European Society of Cardiology Working Group on Myocardial & Pericardial Diseases

Newsletter

Issue 32 – February 2011

Myocardial and Pericardial Diseases
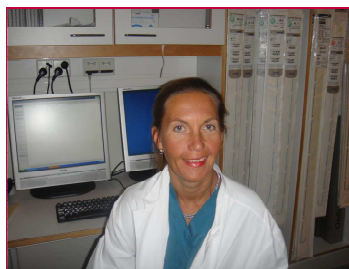ESC Working Group

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Editorial News

Dear Colleagues,
Dear Members of the Working Group,

Please find enclosed the 32nd issue of our Newsletter.

Read the answer to the previous 'case of the month'!

Tiina Heliö

The paper of the month:

Impact of troponin I-autoantibodies in chronic dilated and ischemic cardiomyopathy.

Doesch AO, Mueller S, Nelles M, Konstandin M, Celik S, Frankenstein L, Goeser S, Kaya Z, Koch A, Zugck C, Katus HA.

Department of Cardiology, University of Heidelberg, 69120 Heidelberg, Germany. Andreas.Doesch@med.uni-heidelberg.de

Presented by Alida LP Caforio, MD, PhD, FESC, Cardiology, Dept of Cardiological Thoracic and Vascular Sciences, University of Padova, Italy. alida.caforio@unipd.it

Background

Dilated cardiomyopathy (DCM), the third most common cause of heart failure and the leading cause for heart transplantation (HTX), may be familial/genetic, viral and/or immune-mediated. Experimental and clinical data indicate that in a sizable proportion of patients myocarditis and DCM represent the acute and chronic forms of an organ-specific heart autoimmune disease, occurring in genetically predisposed subjects, with or without a recognized viral trigger. Autoimmune features in human myocarditis/DCM include: a) familial aggregation, b) a weak association with HLA-DR4, c) lymph mononuclear cell infiltrates, abnormal expression of HLA class II and adhesion molecules on endomyocardial biopsy (EMB) in the absence of viral genome by molecular techniques in index patients and family members, d) experimental models of both antibody-mediated and cell-mediated autoimmune myocarditis/DCM following immunization with relevant autoantigen(s) under control of both major histocompatibility complex (MHC) and non-MHC genes, some of which are in common with those associated with genetic control of Type 1 diabetes and other autoimmune diseases, and e) increased levels of circulating cytokines and anti-heart autoantibodies (AHA), directed against multiple antigens, in patients and family members and in about 60% of familial and nonfamilial pedigrees. AHA in myocarditis/DCM may be directed against mitochondrial proteins, cardiac myosin heavy chain, cardiac b1-adrenergic receptors, muscarinergic receptors, the sarcolemmal Na-K-ATPase, cardiac troponin I (cTNI), and other yet unknown targets. AHA predict DCM development among relatives, years before disease onset. Some AHA, e.g antibodies against the ADP/ATP carrier, cardiac myosin, cardiac b1-adrenergic receptors, and cTNI have been shown to possess functional effects on cardiac myocytes in vitro, in animals and possibly in a DCM subset, responsive to extracorporeal immunoadsorption (IA). This is the rationale for the clinical application of IA in an ongoing randomized sham-controlled, double-blind multicenter trial in end-stage DCM. In addition, some AHA, being associated with phases of activation/relapse of the autoimmune process, may provide negative prognostic markers.

Summary

The aim of the study by Doesch et al. was to investigate the prognostic value of cTNI-autoantibodies by enzyme-linked immunosorbent assay (ELISA), including 249 patients with DCM and 141 patients with ischemic cardiomyopathy (ICM). cTNI-autoantibodies (titer of ≥ 1:40) were detected in 18.7% of patients. In TNI-autoantibody positive patients mean left ventricular ejection fraction (LVEF) was 27.6 ± 5.8%, compared to 25.8 ± 5.9% in TNI-autoantibody negative patients, P = 0.03. The combined end-point of death (n = 118, 30.3% of total) or HTX (n = 44, 11.3% of total) was reached in 162 patients (41.5% of total). Kaplan–Meier analysis demonstrated superior survival (combined end-point of death or HTX in patients with DCM versus ICM (P = 0.0198) and TNI- autoantibody positive patients versus TNI-autoantibody negative patients (P = 0.0348). Further subgroup analysis revealed a favorable outcome in TNI-positive patients with DCM (P = 0.0334), whereas TNI-autoantibody status in patients with ICM was not associated with survival. In subsequent multivariate Weibull-analysis, a positive TNI serostatus was associated with a lower all-cause mortality in DCM patients (P = 0.0492), but not ICM. The authors conclude that this might indicate a prophylactic effect of TNI-autoantibodies in DCM.

Comments

The study by Doesch et al. apparently contrasts with most data published until now, showing detrimental effects of cTNI autoantibodies. There are explanations for this apparent discrepancy. Firstly, the number of autoantibody-positive patients (42 with DCM and 31 with ICM) was rather small for subgroup analysis of outcome. Association of negative autoantibody status with all-cause mortality was of borderline significance in multivariate analysis (p = 0.049). Secondly, at baseline the ICM group was older, had lower LVEF, lower VO2 max, a higher proportion of patients in NYHA class III-IV. Thus, it is likely to represent a more advanced heart failure cohort. In a prospective study by Caforio et al. AHA titers were reduced in end-stage DCM. Thus, DCM and ICM should be matched in terms of heart failure stage to detect potential differences in outcome related to autoantibody status. Thirdly, at least two epitopes of cTnI can induce myocardial damage in murine models. The exact binding site of the cTNI antibodies measured in the present study remains unclear, thus it may be that the cTNI detected by ELISA are not those that have been proven to be detrimental for cardiac myocytes in previous studies. Epitope mapping data on ELISA positive sera would be of interest.

AHA data in the literature come from different groups and using different immunological detection methods; at present there are no correlative data on identical DCM and ICM cohorts at baseline and follow-up. An ongoing prospective multicenter multinational study, the ETiCs study has such design and should give relevant information on the functional and/or prognostic role of the major AHA specificities in DCM and ICM.

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

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

Authors:
Cathelijne Dickhoff and Yigal Pinto

Low Voltage EKG, a spot-diagnosis?

A 53-year old woman consulted our department for a second opinion concerning ventricular tachycardias. Initial presentation was with palpitations and vomiting. Her ECG showed remarkable low-voltage, echocardiography revealed normal dimensions and function of the left and right ventricle. Pericardial effusion was absent. She was not obese. Exercise testing was characterized by non-sustained monomorphic VT mainly during recovery. Coronary artery disease was excluded by angiography. Laboratory tests were normal; no sign of infection or systemic disease. MRI showed normal function and motion of both left and right ventricle, however there was pathologic gadolinium uptake in the left ventricle during DHE series.

The patient's mother experienced palpitations at younger age, one uncle from the mother's side had died suddenly at the age of 45 years.
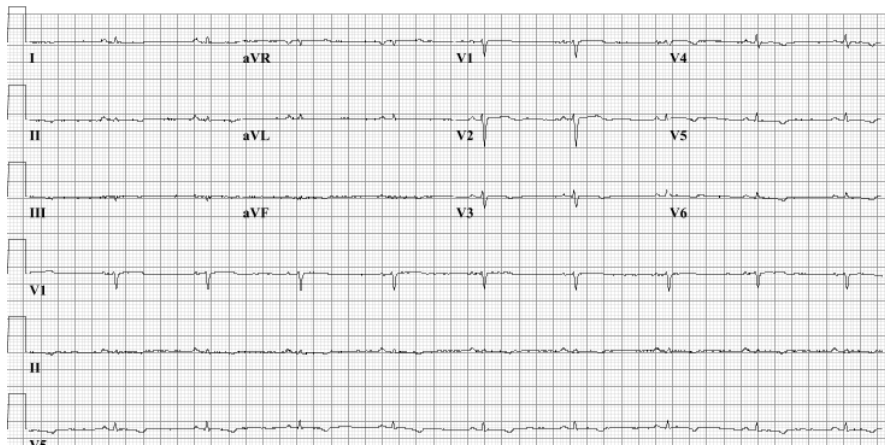

Fig 1.ECG of the patient

Fig.2 NSVT during recovery phase in exercise test

QUESTIONS

1. **What could be the differential diagnosis in this patient?**

2. **Would you perform genetic testing at this moment and if so, what genes?**

3. **What is the origin of the attenuated R-amplitude on the ECG in this case?**

4. **How would you treat the patient?**

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Answer for the previous "Clinical case of the month" presented in January issue

"A previously healthy 41-year old woman resuscitated from ventricular fibrillation"

**Presented by Dr. Tiina Heliö**
Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland

Possible causes of sudden ventricular fibrillation in this previously healthy patient included coronary artery disease or other coronary artery abnormalities, myocardial disease, inflammatory, infiltrative or neoplastic process, congenital heart disease, primary electrophysiological abnormality, electrolyte disturbance, toxic or metabolic disturbances.

When the patient arrived at the hospital, she was in sinus rhythm with no signs of ischaemia. Her serum potassium was low at 2.6 mmol/l (3.3-4.9). Soon after the acidosis and hypokalaemia had been treated, the prolonged QT-interval normalized. Later it was found out that the patient used to consume plenty of liquorice. However the aldosterone and renin values were within normal limits and the hypokalaemia was interpreted to relate mainly to the acute event. The results of DNA tests showed that the patient did not carry any of the four most common LQT mutations in Finland, which cover approximately 70 % of the LQT in our country. LQT syndrome was thus considered to be an improbable cause of the ventricular fibrillation. The ECG was not compatible with any other primary electrophysiologic abnormality. Laboratory analyses did not suggest toxic or metabolic disturbances. Congenital heart disease or coronary anomalies were excluded by echocardiography and cardiac MRI. The family history did not suggest any inherited cardiac disease.

The late enhancement in the cardiac MRI raised the suspicion, that the patient had a localized, possibly inflammatory process in the myocardium (Fig. 1.)
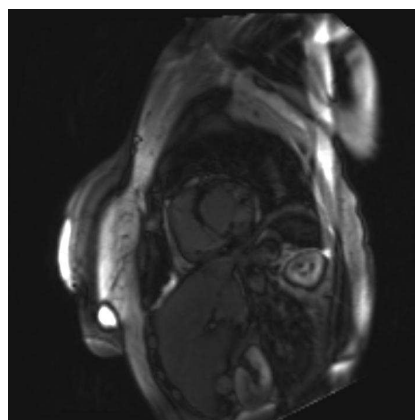
Fig. 1. Cardic MRI shows late enhancement in the basal area of the left ventricle.

Endomyocardial biopsies were taken from the left ventricle. However, the histological findings were non-diagnostic: there was neither sarcoidosis, giant cell myocarditis nor any other type of inflammation or fibrosis to be found. Coronary angiogram demonstrated normal coronary arteries. Thorax X-ray showed transient atelectasis but no enlarged hilar lymphnodes or parenchymal infiltrates.

Due to the cardiac MRI findings cardiac positron emission tomography with FDG (fluorodeoxyglucose) was performed. The posterobasal area of the septum was ^{18} F-FDG -positive as well as mediastinal and hilar lymph nodes. The finding was suggestive of inflammation, such as sarcoidosis. High resolution computer tomography (HRCT) of the lungs did not reveal any parenchymal lesions. Bronchoscopy and bronchoalveolar lavation were carried out showing increased relation of CD4+/CD8+ -lymphocytes, suggestive of sarcoidosis, but otherwise the bronchial biopsies were normal. Since none of the lymphnodes were easily accessible by other means, biopsies were taken in mediastinoscopy. Finally, histology showed non-necrotizing granulomas consisting of epithelioid cells and individual giant cell confirming the diagnosis of sarcoidosis.

The patient received an ICD. The medical treatment comprised prednisolon for approximately one year and thereafter prednisolon was substituted by azathioprine. There have not been any ICD activations. In follow-up the LVEF and dimensions have been restored. The left ventricle was 59/49 mm and LVEF was 52 %.

Sarcoidosis is a multisystem disease histologically characterized by non-caseating granulomas. The prevalence varies between populations and it is known to be high in Scandinavia. Sarcoidosis may affect the heart in up to one fourth of cases. Cardiac sarcoidosis typically manifests as conduction defect, or progressive heart failure but also tachyarrhythmias and sudden death are possible. Signs of granulomatous inflammation may be sought using different imaging modalities. Diagnosis is based on showing noncaseating granulomas in a biopsy. Because of the patchy nature of the inflammation, a negative result of a biopsy does not exclude sarcoidosis. Steroid treatment may be useful at the early phase of the disease. Conventional medical is used for heart failure and in the presence of ventricular arrhythmias, an ICD should be considered.

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List of recently published papers in the field of our WG recommended for further reading:

1. Wu W, Muchir A, Shan J, Bonne G, Worman HJ. Mitogen-Activated Protein Kinase Inhibitors Improve Heart Function and Prevent Fibrosis in Cardiomyopathy Caused by Mutation n Lamin A/C Gene. Circulation2011;123:53-61.

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