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Clinical, genetic, and cardiac magnetic resonance imaging findings in primary desminopathies

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Abstract

We report the clinical, genetic and cardiac magnetic resonance imaging (MRI) findings in 11 German patients with heterozygous E245D, D339Y, R350P and L377P desmin mutations and without cardiac symptoms. Clinical evaluation revealed a marked variability of skeletal muscle, respiratory and cardiac involvement even between patients with identical mutations, ranging from asymptomatic to severely affected. While echocardiography did not show any pathological findings in all 11 patients, cine MRI revealed focal left ventricular hypertrophy in 2 patients and MR delayed enhancement imaging displayed intramyocardial fibrosis in the left ventricle in 4 patients indicating early myocardial involvement. Our data argue against distinct genotype-phenotype correlations and suggest that comprehensive cardiac MRI is superior to conventional echocardiography for the detection of early and clinically asymptomatic stages of cardiomyopathy in desminopathy patients. Therefore, cardiac MRI may serve as a screening tool to identify patients at risk, which might benefit from early pharmacological and/or interventional (e.g. implantable cardioverter-defibrillator devices) therapy.

Keywords: Congenital myopathy; Desminopathy; Cardiomyopathy; Cardiac magnetic resonance imaging; MR delayed enhancement imaging

1. Introduction

Mutations of the human desmin gene on chromosome 2q35 cause a familial or sporadic form of skeletal myopathy frequently associated with cardiac abnormalities (OMIM no. 125660) [1]. Histologically, this disease is characterized by an intracellular accumulation of insoluble pro-

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tein aggregates eventually leading to cell death and replacement fibrosis. The majority of patients with primary desminopathies (DM) exhibit an autosomal-dominant inheritance. However, rare autosomal-recessive cases as well as an increasing number of sporadic cases have been reported [2–4]. Desminopathies usually manifest in the second to fourth decade of life with slowly progressive painless distal muscle weakness and atrophy of the lower extremities [4]. Although symptoms are initially restricted to distal leg muscles, weakness and atrophy of the upper extremities, proximal leg and trunk muscles usually evolve with disease progression. Bulbar symptoms consisting of swallowing difficulties or dysarthria as well as respiratory insufficiency may occur in advanced stages of the disease [4,5].

Cardiac involvement comprising cardiac arrhythmias (various degrees of atrioventricular conduction blocks, supraventricular and ventricular tachyarrhythmias) and restrictive, dilated or even hypertrophic cardiomyopathy is the second clinical hallmark of primary desminopathies [2,4,6–10]. Awareness of potential cardiac involvement, which may either precede, coincide with or succeed skeletal muscle weakness, should take a central position in clinical management of patients harboring desmin mutations, since cardiac arrhythmias, conduction defects or cardiac failure are potentially life-threatening. Therefore, early detection of cardiac involvement is mandatory for timely therapeutic intervention.

Cardiac magnetic resonance imaging (cMRI) in combination with delayed enhancement imaging allows differentiating normal myocardium from a variety of myocardial diseases associated with necrosis or fibrosis. In the present study, we report the clinical, genetic and cardiac MRI findings in 11 German patients from seven families with genetically proven desmin mutations. The special focus of the study was to evaluate whether cMRI in combination with delayed enhancement imaging may be useful to detect early myocardial involvement in desminopathy patients.

2. Materials and methods

2.1. Patients

Thirteen German desminopathy patients from seven different families participated in this study: 11 patients were asymptomatic from the cardiac view point and 2 patients had undergone cardiac pacemaker implantation due to symptomatic bradycardia. Beyond desmin gene sequence analysis, the diagnostic evaluation included physical examination, serum creatine phosphokinase (sCPK) measurements, spirometry, 12-lead electrocardiogram (ECG), 24-h Holter ECG monitoring, 2D-Doppler echocardiography and cardiac MR imaging. Exclusion criteria for MR imaging were established contraindications such as cardiac pacemakers, implantable cardioverter-defibrillator devices (ICDs), other MRI-incompatible biomedical implants, and claustrophobia. The study was approved by the local research ethics committee, and written informed consent was obtained from all participants.

2.2. ECG

Standard 12-lead ECG and 24-h Holter ECG were analyzed by one experienced observer blinded to the clinical data of the patients. Presence of significant arrhythmias such as atrioventricular (AV) blocks and other conduction abnormalities, and atrial or ventricular brady- (<60 beats per minute) or tachyarrhythmias (>100 beats per minute) were assessed. Sporadic supraventricular and ventricular extrasystolic beats, which often occur in the absence of structural heart disease and typically require no therapy in asymptomatic patients, were considered to be unspecific [11].

2.3. Echocardiography

A comprehensive standard transthoracic echocardiography examination was performed using a commercially available diagnostic ultrasound system (Agilent Sonos 5500, Philips Medical Systems, Best, the Netherlands) equipped with a S4 phase array transducer and second harmonic imaging capability.

All measurements such as left ventricular (LV) dimensions and volumes at end-diastole (ED) and end-systole (ES) were performed by an experienced cardiologist blinded to the clinical history and other imaging findings of the patients according to the guidelines of the American Society of Echocardiography [12]. Specifically, LV ED and ES volumes were assessed using the Simpson's volume estimates. Furthermore, regional wall motion abnormalities were evaluated visually differentiating between normokinesia, hypokinesia, akinesia, and dyskinesia using the 16-segment model of the AHA [13,14]. Echocardiographic assessment of the presence/absence of a patent foramen ovale was based on colour flow Doppler imaging including Valsalva manouvers. Cardiac dimensions were corrected for body surface area (BSA).

2.4. Desmin mutation analysis

Genomic DNA of the patients was isolated from peripheral lymphocytes by standard procedures. The complete coding regions and intron–exon boundaries of the desmin gene were screened for variations by direct sequencing of PCR products. Amplification, purification and direct sequencing were carried out using a commercial service offered by Qiagen (Hilden, Germany) [15]. Information on primers and PCR conditions can be obtained from the authors upon request.

2.5. Cardiac MRI

2.5.1. Protocol

Cardiac MR imaging was performed at two different institutions using a Philips (Intera 1.5T, Philips Medical