European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

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Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

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Editorial News

Dear Members of the Working Group,

please find enclosed the 9th issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the answer to the January case.

In addition we are happy participate at the Spring Summit and the Working Group Meeting which will take place at the European Heart House at the beginning of March. We will present there the idea of the monthly newsletter because it contains key scientific content and is a great example of efforts to build a scientific initiative complying with the main task of constituent body of the ESC: knowledge & expertise transfer.

Best wishes for all of you.

The paper of the month:

Re-examination of the Electrocardiogram in Boys With Duchenne Muscular Dystrophy and Correlation With Its Dilated Cardiomyopathy. Thrush PA, Allen HD, Viollet L, Mendell JR. Am J Cardiol; 103: 262-265; 2009

Presented by Prof. Dr. E. Arbustini
Centre for Inherited Cardiovascular Diseases, Molecular Diagnostic Laboratory, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Introduction: Clinical red flags in dilated cardiomyopathies Electrocardiographic changes in patients with Dystrophin gene defects.

Dystrophin (DYS) gene defects may cause Duchenne Muscle Dystrophy (DMD), Becker Muscle Dystrophy (BMD) and X-linked DCM (X-DCM), with or without increased serum Creatin-Phospho-Kinase (sCPK). Both patients with BMD plus DCM and X-linked DCM may reach the clinical attention for cardiologic rather than myology problems. In consecutive series of males with DCM, about 7% are affected by Dystrophin defects (1). The specific diagnosis of DCM caused by *DYS* gene defects can be missed unless specifically investigated. Red flags that may help diagnostic orientation are the DCM phenotype, the male gender, the increased sCPK and ECG changes, whose specificity however is not confirmed. The known ECG finding in these patients are short PR interval, right ventricular hypertrophy (RVH), prolonged QTc interval, and prominent Q waves in leads I, aVL, V5, and V6 or in leads II, III, aVF, V5, and V6.

Summary of the paper

In the January issue of the Am J Cardiol, Thrush et al from the Ohio State University, Columbus published the manuscript entitled **"Re-examination of the Electrocardiogram in Boys With Duchenne Muscular Dystrophy and Correlation With Its Dilated Cardiomyopathy"** (2). The search for clinical "red flags" that may guide cardiologists to specific diagnoses in cardiomyopathies is a major aim of our Working Group. In this manuscript, the Authors revised the electrocardiographic changes of 115 patients with Duchenne Muscle Dystrophy (DMD). Based on the echocardiographic criterion of echocardiographic ejection fraction <55%, the authors diagnosed DCM in 40 patients. Comparing ECG of patients with and without DCM they found no differences between the number of ECG changes in DCM and non-DCM groups (p = 0.279) (table below).

	DMD without DCM (75)	DMD with DCM (40)
Age (yrs) median (range)	12.4 (4-28)	15.3 (5–27)
EF (%), median (range)	60 (55–75)	42 (12–54)
short PR interval	36	14
RVH	18	25
prominent Q waves in leads V5 and V6	28 (V5) 25(V6)	11 (V5) 13 (V6)
prominent Q waves in leads I, aVL, V5, and V6	2	1
prominent Q waves in leads II, III, aVF, V5, and V6	5	4
long QTc interval	0	0
ST depressed	1	1
Flat inverted T waves	23	15

The authors conclude "ECG changes are similar in patients with DMD regardless of presence of DCM. The most common findings are short PR interval and RVH. Prominent Q waves in leads II, III, aVF, V5, and V6 are more likely". Therefore, in DMD, ECG changes are not-specifically present in patients with DCM. The short PR interval deserves attention as poorly outlined in the clinical evaluation as potential ECG marker of myocardial involvement in DYS-related phenotypes. Whether a short PR could constitute an ECG marker of mild BMD with DCM and X-DCM associated with Dystrophin defects could be matter of joint evaluation in our working group. Prominent Q waves are better known ECG markers: Q waves in the lateral leads seem to be much more common than in the inferior leads.

fAlthough in DMD ECG changes do not discriminate patients with and without DCM (2), the ECG changes may assume the role of Dystrophin-related disease markers in male patients with DCM. When flanked by increased sCPK, both with and without clinical signs and symptoms of overt myopathy, and X-linked recessive inheritance, ECG changes may contribute to suspect a Dystrophin-related DCM. Patients with *DYS* gene defects commonly seen first by cardiologists are unlikely to be affected by DMD, which is a paediatric diagnosis, well clinically recognised. BMD patients without DCM are also unlikely to reach the cardiologic attention before the myologic diagnosis.

The possible differential diagnosis as X-linked DCM could be with Barth syndrome, which is a paediatric disease, and is characterised by left ventricular non-compaction, granulocytopenia, methylglutaconic aciduria, hypocholesterolemia, mild increased sCPK and myopthy, and growth deficiency. Ventricular arrhythmia may develop later on the course of the disease (up to 43% of patients with ≥11 years of age). In Barth syndrome ECG changes are present in 58% of the cases (3).

ECG	N = 29 (%)
Left axis deviation	3/29
LV hypertrophy with strain	4/29
Repolarization abnormalities (ST flattening or T-wave inversion)	17/29
Right bundle branch block	1/29
Normal sinus rhythm	27/29
heart block	1/29
prolonged QTc of ≥460 msec	6/30 (20%)
borderline QTc prolongation (450-459 msec)	7/30(23%)

Additional X-linked DCM diseases include Emery-Dreifuss Muscle Dystrophy (EMDM) caused by defects of emerin: patients with EDMD frequently show conduction defects and rare develop DCM. Other X-linked cardiomyopathies, such as Danon, Anderson Fabry Disease typically show HCM phenotypes making unlikely the need for differential diagnosis with DYS-associated DCM.

References

1) Arbustini E, Diegoli M, Morbini P, Dal Bello B, Banchieri N, Pilotto A, Magani F, Grasso M, Narula J, Gavazzi A, Viganò M, and Tavazzi L. Prevalence and characteristics of dystrophin defects in adult male patients with dilated cardiomyopathy. J Am Coll Cardiol 35:1760-68; 2000

2) Thrush PA, Allen HD, Viollet L, Mendell JR. Re-examination of the Electrocardiogram in Boys With Duchenne Muscular Dystrophy and Correlation With Its Dilated Cardiomyopathy. Am J Cardiol; 103: 262-265; 2009

3) Spencer CT, Bryant RM, Day J, Gonzalez IL, Colan SD, Thompson WR, Berthy J, Redfearn SP, Byrne BJ. Cardiac and Clinical Phenotype in Barth Syndrome. PEDIATRICS 118: e337-e346; 2006

The clinical case of the month: *What is your diagnosis?*

Answers will be given in the next newsletter and on the web site

Presented by **A. Serio[1], L. Tavazzi[2], M. Pasotti[1], F. Gambarin[1], E. Arbustini[1]**

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Titel: "Cardiomyopathies *camouflage*: disguising fin

Case Presentation:

A 48-year-old Caucasian Italian man, farmer, with a 15-year history of paroxysmal supraventricular arrhythmias and a 2-year history of congestive heart failure was referred to our Institution for clinical and genetic evaluation. During the last 2 years he had suffered recurrent atrial fibrillation episodes that caused heart failure symptoms and clinical worsening from functional NYHA class I to III.

Past clinical history

At the age of 30 years, he was occasionally diagnosed with asymptomatic paroxysmal atrial fibrillation during a cardiological evaluation performed for sport suitability. In the following years, he suffered several paroxysmal atrial flutter and supraventricular tachycardia episodes. Routine cardiologic examination did not document cardiac disease.

At the age of 45 years, he complained a prolonged episode of chest pain; a non-Q myocardial infarction with angiographically normal coronary arteries was diagnosed.
One year later he underwent isthmo-inferior v.cava-tricuspid radiofrequency catheter ablation due to recurrent atrial fibrillation episodes. He was then given sotalol. The echocardiographic study showed mild left ventricular hypertrophy (12 mm), left ventricle end-diastolic diameter at upper limits, normal systolic function (LVEF 50%), mildly enlarged left atrium area, normal pulmonary pressures. During the following year, the patient showed recurrent supraventricular arrhythmias and heart failure symptoms; sotalol was discontinued and he was given amiodarone. Finally, he underwent ablation of the atrio-ventricular node with implantation of a biventricular pace-maker. He was then referred to our Centre for clinical and genetic evaluation.

Recent clinical history and clinical evaluation

At our first observation the patient showed mild effort dyspnea, peripheral edema. His ECG in sinus rhythm showed a normal PR interval and a wider QRS complex than those recorded in prior ECGs (Fig. 1a). The echocardiographic study showed impaired left ventricular ejection fraction (LVEF 35-40%), minimal enlargement of the left ventricle (end-diastolic diameter 58 mm). Wall thickness was still at upper limits only at the level of the interventricular septum (12 mm). Both atria were dilated; pulmonary pressures were increased, right ventricular function was slightly depressed and there was a mild pericardial effusion. In a few months, the symptoms worsened, as did LVEF (25%), pulmonary pressures and pericardial effusion. The right heart catheterisation showed a depressed cardiac index (1.42 and 1.16 l/min/m^2 in two consecutive evaluations), high left ventricular filling pressures (PWP 25 mmHg) and atrial pressure (RAP 15 mmHg), depressed right ventricular systolic function. Nuclear magnetic

Endomyocardial biopsy excluded storage diseases and showed focal hypertrophy and irregular nuclei and interstitial fibrosis (fig. 1b). The serum creatine phosphokinase (sCPK) was mildly increased (378 U/l). The patient entered the waiting list for heart transplantation and underwent heart transplant 2 years later.

The genetic counselling was very difficult, as the patient had no contacts with his only sister. The family history was initially poorly contributory: the mother died of "cardiac disease" at the age of 50 years (fig. 1c). The patient had no information about the maternal relatives; clinical reports of the mother were not available.

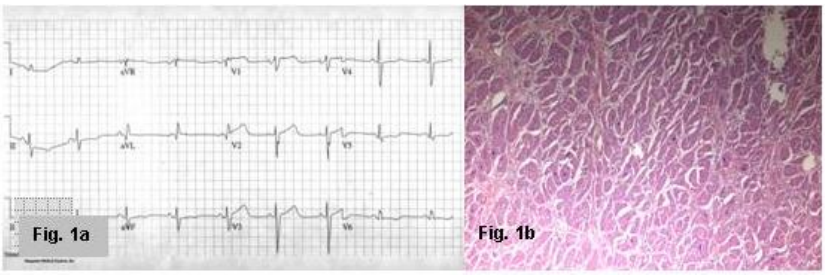

Fig.1a: basal ECG showed normal PR interval and a wider QRS complex than prior ones.
Fig.1b: Tissue studies excluded storage diseases and showed focal hypertrophy, irregular nuclei and interstitial fibrosis

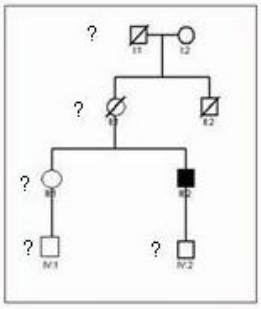

Fig. 1c: complete family tree. The genetic counselling was very difficult, as the patient had no contacts with his only sister. The family history was initially poorly contributory: the mother died of "cardiac disease" at the age of 50 years. Patient had no information about the maternal relatives; clinical reports of the mother were not available.
Legenda:

affected man/woman
healthy man/woman
? patient not available for screening

Which diagnostic hypothesis could be done for this patient?
Which other investigations should be performed to facilitate the diagnosis?

Answer for the previous" Clinical case of the month" in January :
'Refining the diagnosis of "Restrictive Cardiomyopathy": an illustrative case'
by Prof. C. Rapezzi, Dr. O. Leone and Prof. E. Arbustini
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Answers:

At this point, the only possible (provisional) diagnosis is idiopathic restrictive cardiomyopthy (RCM), based on:

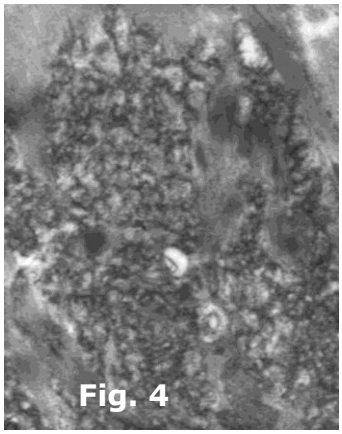
- Restrictive pathophysiology (normal ventricular volumes and left ventricular ejection fraction; increased filling pressure; dip plateau morphology of the right ventricular pressure tracing).
- No apparent sign of specific aetiology (in particular, infiltrative/storage disease).

Nevertheless, some clues could orient the diagnostic work-up towards a more precise diagnosis:

- Famililiality seems highly probable.
- Coexistence of RCM and advanced atrioventricular block at an early age.

These considerations prompted us to reconstruct a complete pedigree, based on clinical history and direct clinical/instrumental examination of living relatives. The pedigree indicated a recessive autosomal familial disease within the context of consanguineous intermarriage. The observation of an apparently idiopathic RCM in a familial context suggested the hypothesis of desmin-related cardiomyopathy. To evaluate this hypothesis, we performed ultrastructural analysis of the myocardial biopsy material and conducted DNA analysis to identify the desmin gene (DES) mutation. Electron microscopy (Fig. 4) demonstrated intracellular accumulation of material compatible with desmin (Fig. 4).

Fig. 4: electron microscopy discloses typical, desmin-related, granulo-filamentous, intracellular material



DNA analysis revealed that the patient was a homozygous carrier of a known pathogenetic mutation (R16C) in the DES gene. Other members of the large family agreed to DNA analysis: as many as 13 first or second degree relatives turned out to be phenotypically unaffected heterozygous carriers of the R16C mutation.

Final diagnosis: Desmin-related familial cardiomyopathy

Comments

In many cases, RCM should nowadays no longer be considered a final diagnosis, but rather a starting point for further assessment. At each diagnostic step, the clinician should be prepared to recognise highly specific (though not necessarily sensitive) signs that can provide clues for the true final diagnosis. In the present case, the combination of RCM and atrioventricular block in a young patient orients the diagnostic work-up.

Desmin is a polypeptide that normally aggregates to form "intermediate filaments" (whose diameter [8–10 nm] is intermediate between that of the myosin filaments and actin filaments) that normally provide link Z disks between adjacent myofibrils, the sarcolemma and nuclear membranes. Pathogenic mutations in the desmin gene give rise to intramyocellular desmin accumulation. The resulting clinical phenotypes are variable, but commonly include systemic myopathies with or without cardiomyopathy. Nevertheless, restrictive (or dilated) without clinically evident peripheral myopathy is also possible. The restrictive phenotype is typically accompanied by atrioventricular blocks. In the context of familial transmission, this combination of features must raise a strong suspicion of desminopathy.

The absence of specific histological alterations in the peripheral muscle and endomyocardial biopsies deserves some comment. Whereas light microscopy assessment of endomyocardial tissue shows nonspecific features, electron microscopy regularly reveals the typical desmin-related granulo-filamentous material which is diagnostic for desmin-related cardiomyopathy. The ultrastructural appearance of the deposits is identical in the myocardium and peripheral muscle. This knowledge is especially important for patients undergoing endomyocardial biopsy: in such cases, an incomplete investigation could lead to a missed diagnosis. Cardiologists and pathologists should be aware of these potential pitfalls.

Since desmin-related RCM is a likely diagnosis in patients with RCM accompanied by atrioventricular block cardiologists should specifically ask pathologists to perform electron microscopy assessment of their biopsy samples.