European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 27 – August 2010

Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

INSIDE THIS ISSUE:

Editorial News

Dear Members of the Working Group,

please find enclosed the 27th 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 case resolution from the July case.

On the last page of the newsletter you will find some recommendations for further reading with a list a recently published papers in the field of our WG……

Best wishes for all of you.

S. Pankuweit

The paper of the month:

Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy

O'Hanlon, R., A. Grasso, M. Roughton, J.C. Moon, S. Clark, R. Wage, J. Webb, M. Kulkarni, D. Dawson, L. Sulaibeekh, B. Chandrasekaran, C. Bucciarelli-Ducci, F. Pasquale, M.R. Cowie, W.J. McKenna, M.N. Sheppard, P.M. Elliott, D.J. Pennell, S.K. Prasad. J Am Coll Cardiol 2010;56 (E paper ahead)

Presented by Dr. Barbara Pfeiffer and Prof. Dr. Hubert Seggewiss, Medizinische Klinik 1, Leopoldina Krankenhaus Schweinfurt, Germany

Summary

One of the major challenges in the clinical management of patients with hypertrophic cardiomyopathy (HCM) is the identification and treatment of the small number of individuals prone to serious events. The impact of new technologies for answering these problems is unclear. O'Hanlon et al. report on the significance of fibrosis detected by late gadolinium enhancement cardiovascular magnetic resonance for the prediction of major clinical events in HCM (7).

In this prospective study the authors analyzed the development of morbidity and mortality with respect to the presence and amount of myocardial fibrosis in 217 consecutive HCM patients with a mean follow-up of 3.1 ± 1.7 years. The pre-specified primary end point was the composite of cardiovascular death, unplanned cardiovascular hospital stay, sustained ventricular tachycardia or ventricular fibrillation, or appropriate implantable cardioverter-defibrillator (ICD) discharge. Two separate secondary end points were predefined. A composite heart failure (HF) end point included unplanned HF hospital stay, progression to New York Heart Association (NYHA) functional class III or IV status, or HF-related death. A composite arrhythmic end point included sustained ventricular tachycardia or ventricular fibrillation, appropriate ICD discharge, or SCD.

136 out of 217 patients (63%) showed fibrosis. In this group the mean percentage of fibrosis was 15.5% (range 1.4% to 54.9%). The analyzes of the conventional risk factors for SCD showed in the fibrosis group a greater percentage of patients with maximal wall thickness >30 mm (8.8% vs. 0%; p=0.0006) and non-sustained VT (11.8% vs. 3.7%; p=0.04) whereas no significant difference was seen in patients with family history of SCD (14.0% vs. 7.4%; p=0.14) and syncope (16.9% vs. 14.8%). The authors did not give results of abnormal blood pressure response during exercise. Overall, the proportion patients with 2 or more risk factors for SCD was higher in the fibrosis group (19.1% vs. 8.6%). No difference was seen in the proportion of patients with rest LVOTO > 30 mmHg (28.7% of patients in the fibrosis group vs. 22.2%; p=0.30) – the numbers of patients with provocable gradients are not given. Finally, the fibrosis group patients were more often symptomatic according to the NYHA classification (43.3% class II and 17.9% class III/IV vs. 34.6% class II and 7.4% class III/IV; p=0.01) and under medical treatment with betablocker (44.1% vs. 28.4%; p=0.02) and antiarrhythmics (16.9% vs. 7.4%; p=0.05).

Thirty-four of the 136 patients (25%) in the fibrosis group but only 6 of 81 (7.4%) patients without fibrosis reached the combined primary end point (hazard ratio [HR]: 3.4, p=0.006). Analyzing the single endpoints a significant difference was seen in the percentage of unplanned cardiovascular hospital admission (17.7% in the fibrosis group vs. 6.2%; p=0.036) whereas no significant differences were seen in CV mortality (5.9% in the fibrosis group vs. 1.2%; p=0.163), VT/VF (5.9% vs. 1.2%; p=0.131), and ICD discharge (1.5% in the fibrosis group vs. 0%).

In the fibrosis group, the overall risk of the primary end point increased with the percentage of fibrosis present (HR: 1.18/5% fibrosis increase, 95% CI: 1.05 to 1.33, p=0.008). Every 5% increase in fibrosis increased the risk of reaching the combined primary endpoint by 15%.

A composite secondary HF endpoint was more often seen in the fibrosis group (24.5% vs. 9.9%; HR: 2.5, p= 0.021), and this risk increased as the extent of fibrosis increased (HR: 1.16/5% increase, p=0.017). All relationships remained significant after multivariate analysis. LAVi (HR: 1.021, 95% CI: 1.01 to 1.03, p<0.001) and LVOTO >30 mmHg (HR: 2.45, 95% CI: 1.2 to 4.9, p<0.013) are independently associated with HF endpoints, too.

A composite arrhythmogenic endpoint showed no significant increase in the fibrosis group (7.3% vs. 2.5%; HR: 3.15, 95% CI: 0.69-14.4, p=0.138). The extent of fibrosis (HR: 1.30, 95% CI: 1.05 to 1.61, p=0.014) and non-sustained ventricular tachycardia were univariate predictors for arrhythmic end points (sustained ventricular tachycardia or ventricular fibrillation, appropriate implantable cardioverter-defibrillator discharge, sudden cardiac death). Non-sustained ventricular tachycardia remained an independent predictor of arrhythmic end points after multivariate analysis, but the extent of fibrosis did not.

Comments

Therapeutic goals in the treatment of patients with HCM are prevention of cardiovascular (CV) and especially sudden cardiac death (SCD) on the one hand and improvement of clinical symptoms on the other hand. It has been shown by Maron et al. (4) that sudden cardiac death is the predominant mode of HCM related death in younger patients (mean age 45 ± 20 years) whereas heart failure causes mortality in elderly HCM patients (mean age 56 ± 19 years) and stroke is the main mode of HCM death in old patients (mean age 73 ± 14 years), mainly due to development of atrial fibrillation.

Furthermore, Varnava et al. could show in a post-mortem study of 75 HCM deaths that fibrosis was related to an increase of heart failure and non-sustained VT, whereas myocardial disarray was linked to premature death, SCD, and abnormal blood pressure response during exercise (9).

Since the introduction of late gadolinium enhancement (LGE) in MRI for the diagnosis of scar/fibrosis in patients with HCM there had been conflicting data about the use of LGE as a new risk factor of SCD in addition to the standard clinical risk stratification model of Elliott et al. (2). In the last months 3 papers discussing this conflict had been published (1,7,8).

O´Hanlon et al. used MRI guided diagnosis of fibrosis by late gadolinium enhancement in order to estimate the prognostic significance (7). The authors excluded patients with gradient-reduction therapies in contrast to Rubinshtein et al. (8). No study gave an exact description of the clinical risk factors according to the mentioned model (2).

Cardiovascular mortality: There was low risk of SCD during follow-up without significant difference with respect to the detection of fibrosis, whereas there was a trend towards a higher incidence of total cardiovascular mortality due to heart failure death (7). These results confirm the study of Varnava et al. (9). Taking into account the mean age of O'Hanlon's study (51.1 years) the findings correspond to the study of Maron et al. (4) who reported that heart failure death was more often found in elderly HCM patients. Rubinshtein at al. (8) and Bruder at al. (1) reported on higher incidence of SCD in patients with LGE. But, Mayo clinic data included gradient-reduction therapy in half of the patients (7). The given data of Bruder et al. are inconsistent with 1 observed SCD in the non-LGE group which is ignored in the published figures (1).

Fibrosis has been shown as the extract for promoting re-entrant ventricular arrhythmias and increased ventricular stiffness. O'Hanlon found more arrhythmogenic events in the fibrosis group but the data are not significant probably caused by the small cohort (7). Due to that result the authors point out that at present the presence or amount of fibrosis do not support the routine deployment of an ICD.

Disease progression: O'Hanlon et al. describe that myocardial fibrosis is an independent predictor of adverse outcome including heart failure (7). The main difference between patients with and without fibrosis is the higher incidence of unplanned cardiovascular hospital stay, heart failure with NYHA class III and IV, and heart failure death. Both the presence and the amount of fibrosis are of independent prognostic significance. Serial studies could show whether the amount of fibrosis would increase over time with increasing risk for HF.

LVOT-Obstruction. In addition to the clinical risk stratification model it has been shown that LVOT-obstruction has negative impact on disease progression and survival (3). Including provocation maneuvers up to 70% of the HCM patients suffer from significant obstruction (5,6). Therefore, the non-use of provoking maneuvers in the baseline examinations and the low rate of resting obstruction (26.3%) is a disadvantage of the study (7). The 2 further papers (1,8) gave also no exact information about obstruction. The Mayo group did not describe the proportion of patient with and without obstruction (8), whereas Bruder et al. did not include the information of the type of obstruction (resting/provocable) (1).

Summarizing, a prospective observational study which includes all factors of the clinical risk stratification model (2), the presence of resting and provocable obstruction, prior gradient-reduction therapies as well as the clinical symptoms of the patients, and LGE is necessary in order to define the prognostic role of MRI findings in HCM. Until this study is performed we would support the statement of the paper of O´Hanlon et al. (7) that a routine deployment of an ICD on the basis of the presence or amount of fibrosis per se is not supported by the present data.

References

1. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, Nassenstein K, Schlosser T, Sabin GV, Sechtem U, Mahrholdt H. Myocardial Scar Visualized by Cardiovascular Magnetic Resonance Imaging Predicts Major Adverse Events in Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2010 Jun 16. [Epub ahead of print]
2. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212–2218, 2000
3. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy; E Heart J 27:1933–1941, 2006
4. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy–related death revisited in a large non–referral-based patient population. Circulation 102:858-864, 2000
5. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 114: 2232-2239, 2006
6. Neugebauer A, Pfeiffer B, Rigopoulos A, McKenna W, Dickie S, Wagner G, Ommen SR, Seggewiss H. Klinische Charakteristik von Patienten mit Hypertropher Kardiomyopathie: Eine vergleichende Analyse an 3 Referenzzentren. Clin Res Cardiol 97 (Suppl 1), 2008
7. O'Hanlon, R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56 (E paper ahead)
8. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, Bos JM, Tajik AJ, Valeti US, Nishimura RA, Gersh BJ. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 3:51-58, 2010
9. Varnava AM, Elliott PM, Mahon N, Davies MJ, McKenna WJ. Relation Between Myocyte Disarray and Outcome in Hypertrophic Cardiomyopathy, Am J Cardiol 88:275-279, 2001

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

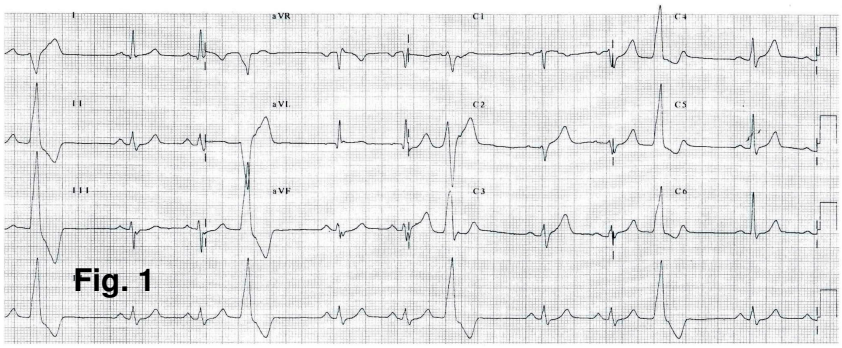
Answers will be given in the next newsletter and on the web site

Presented by Diego A. García and Lorenzo Monserrat
Cardiology Department.
Instituto de Investigación Biomédica and Complejo Hospitalario, Universitario de A Coruña. Spain

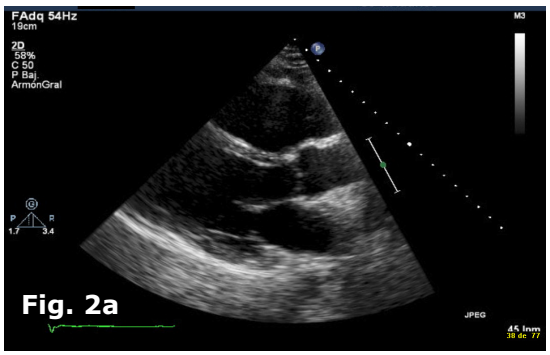
A 46 year-old man with right ventricular dilatation

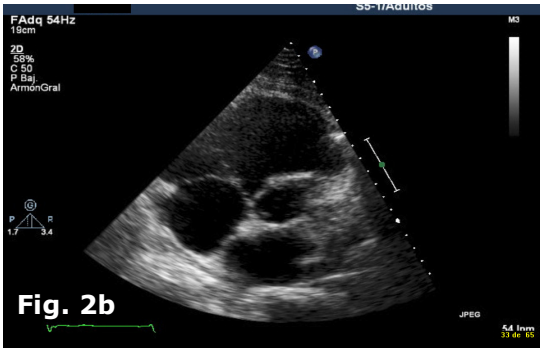
Case Presentation:

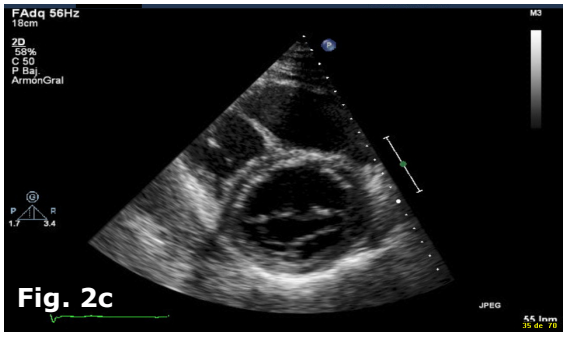
A 46- year-old man was admitted on April 2005 due to atypical chest pain not effort related. He was asymptomatic until 3 months before admission when he presented with exertional dypsnea (class II NYHA), several episodes of atypical chest pain and palpitations. Physical examination was normal. The ECG (fig. 1) showed sinus rhythm, left anterior hemiblock and frequent monofocal ventricular premature beats that could be originated from the right ventricular outflow tract.

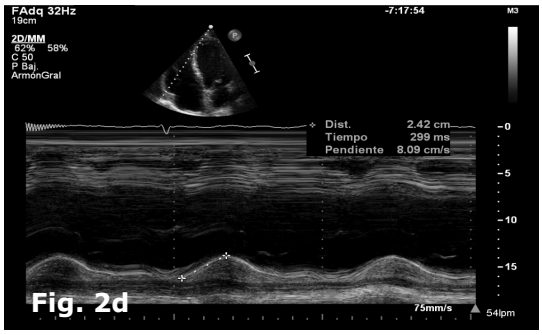


The echocardiogram showed a slightly dilated left ventricle with an end-diastolic diameter of 57mm. The interventricular septal thickness was 9 mm, and the left ventricular posterior wall thickness was 10 mm (Fig 2a). The left ventricular ejection fraction was 45%. The right ventricle was markedly dilated (fig 2 b, fig 2c) with an end-diastolic diameter of 50mm and a normal systolic function (TAPSE 24mm, fig. 2d). Both atria were dilated with a left atrial diameter of 45 mm. A moderate tricuspid regurgitation was observed and the pulmonary pressure was slightly increased. The atrial septum was intact.









At this time, a pulmonary thromboembolism (PE) was suspected, thus a Computerized Tomographic Pulmonary Angiography and a thoracic CT were performed. PE was discarded and it was evidenced a repletion defect in the superior vena cava that might be produced by a "vascular steal" phenomenon. The exercise stress echocardiogram following the Bruce protocol lasted 4.4 minutes, reached 97% of the predicted maximum heart rate and 10 METS. It was negative for ischemia and showed an abnormal relaxation pattern at rest and during exercise.

Family history was remarkable. His 78 year-old father had exertional dypsnea (class II NYHA). Past medical history revealed the presence of several syncopal episodes beginning at 18 years old and episodes of atypical chest pain in the last ten years. The patient had hypertension and presented chronic atrial fibrillation. The echocardiogram showed a slightly dilated left ventricle (end-diastolic diameter 56mm) with global hypokinesia and an ejection fraction of 44%. The right ventricle was slightly dilated with normal systolic function. The aortic valve showed leaflets calcification and a grade III/IV aortic regurgitation was observed. Myocardial ischaemia was discarded by stress echocardiography.

The proband's paternal grandfather had died suddenly at 32 years-old. No further details were available. The patient's mother was unaffected.

After initial evaluation, the proband was referred to our centre due to a suspected familial cardiomyopathy.

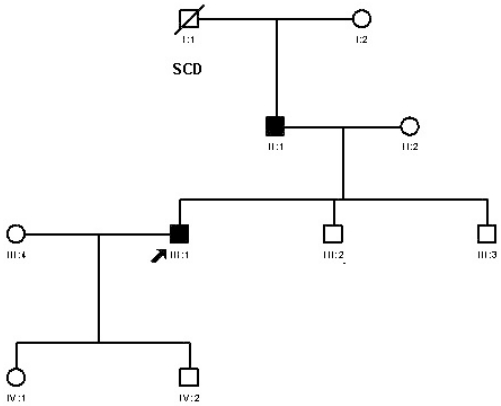


Fig 3. Family pedigree.

At this moment only patients III.1(proband), II: 1 and II: 2 had been clinically evaluated

QUESTIONS

- **What would be the differential diagnosis in this patient?**
- **What would be the diagnostic strategy that you propose?**

Answer for the previous "Clinical case of the month" presented in July

"Confounding presentation phenotype in familial cardiomyopathy"

By F.I. Gambarin, A. Serio, M. Pasotti, L. Tavazzi*, E. Arbustini. Centre for Inherited Cardiovascular, Diseases, Molecular Diagnostic Laboratory, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy *Research Unit, GVM Care and Research, Cotignola, Italy

(This material is original; it has not previously published and is part of a research on Hypertrophic Cardiomyopathies supported by funds from Cariplo Foundation and Health Ministry granted to EA).

Recapitulation about the diagnostic work-up

The patient was first addressed to our attention with the specific request of discriminating between two possible diagnosis: amyloidosis *vs.* storage disease (Anderson Fabry Disease).

1. Amyloidosis

   We excluded this diagnostic possibility *ab initio* for more than one reason, on the basis of hystoric data and of instrumental data:

   - the proband is 42 years old; the age by itself does not exclude the diagnosis of amyloidosis but makes it unlikely especially because the clinical history dates back years before our evaluation
   - there were no K or L light chain bands; Bence Jones protein was absent;
   - both parents are healthy, with normal cardiac and renal function;
   - the echocardiogram recorded on July 31st, 2009 showed severe left ventricular dilation with normal LV wall thickness;
   - the ECG registered at our Centre on July 31st, 2009 (see figure 1 of case presentation) showed positive Sokolow-Lyon criteria for LV hypertrophy.

2. Storage disease (in particular, Anderson-Fabry disease)

   The diagnosis of Anderson-Fabry disease was unlikely because of severe LV dilation, hypokinesia, absence of hypertrophy, absence of extracardiac features of the disease. Nonetheless, due to the specific request of colleagues who addressed the patient to our attention we tested plasma dosage of alpha-galactosidase A activity, which resulted in the normal range.

The patient underwent EMB as per routine in potential candidates to HTx. The following characteristics of the proband could be considered for a *Dystrophn* defect:

1. the severe LV dilation associated with severe systolic dysfunction
2. the presence of T waves modification on ECG in the inferior and lateral leads (see figure 1 of case presentation)
3. the biochemistry abnormalities such as the mild CK and CK-MB increase and the more evident Troponin I increase (see Biochemistry table of the proband in the case presentation).
4. the absence of male-to male transmission of the disease in the family. Before family screening and genetic testing we couldn't exclude X-linked inheritance.

The endomyocardial biopsy showed normal dystrophin immunostain.

Family screening

1. The younger brother of the proband showed hypertrophic phenotype (both on echocardiography and on CMR imaging); this finding empowered the hypothesis that the diagnosis in the family was HCM, still typical in the brother but evolved through dilatation and dysfunction in the proband.

   The younger brother shared with the proband biochemical abnormalities (see Biochemistry table of the proband's brother in the case presentation) and other characteristics in ECG and echocardiography, confirming that the cardiomyopathy was familial.
2. Parents: both mother and father underwent clinical screening (ecg, echo, biochemical testing) that gave negative results: in fact the father showed confounding hypertension and a max wall thickness of 10 mm.
3. The oldest brother showed normal echocardiographic and ECG, normal biochemical data with the exception of very mild increase of lactic acid values (27.1 mg/dl, normal laboratory range 5.7 – 22 mg/dl).

Considering the HCM hypothesis as the most likely, we tested sarcomeric gene associated with HCM and we found a mutation in *MYBPC3* gene, reported as associated with HCM[1].
The genetic cascade screening did not confirm the segregation of the mutation with the phenotype in the family because the carrier father showed normal ECG and echocariographic findings, as well as normal biochemical indexes. The mother tested negative. (Figure 1).

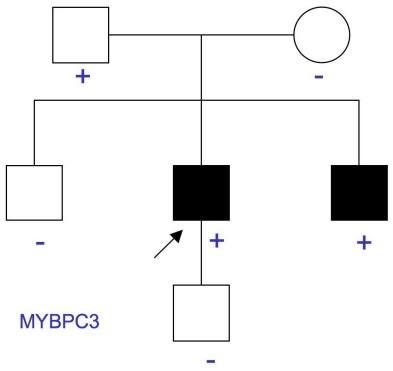


***Figure 1*. Family pedigree**

+ = genetic test positive for the MYBPC3 mutation found in the proband;

- = genetic test negative for the MYBPC3 mutation found in the proband.

Further considerations about the genetic mutation found and the clinical phenotype

The *MYBPC3* mutation is described as causative mutation [1]. *MYBPC3* is known as one of the most frequently involved sarcomeric genes in familial hypertrophic cardiomyopathy characterised by moderate hypertrophy of the left ventricle, with progressive development of hypertrophy and late onset of symptoms [2].

In our family however, the proband came to our attention with a dilated phenotype and LV dysfunction. The younger brother showed mild asymmetrical hypertrophy, with evidence of concomitant hypokinesia and early LV dilation. The father was "healthy" carrier of the *MYBPC3* mutation at the age of 74 years. He only showed LV wall thickness at the upper-normal range (10 mm, concentric) with a confounding history of arterial hypertension.

The echocardiographic study in mother, who had negative *MYBPC3* test, showed septal thickness of 10 mm, posterior wall of 9 mm, and impaired left ventricular diastolic function.

Due to the lack of segregation of the mutation with the phenotype in the family, we completed the screening of sarcomeric genes that gave negative results. The presence of minimal lactic acidosis in the oldest brother, the coexistance of DCM and HCM phenotype in two affetcted members of the same generation and the potential matrilineal inheritance led to the analysis of mtDNA.

Progression through the case resolution

We identified a mtDNA mutation, known to be associated with cardiomyopathy, which was transmitted from the mother to the three sons (figure 2).

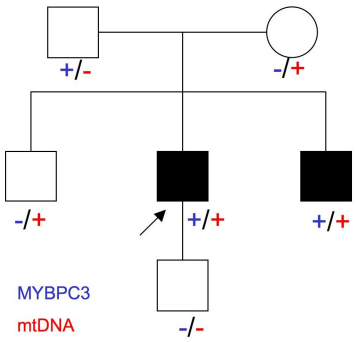


***Figure 2*. Family pedigree**

+ = genetic test positive;
- = genetic test negative
(red: mtDNA mutation; blue: MYBPC3 mutation)

We interpret these data as suggestive of HCM (*MYBPC3*) evolving through DCM (*MtDNA*), with neither mutation sufficient by itself for causing the cardiomyopathy. The follow-up of the brothers with the double mutation will provide confirmation (or not) of this hypothesis.

References

1. Andersen PS, Havndrup O, Bundgaard H, Larsen LA, Vuust J, Pedersen AK, Kjeldsen K, Christiansen M Genetic and phenotypic characterization of mutations in myosin-binding protein C (MYBPC3) in 81 families with familial hypertrophic cardiomyopathy: total or partial haploinsufficiency. Eur J Hum Genet. 2004;12:673-7.

2. Andersen PS, Havndrup O, Bundgaard H, Moolman-Smook JC, Larsen LA, Mogensen J, Brink PA, Dupont Børglum A, Corfield VA, Kjeldsen K, Vuust J, Christiansen M. Myosin light chain mutations in familial hypertrophic cardiomyopathy: phenotypic presentation and frequency in Danish and South African populations. *JMG* 2001;38:*e*43

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

1) ***Severe cardiac conduction disturbances and pacemaker implantation in patients with hypertrophic cardiomyopathy***.
Barriales-Villa R, Centurión-Inda R, Fernández-Fernández X, Ortiz MF, Pérez-Alvarez L, Rodríguez García I, Hermida-Prieto M, Monserrat L. Rev Esp Cardiol. 2010 Aug;63(8):985-8

2) ***Arrhythmia and right heart disease: from genetic basis to clinical practice***.
Capulzini L, Brugada P, Brugada J, Brugada R. Rev Esp Cardiol. 2010 Aug;63(8):963-83

3) ***Survival Following Cardiac Transplantation in Patients with Hypertrophic Cardiomyopathy.***
Maron MS, Kalsmith BM, Udelson JE, Li W, Denofrio D. Circ Heart Fail. 2010 Aug 24

4) ***Prevalence of desmosomal protein gene mutations in patients with dilated cardiomyopathy.***
Elliott P, O'Mahony C, Syrris P, Evans A, Rivera Sorensen C, Sheppard MN, Carr-White G, Pantazis A, McKenna WJ. Circ Cardiovasc Genet. 2010 Aug;3(4):314-22

5) ***Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance.***
Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, Hill S, Mahrholdt H, Voehringer M, Schieber M, Klingel K, Kandolf R, Böhm M, Sechtem U. Circulation. 2010 Aug 31;122(9):900-9.

6) ***Novel missense mutations in exon 15 of desmoglein-2: Role of the intracellular cadherin segment in arrhythmogenic right ventricular cardiomyopathy?***
Gehmlich K, Asimaki A, Cahill T, Ehler E, Syrris P, Zachara E, Re F, Avella A, Monserrat L, Saffitz JE, McKenna WJ. Heart Rhythm. 2010 Aug 11.

7) ***HMGB1: the missing link between diabetes mellitus and heart failure.***
Volz HC, Seidel C, Laohachewin D, Kaya Z, Müller OJ, Pleger ST, Lasitschka F, Bianchi ME, Remppis A, Bierhaus A, Katus HA, Andrassy M. Basic Res Cardiol. 2010 Aug 12

8) ***COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial.***
Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, Ferrua S, Maestroni S, Zingarelli E, Barosi A, Simon C, Sansone F, Patrini D, Vitali E, Ferrazzi P, Spodick DH, Adler Y; on behalf of the COPPS Investigators. Eur Heart J. 2010 Aug 30.