular hypertrabeculation is unknown. Several hypothesis have been raised to explain the phenomenon:

1. Left ventricular hypertrabeculation is a disorder of the endomyocardial morphogenesis. According to this hypothesis, an arrest in the "compaction" process of the myocardium is assumed and made responsible for the development of abnormal trabeculations, which is why the term "non-compaction" was coined [2]. According to the latter hypothesis left ventricular hypertrabeculation develops early in life, and may thus be detectable whenever echocardiographic examinations are carried out. A strong argument against this hypothesis is the present patient, in whom left ventricular hypertrabeculation was not present at least during 3 years before its detection at the age of 65 years.
2. Left ventricular hypertrabeculation is a subtype of hypertrophic cardiomyopathy [5]. This hypothesis is supported by the fact that some patients with left ventricular hypertrabeculation also showed thickening of the left ventricular myocardium in the absence of arterial hypertension and valve abnormalities.
3. Left ventricular hypertrabeculation is a direct manifestation of the cardiac affection by the skeletal muscle disorder [5, 6]. This hypothesis is supported by the frequent association of left ventricular hypertrabeculation with neuromuscular disorders, which often present with myocardial thickening [1–8]. Focal myocardial thickening in these patients could represent a frustrate compensatory mechanism of the functionally impaired myocardium to resist against latent contraction failure. Hypertrophy may be focal because the impaired myocardium is no longer able to thicken homogeneously.
4. Left ventricular hypertrabeculation is due to mutations in a gene so far unknown. A strong argument against this assumption is the frequent association of left ventricular hypertrabeculation and neuromuscular disorders. Why should a double trouble so frequently occur particularly with these disorders?
5. Left ventricular hypertrabeculation is a result of the contraction status of the myocardium, which may be compensatory increased in patients with neuromuscular disorders, leading to focal "crumpling" of the myocardium. To explain the spontaneous development of left ventricular hypertrabeculation, the following speculations were raised: a) Left ventricular hypertrabeculation as well as the skeletal muscle manifestations are due to the same mutation in the dystrophin gene. According to this speculation, both left ventricular hypertrabeculation and Becker's muscular dystrophy are inborn abnormalities with late clinical manifestation. b) Compensatory thickening of the impaired myocardium may reach a point, at which this mechanism is effective only focally. c) The presence or absence of left ventricular hypertrabeculation depends on the contraction status of the myocardium, which might fluctuate. d) Left ventricular hypertrabeculation was present already earlier but finally recognized because of a better technical approach.

Whatever hypothesis holds true, left ventricular hypertrabeculation in the presented patient most likely represents progression of cardiac involvement in the skeletal muscle process.

In conclusion, this case shows that left ventricular hypertrabeculation is not a congenital abnormality of the myocardial morphogenesis exclusively, but may develop during lifetime in single cases. The cause of spontaneous left ventricular hypertrabeculation is unknown, but could be interpreted as a frustrate attempt of compensatory thickening in a damaged, dysfunctional myocardium, involved in a skeletal muscle disorder.

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