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Original contribution

Nonischemic left ventricular scar and cardiac sudden death in the young☆,☆☆,★

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Summary Nonischemic left ventricular scar (NLVS) is a pattern of myocardial injury characterized by midventricular and/or subepicardial gadolinium hyperenhancement at cardiac magnetic resonance, in absence of significant coronary artery disease. We aimed to evaluate the prevalence of NLVS in juvenile sudden cardiac death and to ascertain its etiology at autopsy. We examined 281 consecutive cases of sudden death of subjects aged 1 to 35 years. NLVS was defined as a thin, gray rim of subepicardial and/or midmyocardial scar in the left ventricular free wall and/or the septum, in absence of significant stenosis of coronary arteries. NLVS was the most frequent finding (25%) in sudden deaths occurring during sports. Myocardial scar was localized most frequently within the left ventricular posterior wall and affected the subepicardial myocardium, often extending to the midventricular layer. On histology, it consisted of fibrous or fibroadipose tissue. Right ventricular involvement was always present. Patchy lymphocytic infiltrates were frequent. Genetic and molecular analyses clarified the etiology of NLVS in a subset of cases. Electrocardiographic (ECG) recordings were available in more than half of subjects. The most frequent abnormality was the presence of low QRS voltages (<0.5 mV) in limb leads. In serial ECG tracings, the decrease in QRS voltages appeared, in some way, progressive. NLVS is the most frequent morphologic substrate of juvenile cardiac sudden death in sports. It can be suspected based on ECG findings. Autopsy study and clinical screening of family members are required to differentiate between arrhythmogenic right ventricular cardiomyopathy/dysplasia and chronic acquired myocarditis.

1. Introduction

Nonischemic left ventricular scar (NLVS) is a well-recognized pattern of myocardial injury with features of midventricular and/or subepicardial gadolinium hyperenhancement on cardiac nuclear magnetic resonance (CMR), in patients without significant coronary artery disease (CAD)

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[1]. The anatomical substrate of gadolinium hyperenhancement is represented by expansion of extracellular tissue [2], which corresponds to fibrous or fibroadipose myocardial replacement [3]. In the last few years, the finding of NLVS on CMR has been described in subjects with mutations in desmosomal genes and interpreted accordingly as one end of the phenotypic spectrum of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) [4-7], that is, the left dominant form (LDAC), which mirrors the "classic" form of ARVC/D by showing the left ventricle (LV) consistently more severely affected than the right ventricle (RV) [8]. However, morphologic features of NLVS can be found also in chronic or healed acquired myocarditis in patients who are not mutation carriers [5,8]. To achieve a differential diagnosis between these 2 conditions at autopsy, clinical-cardiologic and CMR screening of the family members as well as molecular investigations on the probands are required. Interestingly, NLVS has been recently reported at autopsy as the anatomical substrate of sudden cardiac death (SCD) in 2 young competitive athletes [3,9]. In both cases, NLVS was the main cardiac finding, although small foci of right ventricular fibroadipose replacement were observed at histology, suggesting a diagnosis of LDAC. These preliminary reports prompted us to systematically evaluate the prevalence of NLVS in a consecutive autopsy series of young individuals who died suddenly, either at rest or during sports activity, and to establish its etiology.

2. Materials and methods

2.1. Autopsy series

From January 2001 to July 2013, 281 cases of sudden death of subjects from 1 to 35 years were consecutively referred to our department (which is the Lazio Region Referral Centre for sudden deaths in this age range) after a complete autopsy, either from medical examiners or from hospital autopsy services. All the pathologic studies were performed on routine autopsy examinations required for diagnostic purposes with the approval of the local ethical committee. The need for consent from relatives was waived. *Sudden death* was defined as an event occurring from natural causes, within 6 hours from the onset of symptoms in a healthy subject or in a subject in stable medical conditions [10]. If death was unwitnessed, subjects were not included in the study, unless they had been observed in healthy conditions at least 24 hours before death. Extracardiac causes of death were ruled out by a complete autopsy in 76 (27%) of 281 cases. Thus, whole hearts of 205 cases were received for gross and histologic examination. The results of toxicological screening were available in 83 of 205 cases.

2.2. Pathologic evaluation

All hearts were weighed, photographed, and examined according to a standardized protocol [11]. After external inspection, the origin and course of epicardial coronary arteries were recorded. They were subsequently cut into 3- to 4-mm-thick cross-sections and processed for microscopic analysis.

Hearts were sectioned according to the short-axis echocardiographic view. The ventricular chamber size, the thickness of the left and right ventricular free walls, and the septum were measured at the midventricular level, halfway between the atrioventricular valves and the apex. Heart valves and myocardium were carefully inspected, and multiple samples were routinely taken from both ventricles and the ventricular septum for histology. The finding of gross lesions led to additional sampling of the myocardium. The conduction tissue was dissected only in cases with clinical history and/or previous electrocardiogram (ECG) records (either referred or available for review) of conduction defects. Twenty to thirty-five blocks were examined for each case, including the coronary arteries and heart valves. A minimum of 2 histologic sections for each block was stained with hematoxylin and eosin and Azan-Mallory trichrome stains. When acute lymphocytic myocarditis was suspected based on the findings of inflammatory infiltrates and myocyte necrosis on hematoxylin and eosin–stained slides, immunohistochemistry was performed to characterize the inflammatory infiltrates.

NLVS was defined as the gross finding of a thin, gray rim of subepicardial and/or midmyocardial linear discoloration in the LV free wall and/or the septum, in absence of significant coronary artery disease. The macroscopic features of NLVS were confirmed by histologic findings of fibrous or fibroadipose myocardial replacement. When fresh or frozen myocardial tissue was available (n = 4 cases), both molecular analyses for viral genomes detection and mutation screening for the genes most commonly involved in ARVC/D were performed according to standardized protocols [12-14] to establish the etiology of NLVS.

2.3. Toxicology screening

A complete toxicological screening had been performed on blood (after deproteinizing treatment) and urine samples, including ethanol search performed by head-space gas chromatography and screening test based on immunoassay (TRIAGE, ASCEND Multimmunoassay; Merck, Darmstadt, Germany) to detect amphetamines, opiates, barbiturates, tetrahydrocannabinol, and tricyclic antidepressants, according to the manufacturer's instruction. This had been followed by gas chromatography/mass spectrophotometry analyses on all samples found positive in the screening analysis.

2.4. Genetic analysis

Mutation screening of the 5 desmosomal genes most frequently involved in ARVC/D was performed by direct sequencing. Briefly, genomic DNA was extracted from frozen myocardial tissue, when available (n = 4), with Wizard Genomic DNA Purification Kit (Promega, Madison, WI). Intronic