Progressive Respiratory Insufficiency in the Absence of Cardiac Disease in Late-Stage Duchenne Muscular Dystrophy

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Introduction

Not only the skeletal muscle but also the heart is frequently affected by the dystrophic process in Duchenne muscular dystrophy (DMD) patients[1] and DMD carriers.[2] Contrary to this paradigm, there are some reports showing absence of cardiac involvement in DMD, even in the late stages of the disease,[3] as in the following case.

Case Summary

The patient was a 25-year-old white male, height 177 cm, weight 55 kg, with a history of diminished movements as a newborn, delayed achievement of motor milestones, and gait disturbance after having achieved walking. At age 5 years he presented with weakness for foot extension, reduced tendon reflexes, pseudo-hypertrophy of the calves, and a positive Gower sign. Creatine-kinase was 8,643 U/L (normal $<$ 70 U/L). Muscle biopsy showed dystrophy and dystrophin-deficiency in almost all muscle cells, so DMD was suspected. At age 6 years a deletion of exons 13–21 of the dystrophin gene was detected by multiplex polymerase chain reaction. By multiplex ligation-dependent probe amplification-analysis at age 25 years, however, a deletion of exons 13–43 was found. The latter deletion was also detected in the mother and sister of the proband. DMD was diagnosed upon the muscle biopsy and multiplex ligation-dependent probe amplification findings. Since the age of 9 years he had been confined to a wheel chair. Because of progressive scoliosis, he underwent surgical stabilization of the spine by means of the posterior-only pedicle screw instrumentation approach at age 13 years, with success. At age 25 years a heterozygote state for the Leyden mutation was detected. He had a history of recurrent pneumonia, but the history for thrombosis was negative.

The family history was positive for muscle disease in his sister and mother (DMD carriers), and positive for the Leyden mutation in his sister and brother of the father. Repeated transthoracic echocardiographies and 24-hour electrocardiograms (ECGs) up to the age 25 years were normal (Table 1, Fig. 1). X-ray of the lung was normal. Routine ECG showed sinus rhythm, with a frequency of 99 beats/min. Pro-brain natriuretic peptide levels were repeatedly normal. Contrary to his normal cardiac findings, he had developed slowly progressive respiratory insufficiency since the first pneumonia at age 21 years, with a vital capacity of only 17% at age 25 years (Fig. 2). Transcutaneous P_{O_2} and P_{CO_2}, however, were normal. From the age of 21 years he experienced pollakissuria, which resolved under tamsulosin.

At age 25 years his mood was stable and he worked regularly as a computer assistant. Somnography with a mobile device at home revealed a mean arterial oxygen-saturation of 97% and normal transcutaneous P_{CO_2}. Sleep-disordered breathing was absent. He was unable to prevent his head from falling backwards without head support. Eye movements were unaffected. He was slightly dysarthric, but verbal communication was unimpaired. There was severe weakness of both upper limbs, with residual muscle force (M3) more in the right than the left hand. There was marked diffuse wasting, absent tendon reflexes, and elbow and ankle contractures. He was able to stretch and bend the knees with M3, but all joints were contract, with right-sided predominance. There was severe wasting, and tendon reflexes were absent. Creatine-kinase at age 25 y was 353 U/L and 503 U/L (normal $<$ 171 U/L), respectively.

Discussion

This case is interesting for 2 aspects. First, the patient was free of any cardiac symptoms, and clinical and instrumental cardiologic investigations were not indicative of cardiac disease, neither during previous years nor at the

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Table 1. Cardiac Findings During the Disease Course

Test	Date			
	July 1997	April 1999	February 2006	September 2011
Electrocardiogram	Normal	Normal	Normal	Normal
Echocardiogram				
Mitral valve prolapse syndrome	Yes	Yes	No	No
Left atrial diameter, cm	Normal	Normal	2.15	Normal
Posterior wall thickness in diastole, mm	Normal	3.2	5.9	9.0
Septal thickness in diastole, mm	Normal	8.1	5.5	13
Ejection fraction, %	Normal	Normal	62	Normal
Fractional shortening, %	Normal	32	28	30

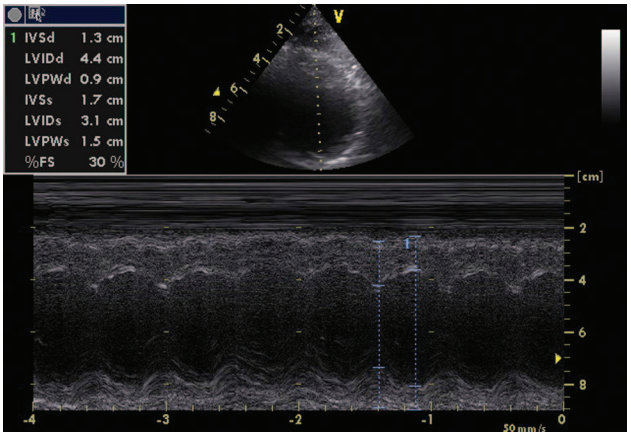

Fig. 1. Two-dimensional and M-mode echocardiographic parasternal short-axis view of the left ventricle showing a normally sized left ventricle with good systolic function, and a slight left ventricular wall thickening

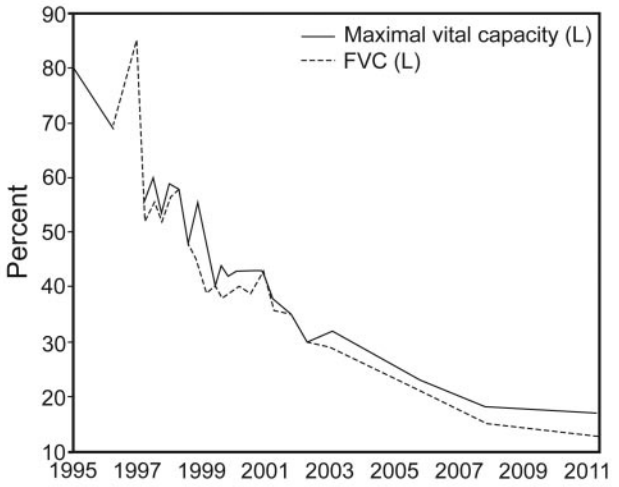

Fig. 2. Continuous decline of the maximal vital capacity and the FVC in percent during 13 year.

last follow-up at age 25 years. In the majority of cases, cardiac involvement starts early and remains subclinical during the first years after onset. In DMD patients < 6 years the ECG is already abnormal in 78% of the cases.[1] In the final stages of the disease, 90% or more of the patients have at least ECG abnormalities.[4] Frequently, cardiac involvement progresses during the course to dilated cardiomyopathy or ventricular arrhythmias.

Absence of cardiac involvement in the advanced stages of the disease is rare and may be explained by several assumptions. Possibly this patient was still too young to have developed cardiac involvement until age 25 years and would develop cardiac disease during the following years. Such an assumption is not improbable, since cardiac involvement in other patients has been shown to be progressive during the disease course[5] or to occur only late in life.[6] Possibly, there are dystrophin mutations, which are not associated with cardiac involvement. There is an ongoing debate about the genotype-phenotype correlation of cardiac involvement in DMD.[7] Some studies indicated that certain mutations favor the development of cardiac involvement,[8,9] whereas others did not confirm this assumption.[7,10] From a study of 4 patients with Becker muscular dystrophy it was speculated that dystrophin deletions around exon 1 impair dystrophin expression selectively in cardiac muscle, sparing the skeletal muscle,[9] and in a study of 320 dystrophinopathic patients, mutations proximal to exon 45 of the dystrophin gene were associated with a higher degree of cardiac involvement than mutations distal to exon 45.[7] In another study a higher incidence of cardiomyopathy was found in DMD patients carrying deletions at the N-terminal portion of dystrophin.[8] Whether a deletion of exons 13–43 is generally associated with absence or delayed occurrence of cardiac involvement remains speculative.

Absence of cardiac involvement may be also attributed to the presence of pure intronic rearrangement, in addition to the deletion, leading to aberrant pseudo-exon inclusion.[11] It is also possible that cardiac involvement was subclinical and could not be detected by the methods applied. The patient might have had subclinical arrhythmias not detectable on long-term ECG recordings. Absence of

cardiac involvement may be also attributed to absence of sleep-disordered breathing. Sleep-disordered breathing may cause pulmonary hypertension, systemic arterial hypertension, myocardial thickening,[12] reduced vagal modulation of the heart rate[13] or ventricular arrhythmias, and sudden cardiac death.[14]

Moreover, the patient presented with a history of continuously progressive respiratory insufficiency due to weakness of the respiratory muscles, resulting in a vital capacity of 17% at age 25 years (see Fig. 2). Interestingly, pulse oximetry at age 25 years revealed normal oxygen saturation, particularly during the night, despite dysfunction of the respiratory muscles. Normal oxygen saturation despite muscular respiratory dysfunction could be explained by the immobility of the patient and the disappearance of muscle cells due to the dystrophic process, conditions that both require less oxygen than normal. The discrepancy between the marked decline of respiratory function and absence of cardiac involvement is not unusual, since cardiac involvement does not seem to be related to respiratory dysfunction,[10] and could be explained by the type of deletion present in this case. Weakness of the respiratory muscles in the absence of cardiac disease has been previously reported in DMD patients.[10] Because of normal oxygen saturation during day and night, there was yet no indication to recommend noninvasive ventilation, despite the fact that respiratory problems are much more frequently the cause of death in DMD than cardiac involvement.

In conclusion, this case shows that single patients with DMD may not develop cardiac involvement until age 25 years, neither clinically nor subclinically. Possibly, dystrophin deletions of exons 13–43 are prone to absence or late development of cardiac involvement. Contrary to cardiac involvement, weakness of the respiratory muscles may continuously progress and may limit life expectancy and outcome in these patients.

Teaching Points

- Single patients with DMD may not develop cardiac involvement or may develop cardiac involvement very late during the disease course.
- Contrary to absence of cardiac involvement, respiratory muscles may be affected and may result in continuous decline of respiratory function.
- Reduced ventilatory capacity may initially not require mechanical ventilatory support in DMD patients.

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