International Journal of Biomedicine 1(3) (2011) 139-142

INTERNATIONAL JOURNAL OF BIOMEDICINE

Clinical Research

Features of the Clinical Courses and Life Prognosis of Patients with the Familial Form of Dilated Cardiomyopathy

Nuraly A. Kurbanov, PhD*, Temur A. Abdullaev, PhD, ScD, Ravshanbek D. Kurbanov PhD, ScD

Republican Specialized Center of Cardiology, Tashkent, Uzbekistan

Abstract

Purpose: To study the prevalence, clinical hemodynamic characteristics and long-term prognosis of patients with the familial form of DCM. **Material and methods:** Over the period between 2000 and 2009, 221 patients with DCM were examined. Of these, 27 (12.2% of 221) cases of familial cardiomyopathy were diagnosed, based on anamnesis and clinical-functional examination. Subsequently, for comparative assessment, two groups were identified: Group I had 27 patients with familial DCM and Group II included 77 patients with the sporadic form. All the patients underwent ECG, ECG by Holter, a 6-minute walking test, roentgencardiometry, coronary angiography and their life prognosis were estimated. **Results:** In this study, it was established that the prevalence of familial DCM totaled to 12.2% versus the non-familial form, was associated with a much younger age group, in 1/3 cases was transmitted through the maternal line, and some patients were characterized by atrioventricular heart block. **Conclusion:** An analysis of near-term prognosis of the patients has revealed that the familial form and age below 30 years are associated with a rapid progression of the clinical course, coupled with increasing mortality in the first 12 months of follow-up. IJBM 2011; 1(3):139—142.

Key words: *familial form of DCM, prevalence, clinical-hemodynamic characteristics, prognosis.*

Introduction

Several studies over the last ten years were dedicated to an etiopathogenetic study of dilated cardiomyopathy (DCM) and different hypotheses were examined from this stand point. According to the new etiological classification (AAC, 2006), primary cardiomyopathies are distinguishable into three groups: genetic, compound and acquired [11]. DCM is related to the compound group; i. e. it can be genetic (familial) or show a non-genetic basis of development [6].

The overall reported prevalence of the DCM familial type ranges from 2% to 56% of the cases. At the same time, some authors report that an examination with family anamnesis found not less than 35% of patients [4, 5, 7]. The discrepancies resulting from the different approaches to family study are pedigree construction on index patient interview [17], clinical examination of the relatives of suspected patients, based on pedigree, to possess the familial form [4]. In addition, this prospective study was set up to assess the prevalence of familial dilated cardiomyopathy by evaluating the patterns of inheritance characterizing the clinical phenotypes and diagnosing early asymptomatic or pre-clinical disease in the relatives of the index patients.

The objective of this investigation is to study the prevalence, clinical hemodynamic characteristics and long-term prognosis of patients with the familial form of DCM.

Methods

Over the period, from 2000 to 2009, 221 patients with DCM, in the age group between 17 and 61 (mean age 41.9±0.6) years, were examined. DCM diagnosis was made according to WHO criteria, based on cardiomyopathy (1995) [8]. However, 27 (12.2% of 221) cases of familial cardiomyopathy were diagnosed based on anamnesis and clinical-functional examination. All the patients underwent

**Corresponding author: Nuraly A. Kurbanov, PhD, Republican Specialized Center of Cardiology, 4, Osiyo str., 100052, Tashkent, Uzbekistan.*

Tel: 998-97-3332812

ECG, ECG by Holter, a 6-minute walking test, roentgencardiometry, coronary angiography and had their life prognosis estimated. They also underwent testing of their close relatives (brother and sisters of the proband). Dilated cardiomyopathy is regarded familial when it occurs in two or more related family members or is seen in a relative experiencing unexpected sudden death, before the age of 35 [2]. The familial form of DCM has been defined in 27 (12.2%) out of the 221 patients, seen from the results of anamnesis, clinical and instrumental measurements. Patients with the familial form of DCM were compared with a sample of the sporadic forms of DCM, randomly matched by year of enrolment in a 3:1 ratio.

Subsequently, for comparative assessment, 2 groups were identified: Group I with 27 patients with familial DCM and Group II with 77 patients having the sporadic form, based on the degree of severity of heart failure from the time of the first examination (Table 1).

Calculation of statistical data was performed using the statistical package «Biostatics for Windows, 4.03». The mean (M), standard deviation (SD), and mean-square error (m) were calculated. The magnitude of the variables was determined using Student's *t*-test. For analysis of the credibility of the variables among the qualitative measures, the χ^2 criterion was used. The variables were considered statistically credible when $p<0.05$. The data presented as M±m.

Table 1

Clinical-hemodynamic description of patients examined during the control period

Parameters	Family n=27	Sporadic n=77	p
Age at diagnosis, years (range)	36.2±2.1 (17-59)	42.6±1.3 (17-58)	<0.01
Male/female, %	62.9/37.1	80.6/19.4	NS
Duration of disease, months	9.1±1.6	12.3±1.5	NS
Average FC of CHF	3.1±0.2	3.3±0.1	NS
I-II	4 (14.8%)	11(14.3%)	NS
III-IV	23 (85.2%)	66 (85.7%)	NS
Distance, meter	244.8±19.9	207.3±10.4	NS
SBP, mm. Hg	107.9±5.8	112.9±2.3	NS
DBP, mm. Hg	70.8±2.9	74.5±1.6	NS
HR, b. p. m.	99.4±3.2	102.5±1.8	NS
CTI,%	63.2±1.1	63.4±1.5	NS

Results

During the comparative analysis variables were seen to show statistic credibility with patient mean age indices significant for the development of the familial form of the disease, at a relatively early age (Table 1).

The intensity of arterial hypotension is an indirect limitation of systolic dysfunction. This was observed in both groups, however, with hypotension not exceeding a blood pressure of 90/60 mmHg, which occurred quite frequently in the group with the familial form of DCM 11 (40.7%) and 15 (19.5%) patients, respectively (χ^2=3.7; p=0.05).

A comparative analysis of the ECG parameters revealed that first-degree atrioventricular heart block was observed, occurring with equal frequency in both the groups compared. (Table 2).

Table 2

Frequency of occurrence and type of cardiac rhythm abnormalities in DCM patients

Cardiac rhythm abnormalities	Groups		p
	I group (n=27)	II group (n=77)	
Atrial fibrillation, n (%)	8 (29.6%)	13 (16.8%)	NS
Including SR recovery, n (%)	-	5 (6.5%)	NS
1st degree AV block, n (%)	7 (25.9%)	20 (25.9%)	NS
Full AV block, n (%)	5 (18.5%)	1(1.3%)	<0.01
LBBB, n (%)	7 (25.9%)	29 (37.6%)	NS
RBBB, n (%)	4 (14.8%)	6 (7.8%)	NS
By Lown-Wolf, n (%) — IVA--IVB-	12 (44.4%) 7 (25.9%)	40 (51.9%) 17 (22.1%)	NS NS

Also, during subsequent observations, the group of patients with the non-familial form of DCM only 1 (1.3%) patient, 8 years later, evidenced an aggravation of complete atrioventricular heart block, whereas in the comparative group, during the course of two to five years (18.5%), 7 patients showed chronic heart failure growing progressively worse, and the atrioventricular heart block culminating in total blockage. Significantly, in all cases, complete atrioventricular heart block combined either with left bundle branch block (LBBB) or right bundle branch block (RBBB) was observed.

Significantly, in 12 (15.6%) patients of Group II having the permanent form of atrial fibrillation, sinus rhythm was restored in 4 (33.3%) cases, using the standard therapy of heart failure, whereas in the group of patients with the familial form, atrial fibrillation remained unchanged in all the cases.

A comparative analysis of the intracardiac hemodynamic studies showed noticeable differences between both the groups, as shown in Table 3. Particularly in II group an increase in the end-diastolic dimension (EDD) were observed in 4.2%, end-systolic dimension (ESD) in 6.5% (p=0.04), a decrease in ejection fraction in 12.1%.

In Group I, in 11 (40.7%) cases the disease was inherited the maternal line (in 5 families); in 6 (22.2%)

cases (in 3 families) and also genetically close relatives (brothers and sisters), and in the other 10 (37%) patients the

Table 3

Echocardiographic parameter features in patients with DCM

Indexes	Groups (M±m)		p
	Familial, n=27	Non-familial, n=77	
LVEDD, cm	7.04±0.1	7.4±0.1	NS
LVESD, cm	5.8±0.13	6.2±0.12	<0.05
LVEF, (%)	34.9±2.02	31.3±1.1	NS
LA, cm	4.5±0.12	4.7±0.09	NS
RV, cm	3.2±0.2	3.5±0.02	NS
VS, cm	0.9±0.04	1.03±0.03	<0.01
Posterior wall of LV, cm	0.97±0.03	1.09±0.03	<0.01

genealogical analysis of family anamnesis showed that at the least one of the family members died suddenly or from heart failure, with figures increasing in the age up to 35.

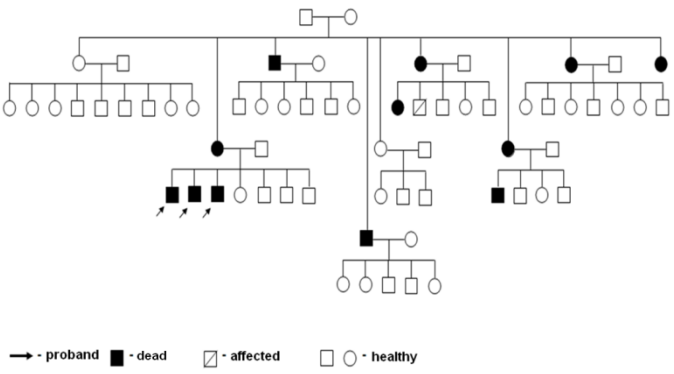
In this study, one pedigree of families with the familial form of DCM is presented:

Case:

DCM was diagnosed in 3 brothers, in the ages of 37, 36 and 33 years, who expired within 6, 8 and 15 months of observation, respectively, due to the development of refractory heart failure (Fig. 1). On closer examination, it became evident that over 3 generations, 7 out of 9 children had also died because of the development of sudden death at a younger age or heart failure that grew progressively worse. In addition, in more than 75% cases the disease was inherited through the maternal line.

Figure 1

Genealogical tree of patient with family form of DCM



The results of nearest patient's life prognosis with the familial form of disease, at the end of a 1-year observation period, were revealed to be12 (44.4%) fatal cases. At the same time, it was established that in the presence of the familial form of DCM, the age below 30 years appeared to be the negative prognosis predictor. Significantly, the frequency of fatal outcomes in these patients constituted 7 (87.5%) out of 8 cases (middle age 20.8±0.8 years), whereas in the cohort 30 years and older, death occurred in 4 (21.05%) out of 19 patients (middle age 40.8±1.03 years) (χ^2=7.7; p=0.005).

At the same time, in group II registered 17 (22.1%) fatal outcomes from 77 patients during the first year, which was less than the group of patients with the familial form of DCM (p=0.05;χ^2=3.9). The fatal outcome was established at 6 (54.5%) out of 11 patients below 30 years, while patients older than 30 years registered 11 (16.6%) death cases out of 66 patients (χ^2=5.8; p=0.016).

A study of patient life prognosis on a long-term observation basis revealed that fatality in Group I constituted 74.1% (20 patients), of which 12 (60%) cases grew progressively worse with heart failure or developing adiaphoria to treatment; in 5 (25%) cases, death occurred suddenly in the face of good health, resulting from the development of acute cardiac abnormalities, whereas in 2 (10%) cases it occurred against background of heart failure, increasing with the development of pulmonary embolism (PE); and in 1 (5%) case the patient died due to cerebral thromboembolism with development of ischemic stroke. In Group II 56 (72.7%) cases of fatal outcomes (χ^2=0.01; p=0.9) were registered, while the number of patients who suddenly died and also those who succumbed to increasing heart failure constituted 13 (23.2%) and 41 (73.2%) from PE and stroke 1 (1.8%) and 1 (1.8%), respectively.

Discussion

By screening all the relatives with informed consent, of the 221 consecutive index patients diagnosed with DCM, a prevalence of 12.2% of evidence-based familial disease was obtained. Similar prevalence values were reported in family studies in which the relatives of all the index patients were examined, independent of their informed histories or pedigrees [4]. Prevalence of the familial form of DCM was around 20% of the entire DCM population by the Italian research data presented by M. Moretti et al., Trieste city, from 1988 to 2007 [10], while Grunig et al., enrolled a large number of patients and screened family members on a potentially informative pedigree [5]. The first symptoms of the disease in patients with the familial form were observed at a much younger age than in patients without an overburdened family history, from the results of our study (Table 1). From the M. Moretti et al., study [10] this data constituted 40±16 against 47±13 years, respectively, (all p<0.01), whereas A. Gavazzi et al., in his study [15] has not shown differences between the groups based on age (42±13.4 and 44.6±10.5 years).

In the clinical presentation of desmins cardiomyopathies, AV conduction disorders appeared in the foreground, which rapidly grew progressively worse, leading to complete atrioventricular heart block. This was in line with the study by D. Li et al., [12] and E. Arbustini et al., [3]. The results of our study concurred in many respects with the data mentioned above. First, the frequency of the complete atrioventricular heart block should be noted in 5 patients with the familial form of DCM.

Three cases of familial dilated cardiomyopathy with early atrioventricular block and LBBB were identified, similar to the results reported by E. Grunig et al., [5] and in one family reported by Mestroni et al. [7]. These rare cases, first reported in some families in Ohio [16], appear to differ

from other dilated cardiomyopathies, given the long interval between the appearance of the atrioventricular block and DCM.

During nearest patients' life prognosis study with the familial form of DCM, attention was drawn to the pernicious juvenile familial form of DCM in 7 young patients included in the investigation, who died due to refractory heart failure within a few months since the disease began. These data fully confirmed the observations of Valantine et al., [13] that familial juvenile dilated cardiomyopathy rapidly evolves to end-stage disease, far worse than the juvenile non-familial form of DCM. Similar results were obtained from investigations by A. Gavazzi which showed the pernicious course of the familial form of DCM in 4 young patients who underwent emergency heart transplantation, a few months following the onset of the first symptoms of heart failure. [15]. M. Csonady et al., also identified that the familial form of DCM develops progressively faster than the non-familial form [1]. At the same time, M. Moretti et al., [10] revealed that there was no difference between patients with the sporadic or familial form of DCM after the manifestation of heart failure symptoms. The basic cause of the death of the patients with the familial form of DCM was sudden cardiac death, whereas for patients with the non-familial form of DCM, it was stagnant heart failure. V. Michels contributed this with joint author, R. C. Bahler [9, 17]. The results of this study regarding life prognoses concurred with the results of the works referred. However, from the analysis of the causes of death, in an overwhelming majority of patients with the familial form of the disease, refractory heart failure has been identified as the culprit, in this study.

Conclusions

Prevalence of the familial form of DCM averages at 12.2% and in contrast to the non-familial form of disease is associated with a much younger age; in 1/3cases the disease comes through the female (maternal) branch; several patients are characterized by the development of a complete atrioventricular block and low blood pressure, which are the negative prognostic signs. The study results of DCM patients life prognosis over a long observation period revealed mortality indices over a 9-year period as 76 (73.1%) cases and showed no appreciable difference between the groups studied. However, a study of the immediate patients life prognosis showed that patients with the familial form and age below 30 years rapidly grow progressively worse, accompanied by an increasing mortality rate during the first 12 months of observation.

References

1. Csonady M., Hogya M., Kallai A. Familial dilated cardiomyopathy: a worse prognosis compared aith sporadic forms. British Heart J 1995; 74:171-173.

2. Elliott P, Andersson B, Arbustini E et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008; 29:270-276.

3. Arbustini E, Pilotto A, Repetto A. et al. Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease J Am Coll Cardiol 2002; 39:981-990.

4. Keeling PJ, Gang Y, Smith G et al. Familial dilated cardiomyopathy in the United Kingdom. Br Heart J 1995; 73:417-421.

5. Grunig E, Tasman JA, Kucherer H. et al. Frequency and phenotypes of familial dilated cardiomyopathy J Am Coll Cardiol 1998; 31:186-19.

6. Osterziel KJ, Scheffold T, Perrot A et al. Genetics of dilated cardiomyopathy. Z Kardiol 2001; 90:461-469.

7. Mestroni L, Rocco C. Advances in molecular genetics of dilated cardiomyopathy. Cardiology Clinics 1998; 16:603-609.

8. Richardson P, McKenna W, Bristow M et al. Report of the 1995 World Organization. International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996; 93:841-842.

9. Bahler RC. Assessment of prognosis in idiopathic dilated cardiomyopathy. Chest 2002; 121:1016-1019.

10. Moretti M, Merlo M, Barbati G et al. Prognostic Value of a Systematic Familial Screening in Idiopathic Dilated Cardiomyopathy: The Experience of Trieste Heart Muscle Disease. Circulation 2009; 120: S904.

11. Maron B, Towbin J, Thiene G et al. Contemporal definitions and classifications of the cardiomyopathies. Circulation 2006; 113:1807-1816.

12. Li D, Tapscoft T, Gonzalez O et al. Desmin mutation responsible for idiopathic dilated cardiomyopathy. Circulation 1999; 100:461-4.

13. Valantine HA, Hunt SA, Fowler MB et al. Frequency of familial nature of dilated cardiomyopathy and userfulness of cardiac transplantation in this subset. Am J Cardiol 1989; 63:959-63.

14. Zachara E, Caforio AL, Carboni GP et al. Familial aggregation of idiopathic dilated cardiomyopathy: clinical features and pedigree analysis in 14 families. Br Heart J 1993; 69:129-35.

15. Gavazzi A, De Maria R, Renosto G et al. The spectrum of left ventricular size in dilated cardiomyopathy: clinical correlates and prognostic implications. SPIC (Italian Multicenter Cardiomyopathy Study) Group. Am Heart J 1993; 125:410-22.

16. Graber HL, Unverferth DV, Baker PB et al. Evolution of a hereditary cardiac conduction and muscle disorder: a study involving a family with six generations affected. Circulation 1986; 74:21-35.

17. Michels VV, Driscoll DJ, Miller FA. et al. Progression of familial and non-familial dilated cardiomyopathy: long-term follow-up. Heart 2003; 89:757-761.