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Electrocardiographic Signs of Right Ventricular Hypertrophy in Desmoglein-2 and Plakophilin-2 Related Arrhythmogenic Cardiomyopathy

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ABSTRACT

Desmoglein-2 mutations in arrhythmogenic cardiomyopathy produce myocyte ventricular hypertrophy due to necrosis and severe calcification. This study aimsto investigate the presence of electrocardiographic signs of right ventricular hypertrophy in patients with desmoglein-2 mutations.

Method: The electrocardiographic signs of right ventricular hypertrophy (RVH) were anaylzed in the ECG 0f 21 patients with desmoglein-2 mutations and 20 patients with plakophilin-2 mutations (29 males, mea nage 42.4 +/- 8.5 years). ECG signs of right ventricular hypertrophy were defined as modified Sokolow-Lyon index (R in V1/S in V6 > 1.07), R/S ratio in V1 > 1, and shallow S wave syndrome in lead V1.

Results: In desmoglein-2 patients signs of RVH were present in 11/21 cases (52%). In plakophilin-2 mutations there were no signs at all.

Conclusions: Electrocardiographic signs of RVH might be a diagnostic marker of desmoglein-2 mutations. Necrosis and severe calcification is only described in arrhythmogenic cardiomyopathy with desmoglein-2 mutation as especial form of the disease.

INTRODUCTION

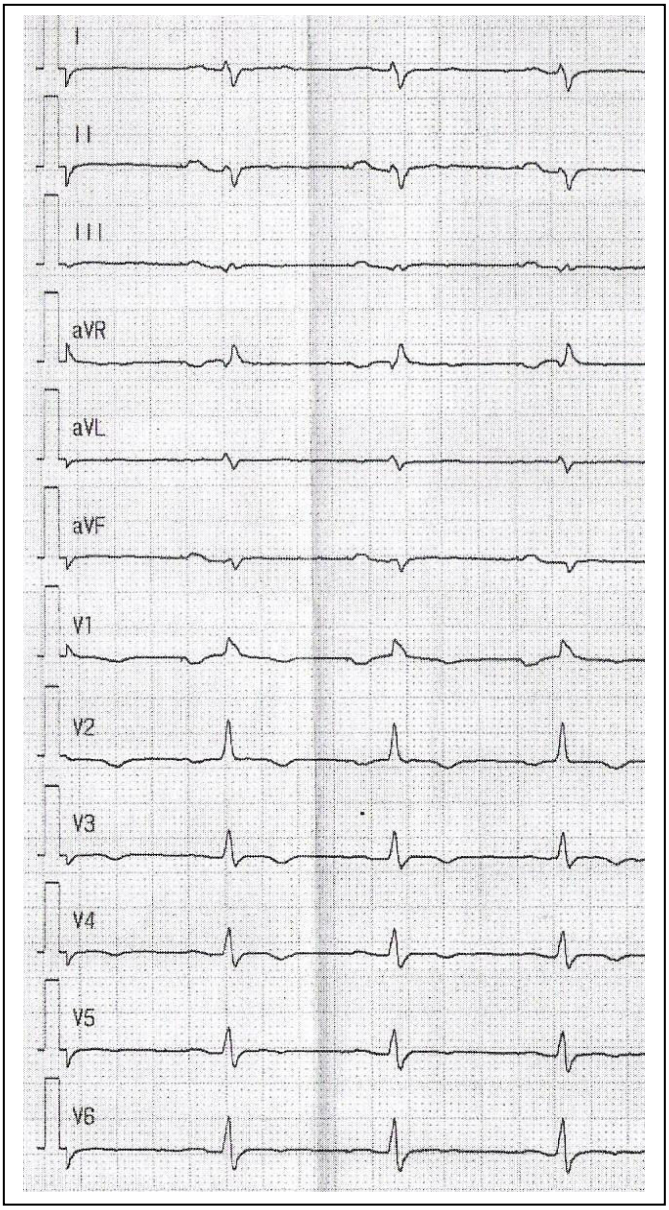
In the description of a human case and a mouse model of desmoglein-2 related arrhythmogenic right ventricular cardiomyopathy the ECG of the patient revealed electrocardiographic signs or RVH with a R/S ratio in lead V1 > 1 [1]. Histologic evaluation showed spotty calcification representing myocardial necrosis. In the mouse model myocardial necrosis leads to right ventricular myocyte hypertrophy (Figure 1).

The question is whether myocyte hypertrophy correlate to electrocardiographic RVH signs in desmoglein-2 mutation related arrhythmogenic cardiomyopathy and if it is present in other forms of arrhythmogenic cardiomyopathy.

METHODS

Data of 21 patients with desmoglein-2 related arrhythmogenic cardiomyopathy were compared to 20 patients with plakophilin-2 related arrhythmogenic cardiomyopathy (29 males, mean age 42.8 +/- 8.5 years) with regard to electrocardiographic signs of RVH. ECG's of patients with desmoglein-2 mutations were sent to the author by Estelle Gandjbakhch, co-author of the paper entitled *High-risk of heart failure associated with desmoglein-2 mutations compared to plakophilin-2 mutations in arrhythmogenic right ventricular cardiomyopathy/dysplasia* [2]. Patients with plakophilin-2 mutations were analyzed from the author's own cohort published in

numerous papers. Three desmoglein-2 mutation encoded patients were transplanted because of biventricular heart failure, three patients were asymptomatic mutation carriers, the other patients had phenotypic arrhythmogenic cardiomyopathy with right ventricular dysfunction. One plakophilin-2 mutation patient was transplanted because of biventricular heart failure, six patients were asymptomatic mutation carriers, the other patients had symptomatic ventricular tachycardia.



Electrocardiographic signs of right ventricular hypertrophy were analyzed as follows:

- modified Sokolow-Lyon index (R V1/S V6) > 1.07 [3]
- shallow S-wave syndrome in lead V1 [3]
- R / S ratio in lead V1 > 1 [3]

Statistical analysis should be described in details.

The diagnosis of arrhythmogenic cardiomyopathy were made by echocardiography, right ventricular angiography, cardiac MRI, electrocardiography, and incomplete genotyping in my own cohort. In the group of patients with desmoglein-2 mutations some patients were related, in my own cohort all patients were unrelated. In patients requiring heart transplantation left ventricular ejection fraction were low (< 40%), in all other patients LVEF were normal.

In patients with desmoglein-2 mutations a table with basal clinical characteristics and different electrocardiographic signs is listed in the original paper [2].

RESULTS

In patients with desmoglein-2 mutations there were 11/21 patients (52%) with electrocardiographic signs of RVH. Two cases with positive modified Sokolow-Lyon index, two cases with R/S ratio > 1 with low voltage ECG, and seven cases with shallow S wave syndrome in lead V1. Out of the three patients who required heart transplantation one had RVH, one had low voltage ECG and RVH and the last one had epsilon wave and right precordial T wave inversions. Patients with plakophilin-2 mutations had no electrocardiographic signs of RVH.

DISCUSSION

Right ventricular myocyte hypertrophy is described in a mouse model with mutated desmoglein-2 [4]. After damage and necrosis of right ventricular myocytes RVH developed especially in most advanced forms of arrhythmogenic cardiomyopathy with left ventricular involvement.

Necrosis is not only described in animal models but also in an explanted heart of a proband carrying the DSG2-N266S mutation with massive calcification [1].

The rate of desmoglein-2 mutations in arrhythmogenic cardiomyopathy is about 3 – 15%, but in a cohort of 434 patients with typical arrhythmogenic cardiomyopathy exactly 3% [5]. The theory is that signs of right ventricular hypertrophy are desmoglein-2 mutation - dependent. Necrosis with massive calcification is for all we know only described in desmoglein-2 mutations in arrhythmogenic cardiomyopathy.

Special ECG features of arrhythmogenic cardiomyopathy are described for TMEM43 mutations and phospholamban mutations [6]. In plakophilin-2 mutations electrocardiographic signs of RVH could be ruled out, the same is true for TGF beta 3 and ryanodine-2 receptor mutations [7].

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Electrocardiographic signs of right ventricular hypertrophy might be a diagnostic hint for desmoglein-2 mutations, although all kinds of advanced arrhythmogenic cardiomyopathy can proceed with histologic right ventricular myocyte hypertrophy possibly interacting with this theory. This is a very strong statement based on few patients transplanted in this study. It is based on other studies/reviews then reference showed be mentioned.

LIMITATIONS

The number of patients analyzed in this study is very low. In my own cohort the patients are incompletely genotyped and only 21 of 27 ECG's of patients included in the desmoglein-2 study were sent to me.

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