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Electrocardiographic Signs of Necrosis and Calcification in Arrhythmogenic Cardiomyopathy

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Keywords: Arrhythmogenic cardiomyopathy; Desmoglein-2; Necrosis; Calcification; Shallow S wave syndrome.

Abstract

Introduction: Necrosis and massive calcification has been described in arrhythmogenic cardiomyopathy mainly in desmoglein-2 mutations according to mouse models and single human case reports. The overall expected rate of desmoglein-2 mutations is about 5-10 %. In transplanted hearts due to desmoglein-2 mutations signs of right ventricular hypertrophy and other typical findings like right precordial T-wave inversions and epsilon waves were found in about 50% of cases, making right ventricular hypertrophy a unique, typical sign of desmoglein-2 mutations and to a lesser extent Desmocollin-2 and plakoglobin mutations.

Method: In a cohort of 434 patients with typical arrhythmogenic cardiomyopathy (296 males, mean age 46.6 +/- 11.3 years) were analyzed with regard to Sokolow-Lyon amplitude criteria for right ventricular hypertrophy and shallow S wave syndrome in lead V1.

Results: Shallow S wave in lead V1 were present in 11 cases, a manifest form of right ventricular hypertrophy with an R wave in lead V1 > 1.5 mm with right bundle branch block and in another case without right bundle branch block. All but one patient suffered from heart failure. Total rate of right ventricular hypertrophy was 3%.

Conclusions: Necrosis and massive calcification are possibly characterized by signs of right ventricular hypertrophy together with typical electrocardiographic signs of arrhythmogenic cardiomyopathy. The theory is that massive necrosis produce right ventricular myocyte hypertrophy and electrocardiographic right ventricular hypertrophy. As only in 50% of cases right ventricular hypertrophy by ECG occurs, the total rate of 3 % justifies the assumption that right ventricular hypertrophy in ECG is synonymous with massive necrosis and calcification. Electrocardiographic right ventricular hypertrophy clarify and limit mutation status to desmoglein-2, desmocollin-2, and plakoglobin.

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Introduction

Arrhythmogenic cardiomyopathy is an inherited disease with fibrosis and lipomatosis of right and / or left ventricular myocardium. ACM is mainly caused by mutations in the desmosomal genes plakophilin-2 [1], desmoglein-2 [2], desmocollin-2 [3], plakoglobin [4] and desmoplakin [5]. Non-desmosomal mutations are also described like titin, Lamin A/C, phospholamban, Filamin C, desmin and others.

With the help of advanced techniques of electrocardiography and cardiac MRI a predominant right ventricular, a biventricular and a predominant left ventricular form can be differentiated.

In rare cases arrhythmogenic cardiomyopathy presents with massive calcification and necrosis, predominantly in cases of desmoglein-2 mutations and in a lesser extent in other mutations [6]. In desmoglein-2 mutations a mouse model and a few case reports has been described [7].

In a collective of transplanted patients with desmoglein-2 mutations has the electrocardiographic phenomenon of right ventricular hypertrophy either in cases with complete Right Bundle Branch Block (RBBB), without RBBB and in another sign of right ventricular hypertrophy called shallow S wave syndrome in lead V1 [8] due to right ventricular myocyte hypertrophy forced by calcification and necrosis in about 50% of cases. These findings were correlated with plakophilin-2 mutations where no case with right ventricular hypertrophy occur [9].

In systematic genetic testing desmoglein-2 mutations can be expected in a range between 5-10%.

Material and Methods

In a cohort of 434 patients with typical arrhythmogenic cardiomyopathy (296 males, mean age 46.6 +/- 11.3 years) patients were analyzed with regard to right ventricular Sokolow-Lyon amplitude criteria, and shallow S wave syndrome in lead V1 [8], additionally with typical electrocardiographic signs of arrhythmogenic cardiomyopathy such as T wave inversions in right precordial leads, epsilon potentials, localised right precordial QRS prolangation and large Q waves, small R waves and inverted T-waves not exceeding 2mm in lead aVR.

For statistical analysis the number of patients with right ventricular hypertrophy were summarized and correlated with the range of desmoglein-2 mutation findings.

Results

In the collective of 434 patients only three patients were transplanted, but no one had right ventricular hypertrophy. Amplitude criteria were rare, after careful ECG analysis shallow S wave syndrome in lead V1 was documented in 2.5%.

Shallow S wave in lead V1 was present in 11 cases, a manifest form of right ventricular hypertrophy with an R wave in lead V1 > 1.5 mm with right bundle branch block criteria (RBBB) in 1 case and a manifest form of right ventricular hypertrophy without RBBB in another case. All but one patient suffered from heart failure.

Total rate of all forms of right ventricular hypertrophy was 3%.

Discussion

Necrosis and massive calcification are possibly characterized by signs of right ventricular hypertrophy together with typical electrocardiographic signs of arrhythmogenic cardiomyopathy. The theory is that massive necrosis produce right ventricular myocyte hypertrophy and electrocardiographic right ventricular hypertrophy. As only in 50% of cases right ventricular hypertrophy in desmoglein-2 mutations by ECG occurs [9], the total rate of 3 % justifies the assumption that electrocardiographic right ventricular hypertrophy is synonymous with massive necrosis and calcification not only in transplanted patients but also in non-transplanted patients. In this collective of patients three patients were transplanted, but no one of the transplanted patients had right ventricular hypertrophy by ECG means.

In the literature the most frequent finding is that desmoglein-2 mutations produce calcification and necrosis. In a mouse model desmocollin-2 produce calcification and necrosis, too [10]. In other mutations for example the most frequent mutations plakophilin-2 and desmoplakin calcification has been not described. Calcification and necrosis is a rare event mainly due to desmoglein-2 and to a lesser extent desmocollin-2 and plakoglobin (Naxos disease).

In a mouse model necrosis is possibly discussed as episodic nature leading to dystrophy [10] in the end. Calcification is seldomly seen in autopsy very early replaced by inflammation and fibrosis. Necrosis might be the key promoter of arrhythmogenic cardiomyopathy leading to inflammation and fibrosis at autopsy status. However, right ventricular hypertrophy by ECG means leading to typical signs of arrhythmogenic cardiomyopathy has not been described in any ECG studies. The case of electrocardiographic right ventricular hypertrophy in a long-standing Naxos disease [6] reveals that massive calcification (petrified right ventricle) is the status at the end of the disease and not an episodic phenomenon.

Consequently, ECG signs of right ventricular hypertrophy in arrhythmogenic cardiomyopathy remains a predominant marker of calcification and necrosis mainly in desmoglein-2 mutations, but also in desmocollin-2 and plakoglobin mutations in a significantly lesser extent with the special feature of right ventricular myocyte hypertrophy. This ECG sign helps clarify and limit mutation status to desmoglein-2, desmocollin-2 and in rare cases plakoglobin.

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