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Sudden death in mild hypertrophic cardiomyopathy with compound *DSG2*/*DSC2*/*MYH6* mutations: Revisiting phenotype after genetic assessment in a master runner athlete

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ABSTRACT

Cardiomyopathies represent a well-known cause of heart failure and sudden death. Although cardiomyopathies are generally categorized in distinct nosographic entities, characterized by single gene-to-disease causal relationships, recently, oligogenic mutations have also been associated to relevant cardiac clinical features. We report the case of a master athlete carrying trigenic mutations in desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*) and heavy chain myosin 6 (*MYH6*), which determine a mild hypertrophic phenotype associated both to ventricular tachyarrhythmias and atrio-ventricular block. We discuss the differential diagnosis and prognostic approach in patient affected by complex cardiomyopathy phenotype, along with the importance of sport restriction and sudden death prevention.

Introduction

During the past 25 years, scientific research has remarked the importance of studying cardiomyopathies for the prevention of heart failure and sudden death [1]. We generally categorize cardiomyopathies in distinct nosographic entities: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular non compaction (LVNC), restrictive cardiomyopathy (RCM) and channelopathies. Distinct forms of cardiomyopathies present both distinct specific gene-related phenotypes and clinical and genetic heterogeneity [2]. The cardiological literature of the last decade highlighted a number of digenic and compound mutations that are significantly associated with clinical features and might be seen as independent predictors of lifetime arrhythmic events [3,4], which in turn are particularly dangerous for patients that do not accept sport restriction or that, generally, do not cope well with the disease [5]. Here, we present a patient affected by hypertrophic cardiomyopathy with mild wall thickness and stigmas of arrhythmogenic cardiomyopathy, with both ventricular tachyarrhythmias and atrioventricular (AV) block, carrier of mutations in three different genes.

Case report

A 49 years old male was rescued by his wife in a car accident. She referred he had a sudden loss of consciousness. The patient was a master athlete, involved in marathon competitions and training sessions in mountain running, with no past medical history and drug assumption. Familial history was negative for sudden death, while we noticed a high prevalence of cancer related deaths at young age. ECG performed by emergency nurse showed paroxysmal complete AV block with junctional rhythm at 30 bpm (Fig. 1A). The patient was then transferred to the Cardiac Care Unit for evaluation and eventual pacemaker implantation. A previous ECG showed sinus rhythm with high R wave amplitudes and negative T wave in lead DI, DII, DIII, aVL, aVF and V2-V6, associated to incomplete right bundle branch block (RBBB) (Fig. 1B). An echocardiography showed mild symmetric cardiac hypertrophy (septal thickness 15 mm) with preserved ejection fraction. During hospitalization, he was in sinus rhythm, while we observed repetitive episodes of non-sustained fast ventricular tachycardia (200 bpm) at rest with superior axis and RBBB-morphology, as originating by left ventricular apex (Fig. 1C), and periodic Luciani-Wenckebach AV block. A cardiac MRI was performed, showing mild symmetric cardiac hypertrophy and the presence of isolated aneurism of left ventricular apex, with late gadolinium enhancement of the same region, as expression of cardiac fibrosis (Fig. 1D). Coronary angiography did not show significant atheromasic lesions. At this point, we discussed with the patient the opportunity to

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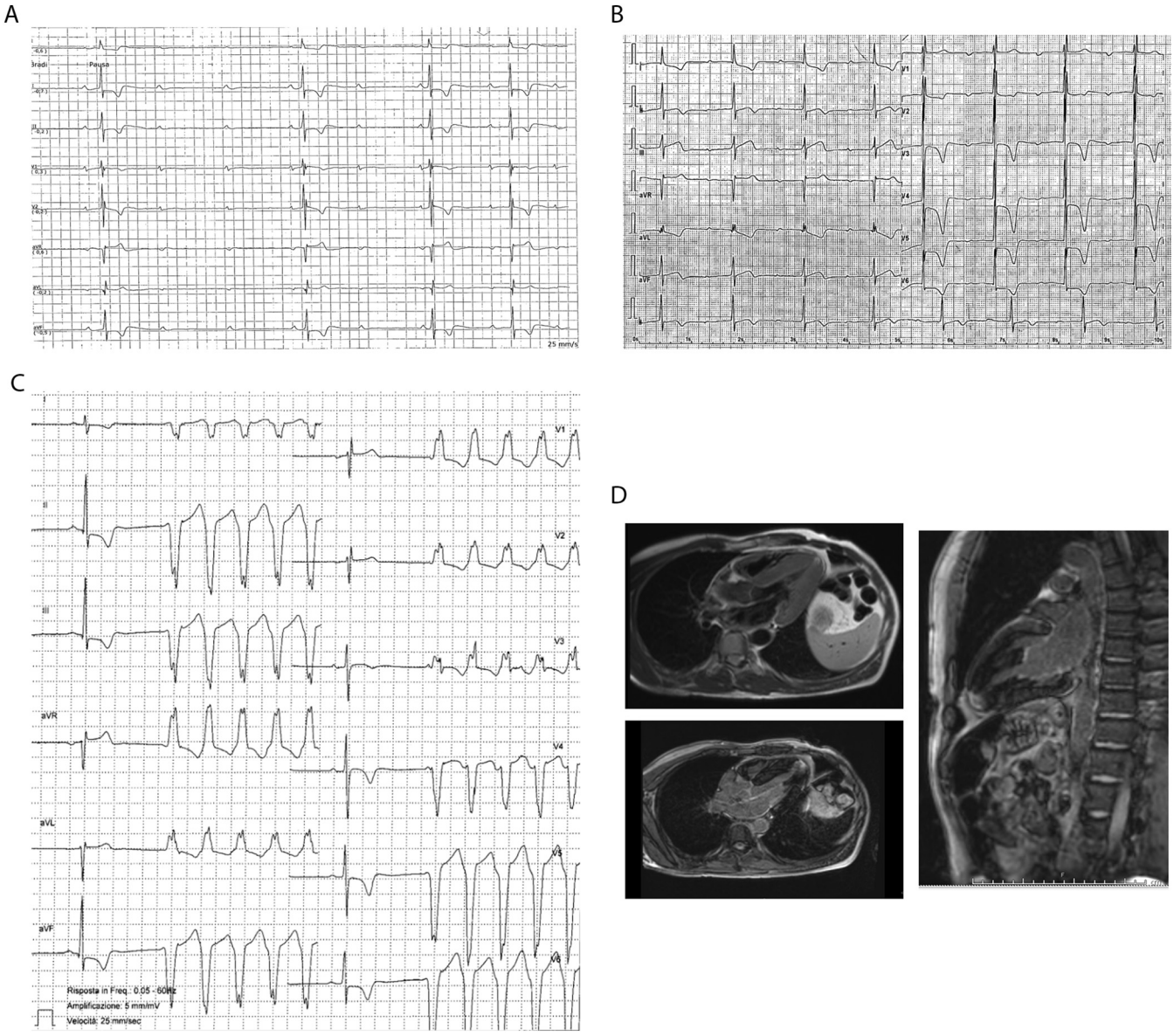

Fig. 1. A) Complete AV block; B) ECG at a previous evaluation; C) non sustained ventricular tachycardia; D) cardiac MRI showing apical aneurism with LGE.

implant a cardiac defibrillator in presence of both paroxysmal complete AV block and ventricular arrhythmias. The patient did not accept to cope with the disease diagnosis, and denied his consent to the implantation of either a cardiac defibrillator or a pacemaker. Then, we proposed the application of a loop recorder, but he refused again and asked to be discharged. At follow up, he did not present any syncope or heart failure symptoms. The patient underwent cardiac electrophysiological study from another center, which did not induce any ventricular arrhythmias. Nine months later, the patient died suddenly at rest. Written informed consent to publication was obtained from the patient and his son. Ethics Committee's approval for publication was not necessary because personal information or patient photos were not included in the manuscript.

Materials and methods

Libraries preparation and next-generation sequencing (NGS)

A Cardiac Disease Sequencing Panel of 76 genes, including genes related to hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic cardiomyopathy, was designed according to data obtained from scientific literature. Probes were designed using Agilent SureDesign Custom design tool (https://earray.chem.agilent.com/suredesign/): the regions of interest (ROI) for this panel included all exons plus 25 bp flanking intron regions. The total amplicon number was 19.648 and the target size was 366.196 Kb with a theoretical coverage of 99.32% for our targeted regions.

Peripheral blood samples were taken from the patient and his son, and genomic DNA was isolated by using Bio Robot EZ1 (Quiagen, Solna, Sweden). The quality of DNA was tested on 1% electrophorese agarose gel, and the concentrations was quantified with Nanodrop 2000C spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

A library of all coding regions of the 76 genes was obtained using the Haloplex target enrichment kit (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturer's instructions.

The libraries were pooled, and Next Generation Sequencing (NGS) was performed on a MiSeq sequencer (Illumina, San Diego, CA, USA) using a MiSeq Reagent kit V3 300 cycles flow cell.

Bioinformatics analyses

Initially, the generated paired-end reads were checked for their quality with the FastQC tool [*Andrews S.* (*2010*). *FastQC*: *a quality control*

tool for high throughput sequence data. Available online at: *http://www.bioinformatics.babraham.ac.uk/projects/fastqc*] and then mapped to the hg19 reference genome sequence by means of Bowtie 2 [6]. Depth of coverage statistics for the target regions were calculated by TEQC ver. 3.4 [7].

Variants were called by means of the *HaplotypeCaller* tool of GATK ver. 3.5 [8] and were annotated with ANNOVAR, using RefSeq genes and transcripts annotations (updated to Dec 2016) [9]. Variants were found in dbSNP ver. 147 [10], ExAC ver. 0.3 [11], and Exome Variant Server (*http://evs.gs.washington.edu/EVS*, *accessed at December 2016*), HRC [12], Kaviar [13] and ClinVar [14]. Missense variants were further annotated by querying the dbNSFP ver. 3.2 resource and retrieving pre-computed pathogenicity predictions and evolutionary conservation measures [15].

Different filtering strategies were applied in order to determine the candidate causative variants for the patient. Interesting variants were those exhibiting relevant functional annotations (e.g., they were either missense, or splicing, or stopgain, or stoploss or frameshift mutations), clinical significance according ClinVar, low (≤0.05) or absent Minor Allele Frequency in public population databases, absence in healthy samples or presence in samples with same phenotype.

The stability of the DSG2 protein upon mutation was investigated thermodynamically through the FoldX [16] algorithm (see Results). This study was conducted on the wild-type protein model obtained from the Protein Data Bank [17] (PDB id: 5erd). It was mutated *in-silico* through UCSC Chimera [18], yielding a second protein model. Both were minimized, namely all the side chains were slightly moved in order to reduce the Van der Waals' clashes, before being analyzed by FoldX. The standalone version of FoldX is downloadable from *http://foldx.crg.es*. It was run with standard parameters and used to compute the total energy values of the wild-type and mutated models of DSG2. These values were used to predict the overall protein stability, with and without mutation.

Sanger sequencing

All putatively pathogenic variants were confirmed by Sanger sequencing. PCR products were sequenced using ABI Prism 3100 Genetic Analyzer (Thermo Fisher Scientific Waltham, Massachusetts, USA) and the BigDye Terminator v1.1 sequencing kit (Applied Biosystems, Foster City, CA, USA).

Results

A total of 1.25 million paired-end reads were produced for the patient with a 33 average site-specific quality (Phred) score, as computed by the FastQC tool. We achieved a 300× mean (±170× st. dev.) depth of coverage through the target regions, which caused that the 93% of target bases were covered at least 20 times. Regarding the patient's son, we obtained 2.3 million paired-end reads with a mean depth of coverage of 560× (±330 st. dev.) and 96% of target sites covered by at least 20 reads. After the variant prioritization step, three mutations affecting *DSG2*, *DSC2* and *MYH6* genes emerged. Details are reported in the Table 1. *MYH6* mutation hits a splice donor site (rs745523742) and it is predicted to be deleterious by four software packages: MutationTaster [19], CADD [20], DANN [21] and FatHmm [22]. This mutation breaks the splice donor site associated to the 18–19 intron, probably causing a premature stop after the 755 amino acid site of the 1939 amino acid long reference protein (UNIPROT accession number: P13533-1). The 2-nucleotides insertion within the sequence of the Desmocollin-2 exon 16 (rs200056085) causes a premature stop during protein translation (NP_077740:p.Ala897Lysfs; canonical protein length: 901 amino acids). MutationTaster assigns a "disease-causing" functional prediction for such indel (with a probability value of 0.99). Consistently, FatHmm-Indel reports a functional score of 0.927, thus indicating a possible pathogenic effect for the variant. Regarding the non-synonymous variant in *DSG2* (rs2230234), it is predicted to be harmful by several pathogenicity predictor software: SIFT [23], PolyPhen2 [24], LRT [25], CADD, DANN, FatHmm. Furthermore, the free energy calculations for this variant were $\Delta G_{mut} = 266.123$ kcal/mol and $\Delta G_{wt} = 264.733$ kcal/mol, from which $\Delta\Delta G = \Delta G_{mut} - \Delta G_{wt} = +1.39$ kcal/mol. The difference in free energy resulted to be positive and in the range to classify the I293V DSG2 variant as *destabilizing*; the localization of the variant is depicted in Fig. 2.

Discussion

The described clinical case provides several interesting point to be addressed for both clinical approach and cardiomyopathies management.

The initial syncope at rest, a loss of consciousness determining the car accident, represents a crucial symptom for risk stratification in diagnostic and prognostic work up. Electrocardiographic findings recorded two months earlier were clearly pathologic, arising suspects for left ventricular hypertrophy, as underlined by high voltage (Sokolow-Lyon criteria), associated to negative T wave in DI, aVL e V3-V6 leads. Despite this abnormal pattern, the patient still pursued training session in mountain running without symptoms as angina, dyspnea, palpitations or syncope.

The arrhythmic phenotype was characterized by complete AV block with 6 s asystole, during daytime. Among master athletes it is common to find extreme bradycardia or 2:1 AV block for training related vagal tone stimulation; anyway, complete AV block is related to conduction system disease, likely subhissian, and represents an exclusion criteria for agonistic sport activity if associated to >3 s pause [26]. On the other side, we observed frequent and repetitive ventricular arrhythmias (non-sustained ventricular tachycardia), with a prevalent morphology RBBB-like and superior axis, with Q wave in V3-V6 leads, as originating from the apex.

Echocardiographic examination confirmed the suspected hypertrophy, also at level of right ventricle, yet cardiac MRI with late gadolinium enhancement (LGE) highlighted the presence of a small left apical aneurysm, with fibrotic component (Fig. 1D); this finding was likely the re-entry circuit responsible for the above mentioned ventricular arrhythmias.

At initial evaluation, clinical and diagnostic finding pointed out for indication to ICD, according to European guidelines on diagnosis and treatment of hypertrophic cardiomyopathy, with an estimated sudden death risk about 7% at 5 years [27]. Nevertheless, the patient did not accept diagnosis and new discovered clinical conditions, therefore refused ICD implantation and decided for an additional evaluation in another hospital. Afterwards, he underwent cardiac electrophysiological study

Table 1
Genomic position, gene symbol, Genotype (GT), Allele frequency (AF) of the detected mutations. Allele frequency and counts (AC) refer to the variant databases reported into brackets.

Samples	Genomic Position (hg19)	Gene	GT	Variant	AF; AC
Patient	14: 23865901:A > G	*MYH6*	het	NM_002471:exon19:c.2292 + 2 T > C	8.24e-6; 1 (ExAC)
	18:28647999:T > TTC	*DSC2*	het	NM_024422:exon16:c.2688_2688delinsGAA	3.6e-3; 18 (dbSNP)
	18:29104714:A > G	*DSG2*	homo	NM_001943:exon8:c. 877A > G:p.Ile293Val	0.03; 162 (dbSNP)
Son	14: 23865901:A > G	*MYH6*	het	NM_002471:exon19:c.2292 + 2 T > C	8.24e-6; 1 (ExAC)
	18: 29104714: A > G	*DSG2*	het	NM_001943:exon8:c.877A > G:p.Ile293Val	0.03; 162 (dbSNP)

Fig. 2. Location of the Ile293Val mutation in the DSG2 protein.

by programmed electrical stimulation (PES), negative for ventricular tachycardia induction. This result, as underlined by several studies cited in recent guidelines, has a low negative predictive value, with the clear statement that PES is not useful for sudden cardiac death stratification.

Family screening by means of clinical history, examination, ECG and echocardiography conducted among patient's sons did not show any pathological finding.

Genetic screening highlighted the pathologic composite mutations for both *MYH6*, *DSC2* at heterozygous state and *DSG2* at homozygous state, with the last one representing a major criteria for arrhythmogenic cardiomyopathy by Task Force 2010 [28]. As previously reported, the p. A897KfsX4 variation identified in several Italian healthy control subjects, altering only one of the two DSC2 isoforms, could be considered a rare polymorphism that may affects the phenotypic expression of concomitant ARVC/D mutations [29].

At this point, the unrevealed genetic substrate will further affect patient management, confirming the higher arrhythmic risk, in an overlapping phenotype between hypertrophic and arrhythmogenic cardiomyopathy, beyond the risk derived by HCM per se (SCD HCM risk calculator_V2., http://www.doc2do.com/hcm/webHCM.html); left apical aneurism could be the result of a *locus minoris resistentiae* linked to desmosomes dysfunction.

In the last years, we observed a changing concept on arrhythmogenic cardiomyopathy, from a right ventricular disease to a biventricular or even left predominant disease. Consequently, we should revise diagnostic criteria, as left aneurysm presence, frequent premature ventricular contractions (PVC >1000/24 h), left originating non sustained ventricular tachycardia, associated to pathologic mutations for desmosome related gene, would represent valid criteria for left arrhythmogenic cardiomyopathy. Once agreed on these observations, the patient sudden cardiac death risk profile would dramatically increase, considering that unexplained syncope and non-sustained ventricular tachycardia per se raise sudden death risk close to 10% at one year, beside minor risk factor as male gender, composite mutations, frequent PVC and negative T wave presence [30].

The presence of complete AV block and R-BBB could represent an expression of desmosome disease involving conduction system [31].

On the other side, biventricular hypertrophic phenotype is related to *MYH6* mutation, linked both to dilatative and hypertrophic mutation, and to sinus node disease. The presence of composite mutations with pathogenic significance for a cardiomyopathy different from the apparent phenotype will dramatically change the patient management, reinforcing the role of an expanded genetic characterization in cardiomyopathies approach.

Beyond cardiac implication, we observed a high prevalence of cancer related death at young age among first and second degree relatives for pulmonary and gastric neoplasm. In recent years, scientific researches have shown that desmosomes dysfunctions caused by mutations in desmocollin-2 and desmoglein-2, are associated to gastric and epithelial tumors, supporting the pathological familial evidences finding in our clinical case [32,33]. This finding implies a strict and global patient assessment during follow up of family members affected by these mutations, concerning cardiac and oncologic evaluation.

Psychological impact of diagnosis in patients affected by cardiomyopathies, particularly in athletes, is of paramount importance, further than disease detection. The latter is an emotionally vulnerable population, which perceived disease diagnosis throw different psychological phases, going from immediate reaction, to coping efforts, adaptation to new lifestyle and finally acceptance. This long inner journey needs specific support and a multidisciplinary and coherent approach [34]. At same time, sport restriction in the initial phase would be hard to obtain, in case of denying reaction.

According to international consensus, agonistic sport activity must be denied to people carriers of pathogenetic mutations in desmosomal genes, in presence of clear hypertrophic phenotype (as showed in this case by echocardiography and cardiac MRI), and in presence of syncope due to complete AV block or ventricular arrhythmia (as in our case). Unfortunately, after the questionable and reassuring negative electrophysiological study, our patient continued to pursue agonistic running and training session in mountain running, a physical activity with massive aerobic and anaerobic cardiocirculatory involvement.

The heavy heritage of this mournful clinical case, underlines that a second opinion in an additional referral center should be always encouraged to avoid patient perplexity in case of disagreement, relaying on existing national and international scientific societies network.

Conclusions

Prevention of sudden cardiac death in patients carriers of compound genetic mutations showing overlapping phenotypes, represents an important challenge in clinical practice. A multidisciplinary approach is of paramount importance for prevention of sudden death, adequate heart failure treatment, psychological support and sport-related restriction during follow up.

A multidisciplinary scientific and clinical network among secondary and tertiary care center, represents the adequate solution for the right management of complex patients. Furthermore, a complete genetic screening, beyond the observed clinical phenotype, will add more relevant informations for risk stratification, avoiding underestimation of the

current prognostic score, and underlying the role of an expanded genetic characterization in cardiomyopathies approach.

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Conflict of interest statement

The authors declare no conflict of interest.

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