Dear Colleagues,

Dear Members of the Working Group,

Please find enclosed the 33rd issue of our Newsletter.

I’d also like to draw your attention to the link

http://www.escardio.org/communities/Working-Groups/cmp/education/meeting-resources/Pages/Coruna-2010.aspx

by which you can access the presentations given at the annual congress of our working group (The Frontiers of Myocardial, Pericardial Disease and Ventricular Dysfunction) at A Coruña, Spain, September 30th- October 2nd 2010.

Tiina Heliö
The paper of the month:

**Desmosomal Mutations in Dilated Cardiomyopathy.**


**Presented by**

Dr Torsten B Rasmussen, Dr Tenna Gadgaard & Dr Jens Mogensen, Department of Cardiology, Aarhus University Hospital, Skejby, Denmark

**Summary**

Dilated cardiomyopathy, (DCM), is a heart muscle disease characterised by unexplained dilatation of the left ventricle, impaired systolic function and histological abnormalities dominated by myocardial fibrosis. The condition has an estimated prevalence of 1:2.500 and is a frequent cause of heart failure and cardiac transplantation in the young (1-3). Patients may experience severe disease complications including thromboembolic events and sudden death due to malignant arrhythmias.

The aetiology of DCM is poorly understood and appears to be very heterogeneous. Viral infections, autoimmune disease and toxic substances are believed to be causative in a proportion of DCM although definitive proof has often been difficult to obtain. Recent studies have suggested that DCM has a familial appearance in 30-50% of cases implying that genetic factors may play an important role in disease development in a substantial proportion of patients (3). More than 40 disease genes have been identified encoding proteins involved in a variety of cell functions ranging from force generation within the sarcomere to regulation of ion-channels. Most affected families present with a “pure” cardiac phenotype and in these families autosomal dominant transmission is most frequent followed by recessive and X-linked inheritance. Recent studies have suggested a particular severe disease expression in DCM patients carrying mutations in the gene for lamin A/C, encoding a nuclear enveloped protein, expressed in most human cells.

In the paper of the month the authors report the frequency of desmosomal protein gene mutations in a cohort of 100 unrelated DCM probands. Previous studies have identified mutations in the same genes in patients with arrhythmogenic right ventricle cardiomyopathy, (ARVC), which is a condition characterised by dilatation of the right ventricle, development of myocardial aneurysms, ventricular arrhythmias, and fibro-fatty replacement of myocytes. Since some ARVC patients present with biventricular disease the authors hypothesized that desmosomal gene mutations may also be associated with DCM (4). All patients in the current study fulfilled diagnostic criteria of DCM without any signs of ARVC. Five mutations were identified in 5 probands in addition to sequence variants of uncertain pathogenic significance in an additional 13 probands. Relatives were available for clinical and genetic investigations in 2 families in which a total of 6 mutation carriers presented with a heterogeneous disease expression.

This paper is the first to report that desmosomal gene mutations are responsible for a significant proportion of DCM and not only restricted to be the causative agent in ARVC. The results illustrate that genetic investigations have provided important knowledge about the aetiology of hereditary cardiac conditions and underscores that mutations in the same gene may lead to a variety of different cardiac conditions and manifestations. In addition to the disease associated mutations reported a fairly large
number of sequence variations within the genes investigated were identified. However due to the limited number of affected individuals available for the study it was not possible to establish if these variations were disease associated which illustrates the difficulties in how to interpret the results of the genetic investigations. The authors rightfully argue that a conservative approach is preferable and that additional affected individuals carrying identical mutations should be available before sequence variants should be used for genetic counselling.

The paper illustrates some of the challenges we are facing in genetic diagnosis of hereditary conditions in the years to come not least due to the rapid development in gene technology. Next Generation Sequencing, (NGS), platforms have been developed enabling large-scale genotyping of many disease genes, very quickly and at low costs (5;6). The amount of data created by NGS is tremendous and skilful staff in bioinformatics is required with powerful computers to investigate which sequence variants are likely to be disease associated and may have an impact on disease expression. In this context the establishment of European registers gathering genotype-phenotype information is becoming increasingly important in order to provide solid evidence of whether sequence variations are likely to be disease associated or not. Such registers will contribute to create a more solid basis for counselling affected families in the future.

References


A 37- year old woman with a 5-year history of treated hypothyreosis was admitted to the local hospital for shortness of breath. Echocardiographic examination revealed non-dilated left ventricle (LV) with moderate systolic dysfunction (ejection fraction 35%). Coronary angiography excluded any coronary artery pathology and the patient was treated as a new-onset heart failure due to non-ischemic dilated cardiomyopathy, possibly acute myocarditis. Within 3 weeks of therapy including ACE-inhibitor, diuretics and beta-blocker she felt much better. Echocardiography showed recovery of the LV systolic function with calculated ejection fraction 56%. However, after 5 weeks she again started to suffer from progressive dyspnea with worsening of the LV systolic function as documented by echocardiography. Based on these findings she has been referred to our department for further thorough evaluation of the etiology of the LV dysfunction.

Upon admission the patient was haemodynamically stable, with blood pressure of 120/70 mmHg and heart rate of 60 beats/min. Apart from obesity no other abnormality was revealed by physical examination. Her family history was not suggestive of familiar cardiomyopathy.

**Fig. 1.**

ECG showed sinus rhythm with normal PQ and QT intervals, low voltage in limb leads and negative T waves in leads I, II, aVL, V5, V6.
Fig. 2. Echocardiographic examination demonstrated diffuse LV hypokinesis with moderate systolic dysfunction (ejection fraction 40%).

The LV was mildly dilated with end-diastolic diameter of 61mm. The left atrium was also mildly dilated (33ml/m²), while the right chambers were of normal size. There were no moderate or severe valvular abnormalities. Pulmonary artery systolic pressure was not elevated. Pericardial effusion was not detected. Chest X-ray revealed no abnormality. Laboratory examinations showed elevated erythrocyte sedimentation rate (FW 64 mm/h) and mild increase in CRP (24mg/l). Troponin I was mildly elevated (0,18ug/l) and CK level was in a normal range. Minerals, glucose, urea, creatinine, liver enzymes and thyroid hormones were normal. A mild elevation of B-type natriuretic peptide was observed (414 ng/l). Blood count was normal. Serological tests for Borrelia burgdorferi, HIV and for hepatitis A, B and C were negative.

Cardiac MRI examination confirmed the presence of diffuse hypokinesis of the mildly dilated LV with ejection fraction 42%. T2-weighted imaging did not reveal signs of myocardial oedema. Late gadolinium enhancement (LGE) was present in midwall of the middle part of the interventricular septum and anterolateral wall of the LV, some LGE could be found also in the basal part of the anterolateral papillary muscle (Figure 3).

Fig. 3. Cardiac MRI of the patient.

QUESTIONS

1) Can we make the final diagnosis based on the above cited results?
2) If not, which examination would you recommend to perform further?

Answers will be given in the next newsletter and on the web site.
Answer for the previous “Clinical case of the month” presented in February issue

Low Voltage ECG, a spot-diagnosis?

Authors: Cathelijne Dickhoff and Yigal Pinto

Question 1: What could be the differential diagnosis in this patient?

Answer: The ECG pattern with microvoltages can be concordant with several clinical circumstances. It is seen with extreme obesity, pericardial effusion, myocarditis, massive ischemia or myocardial infarction, but none of these conditions were present in this patient. It can also be seen in cardiac amyloidosis and other metabolic or storage disorders, however in this patient there are no laboratory anomalies, normal systolic function, no signs of restrictive CMP on echocardiography, and in the case of amyloidosis one would expect more widespread heterogeneous myocardial enhancement with other supporting features of infiltrative myocardial disease on MRI. Rare endocrine disorders that can cause microvoltage ECG like myxoedema are excluded by normal lab results.

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

Answer: Patient has clearly pathological ventricular tachycardias and a family history of sudden death. Having excluded all above mentioned possibilities using standard medical examination to explain these tachycardias, there is rationale to perform genetic testing. Mutations in the lamin A/C gene, SCN5A, genes associated with ARVC can be considered. In addition, sympathetic activity seems to trigger the non-sustained VTs. This could suggest mutations in cardiac ryanodine receptor and calsequestrin 2, that have been associated with exercise related ventricular tachycardias. However, the clear microvoltage ECG suggests a mutation in the phospholamban (PLN) gene (ref 1). Indeed, genetic testing revealed that our patient is heterozygous for a c.40_42del (pArg14del) mutation in the gene encoding PLN, a transmembrane protein that, in its dephosphorylated state, inhibits the sarcoplasmic reticulum calcium ATPase (SERCA2a). Deletion of PLN Arg-14 (PLN-R14Del) is associated with inherited human DCM and premature death. Some of the heterozygous individuals develop mild left ventricular dilation and dysfunction with frequent ventricular extra systolic beats and ventricular tachycardia episodes, leading to progressive left ventricular dilatation and heart failure.

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

Answer: The most striking phenotype among PLN-R14Del carriers is the attenuated R amplitude on ECG. The fact that these features are not observed in relatives negative for the mutation indicates a mutation-associated phenotype irrespective of the presence or absence of echocardiographic abnormalities. Significant QRS amplitude attenuations are related to left ventricular late gadolinium enhancement in cardiac magnetic resonance imaging study. Therefore, cardiac fibrosis may represent the electro-anatomic substrate for low R amplitudes. Cardiac fibrosis and scar tissue are common findings in patients with DCM and are mainly considered secondary phenomena. However, in this patient there is preserved cardiac function together with significant late gadolinium enhancement. The early presence of cardiac fibrosis in the absence of cardiac dysfunction would make fibrosis as a secondary process in reaction to loss of...
cardiomyocytes less likely. In contrast, PLN mutations seem to trigger primary cardiac fibrosis ultimately leading to heart failure or arrhythmias.

**Question 4: How would you treat the patient?**

**Answer:**
The pathophysiology of mutations in PLN, as those in cardiac ryanodine receptor and calsequestrin 2 are most likely related to disturbed calcium homeostasis in the ventricular myocyte. The relation to exercise suggests disturbances that are under influence of sympathetic activity, which is known to modulate calcium trafficking in the cardiac myocyte. Therefore, beta-blockade seems quite rational. At the time of presentation at our department the patient was already on beta blockers and indeed this was quite effective as there were no long NSVTs any more. Holter monitoring now only showed solitary monomorphic PVB with LBBB configuration, originating from the RVOT (Fig.1). An ICD is not indicated as there is no syncope, preserved left ventricular ejection fraction, no more NSVTs under beta-blockade and normal left ventricular dimensions.

![Fig. 1 Holterregistration while patient is on betablockers](image)

**References:**


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


