საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 2, №3, 2008
BULLETIN OF THE GEORGIAN NATIONAL ACADEMY OF SCIENCES, vol. 2, no. 3, 2008

Experimental Medicine

Clinical Manifestation and Long-Term Prognosis of Viral and Idiopathic Dilated Cardiomyopathy

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ABSTRACT. The aim of the present study was to evaluate and compare a long-term prognosis and clinical courses of viral and idiopathic (two of the most widespread and heavy) forms of dilated cardiomyopathy (DCM). In total 144 patients (mean age 43.8±12 years, range 15-68 years, m122/f22) with DCM were enrolled in the study since 1991. Besides standard examinations, serologic tests for antibodies to cardiotropic viruses (ELISA method) were performed. The patients were divided into 2 groups (Gr.) according to the results of serologic tests and patient's clinical and history data. In case of lethal outcomes we used existing medical reports and/or interviewed family members to define the cause of death. The Odds and Hazard Ratio, Kaplan-Meyer methods were used for statistical analyses of the data achieved. In 77 (53.5%) out of 144 patients with DCM, together with acute respiratory infections in anamnesis we observed positive serologic reaction to cardiotropic viruses (Gr.1). 67 (46.5%) patients with idiopathic DCM entered Gr.2. During the 5-year observation period 69 (47.9%) patients died while 75 (52.1%) patients survived. Life-expectancy was 4.1±2.0 and 4.9±2.8 years for Gr.1 and Gr.2, respectively. 3-year mortality rate was 33.8% and 26.5%, 5-year mortality rate - 53.2% and 41.8%, respectively. The most common causes of DCM mortality were progressive heart failure and sudden death (in gr.1 – 43.9% vs 31.7% and in gr.2 – 35.7% vs 46.4%, respectively.)

We conclude that more than half of DCM cases are of viral aetiology. Viral DCM is characterized by higher severity of clinical manifestation, more rapid development of progressive heart failure and higher mortality rates than idiopathic DCM. *© 2008 Bull. Georg. Natl. Acad. Sci.*

Key words: *Dilated Cardiomyopathy, cardiotropic viruses, heart failure, sudden death, arrhythmias, prognosis, survival.*

Introduction and Objectives

Dilated Cardiomyopathy (DCM) is the most widespread form of cardiomyopathy, it comprises 60-87% of all cases and is one of the severest, most clinically heterogeneous and difficult to diagnose pathologies among Cardiovascular diseases (CVD). DCM is characterized by the progression of treatment-resistant heart failure; arrhythmias and blockades of various grades; development of thromboembolisms and high mortality rates. Classification and explanation of the condition have changed several times (Table 1). Today, the following classification, reported by the WHO/ISFC Task Force in 1995, is used: 1. Dilated Cardiomyopathy, 2. Hypertrophic Cardiomyopathy 3. Restrictive Cardiomyopathy. 4. Arrhythmogenic right ventricular Cardiomyopathy. 5. Specific Cardiomyopathies. 6. Unclassified Cardiomyopathies [1].

Morbidity with DCM is observed to be 7-8 new cases in 100000 men in a year [2]. 36 cases of DCM are observed in 100000 people in the USA [3]. More than 10000 men die from cardiomyopathies in the USA, and most cases are DCM [4]. DCM is observed in 36% of

Table 1

Early Classifications of Cardiomyopathies

• Goodwin J.	1961
• WHO	1963, 1980, 1983
• Braunwald, Wynne	1984
• Kipshidze N.N.	1985

WHO/ISFC Task Force in 1995:

- *Dilated Cardiomyopathy*
- *Hypertrophic Cardiomyopathy*
- *Restrictive Cardiomyopathy*
- *Arrhythmogenic right ventricular Cardiomyopathy*
- *Specific Cardiomyopathies*
- *Unclassified Cardiomyopathies*

patients with heart failure [5]. DCM is one of the main reasons of chronic heart failure among men under 40 years old [6].

Nowadays great attention is paid to the study of various etiopathogenic factors of DCM of undetected etiology, so-called idiopathic DCM. One of the most important of them is the role of cardiotropic viral infections, and today the correlation between the Viral Myocarditis and DCM - i.e. transformation of viral Myocarditis to DCM - is widely recognized [7-11].

Thus, the main objective of our study was the evaluation of long-term prognosis and specific features of clinical manifestation of these two, the most widespread forms of DCM, characterized by the severest course.

Material and Methods

In total 144 patients (mean age 43.8±12.0, range 15-68yrs, male 122/female 22) who were treated with the diagnosis of DCM in the department of Cardiomyopathy and ischemic heart disease of the National Center of Therapy since 1991, were enrolled in the study. At the moment of their inclusion in the study groups DCM was strictly differentiated from such pathologies as myocarditis of different genesis, specific and systemic diseases of heart muscles, heart valvular pathologies, arterial hypertension at present or in the anamnesis, coronary heart disease, myocardial infarction, allegro/toxic heart damage; special attention was paid to ischemic, alcoholic and other secondary DCM differentiation.

Beside the standard clinical and biochemical examinations (necessary to obtain thorough anamnesis) Doppler Echocardiography, Chest X-ray, 24-h Holter monitoring and Treadmill test were performed to verify DCM diagnosis and assess current clinical symptoms of the disease. High sensitivity immunoenzyme serologic tests (*ELISA* method) were used to reveal the antibodies to cardiotropic and hepatotropic viruses. In a part of the patients immunologic and immunogenetic (HLA markers) tests were performed. Determination of IgM and IgG to cardiotropic viruses was performed in double serum using "Virotech" (Austria) reagents. Results were assessed with VE (Virotech Units) as follows: VE<9.0 – negative; 9.0<VE<11.9 – borderline; VE>11-positive.

In 18 patients coronary angiography was carried out to exclude artery stenosis. Due to the presence of treatment-resistant arrhythmias and conduction disorders, radio-frequency ablation of atrioventricular nod and pacemaker implantation were performed in 5 patients at the department of Surgical Treatment of Rhythm Disorders. In a few cases the diagnosis was confirmed by autopsy.

Angiotensin converting enzyme inhibitors and Angiotensin-II receptor blockers, loop diuretics, beta-blockers, peripherial vasodilators, Spironolacton, cardiac glycosides were included in the basic treatment; vitamin B_2 and Selenium deficiency were treated, antiviral and immune-correction therapy was initiated when positive serologic reaction to cardiotropic viruses was revealed. If necessary, antiarrhythmic drugs, agents with positive inotropic effect and other drugs were administrated, but the use of 1A/1B class antiarrhythmic drugs was restricted.

Based on the results of serologic tests, anamnesis and clinical data the patients were separated into the following groups (gr):

Gr.1 - Patients with DCM of viral etiology.

Gr.2 - Patients with DCM of idiopathic etiology.

While differentiating various etiologic forms of DCM, we took into consideration positive serologic reactions to cardiotropic viruses and acute respiratory infections in anamnesis, presence of pneumonia and viral hepatitis and pericardium leaflet scarring/separation and valve thickening detected by echocardiography. When possible, repeated serologic tests were performed to reveal viral infections associated with DCM.

Statistically, the data achieved were processed using Computer Statistical Program - Minitab Release – 13 (Minitab Inc, USA, 2000). We determined Hazard and Odds Ratio (OR) and 95% Confidence Interval (CI), χ^2 statistics. Student's (t) criterion was used to compare mean values and Kaplan-Meyer analysis for survival were performed using Cox F- and Gehan-Wilcoxon Tests.

Results and Discussion

Identification of seropositive (to cardiotropic viruses) cases of DCM: Most of the patients informed that prior to symptom manifestation they had acute res-

piratory infections (gr.1 – 97%, gr.2 – 13.7%), while pneumonia was mentioned in 38.1% and 7.8% respectively. Out of 144 DCM patients enrolled in the study 77 (53.5%) had positive serologic reactions to cardiotropic viruses. Based on these 77 patients with viral DCM were separated to gr.1, while the remaining 67 (46.5%) patients with idiopathic DCM comprised gr.2.

In 33 (42.9%) patients from gr.1 we revealed Coxsackie B virus; in 17 patients (22.1%) – adenovirus and in 15 (19.5%) patients – influenza A virus. In one single case Cytomegalovirus, Herpes virus, Echo-virus, Epstein-Barr virus, Hepatitis C, Coxsackie A, influenza B and other viral infections were found (Fig 1).

Single virus invasion was registered in 36 cases (46.8%), two viruses – in 21 (27.3%), three viruses-in 15 (19.5%) and four viruses – in 4 (5.2%) cases. In 5 cases we observed repeated viral infections and development of Myocarditis that aggravated the course of DCM.

In the structure of DCM, the high specific share of Cardiomyopaties of viral etiology is determined by the number of researches. Endomyocardial biopsy and polymerase chain reaction (PCR) compared with slot-blot hybridization has shown genomic viral persistence in myocardial tissues in a widely variable percentage (ranging from 0-76%) of patients with DCM [7, 12-18].

Patients' history data. When comparing age and sex distribution between the groups (Table 2), in Gr.1 we found the tendency to a younger age of the disease. Mean age in gr.1 was 41.1.7±12.2yrs, while in gr.2 it was

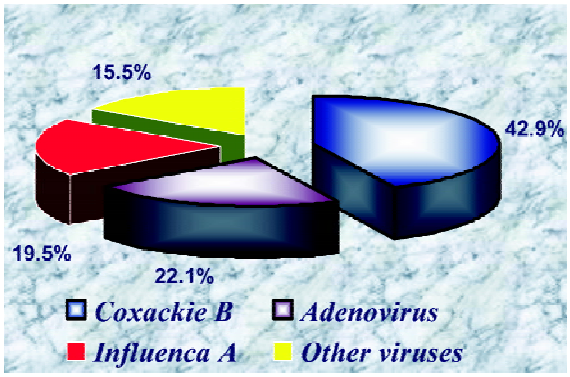

Fig. 1. Ratio of cardiotropic viruses in patients with DCM

44.9±11.7yrs. Age at diagnosis was 42.7±12.4 and 46.8.0±11,5yrs, respectively. Age range was 15-68 yrs. We found that most frequently DCM developed in 31-50yr. age group. Number of females in gr.1 was slightly higher than in gr.2. Anamnesis time (from the first manifestation of symptoms to the DCM diagnosis) varied from 3 months to 2.7 years, with mean duration of 1.6±1.2 and 1.9±1.8yrs, respectively.

The average ages of patients with DCM in our material contradict with the data of several authors. E.g. by *Y. Matsumura and co-authors 2006* [19], the average ages of the patients exceed 59 years. However, according to the majority of the authors [7, 8, 11, 17, 20], the average ages of the patients with DCM are comparatively low. According to [21], unlike other authors, the

Table 2

Distribution of patients with DCM according to age and sex (n=144).

DCM GROUPS	TOTAL (n=144)	VIRAL DCM (n=77)	IDIOPATHIC DCM (n=67)
Age at diagnosis (yr.)	44.9 ± 12.0	42.7 ± 12.4	46.8 ± 11.5
Age at revealing (yr.)	42.7 ± 11.8	41.1 ± 12.2	44.9 ± 11.7
Sex (male/female)	122/22	65/12	57/10
AGE (yrs.)	NUMBER OF PATIENTS		
< 20	7 (4.9%)	5 (6.5%)	2 (3.0%)
21-30	10 (6.9%)	6 (7.8%)	4 (6.0%)
31-40	43 (29.9%)	24 (31.1%)	19 (28.4%)
41-50	45 (31.3%)	23 (29.9%)	22 (32.8%)
51-60	31 (21.5%)	15 (19.5%)	16 (23.9%)
> 60	8 (5.5%)	4 (5.2%)	4 (6.0%)

Table 3

Baseline ECG and chest X-ray data in patients with DCM.

ECG INDICES	TOTAL (n=144)	VIRAL DCM (n=77)	IDIOPATHIC DCM (n=67)	OR (95%CI)
Ventricular arrhythmias	44 (30.6%)	27(35.1%)	17(25.4%)	1.59 (0.77-3.27)
High grade VA	61 (42.4%)	37(48.1%)	24(35.8%)	1.66 (0.85-3.24)
SupraVA	37 (25.7%)	24(31.2%)	13(19.4%)	1.88 (0.87-4.08)
Atrial fibrillation/flutter	44 (30.6%)	27(35.1%)	17(25.4%)	1.59 (0.77-3.27)
LBBB	37 (25.7%)	17(22.1%)	20(29.9%)	0.67 (0.31-1.41)
Bilateral BBB	8 (5.6%)	4(5.2%)	4(6.0%)	0.86 (0.21-3.54)
Atrioventricular block	25 (17.4%)	15(19.5%)	10(14.9%)	1.38 (0.57-3.32)
QTc interval, ms	413.1 ± 2.4	403.9 ± 53.0	425.5 ± 51.9	P = 0.015
QRS complex length, ms	114.0 ± 1.8	116.0 ± 11.2	112.0 ± 12.5	P = 0.045
Low-voltage ECG	24 (16.7%)	15(19.5%)	9(13.4%)	1.56 (0.63-3.84)
Cardiothoracic index	0.63 ± 0.10	0.64 ± 0.10	0.61 ± 0.11	p = 0.089 (NS)

average age of the patients with Viral Miocarditis and with DCM exceed 47-49yrs and are not greatly different.

Clinical status of patients at entry. Comparing gr.1a and gr.2, ECG data show that high grade arrhythmias (48.1% vs 35.8%), supraventricular arrhythmias (supraVA) (31.2% vs 19.4%), atrial fibrillation and flutter (35.1% vs 25.4%) are observed more frequently in gr.1. A statistically not valid difference was found when comparing ventricular arrhythmias (VA) (84.4% vs 88.1%),

Table 4

Doppler-echocardiography data in patients with DCM.

INDICES	TOTAL (N=144)	VIRAL DCM (N=77)	IDIOPATHIC DCM (N=67)	P
LVedD, cm	7.1 ± 0.8	7.3 ± 0.8	6.9 ± 0.8	p=0.003 NS
LAD, cm	4.7 ± 0.7	4.8 ± 0.6	4.6 ± 0.7	p = NS
RVedD, cm	4.2 ± 0.8	4.2 ± 0.9	4.3 ± 0.9	p = NS
RAD, cm	4.2 ± 0.8	4.2 ± 0.9	4.3 ± 0.8	p = NS
LVPWTh, cm	1.0 ± 0.17	0.98 ± 0.16	1.02 ± 0.17	p = NS
IVSTh, cm	0.96 ± 0.13	0.94 ± 0.12	0.99 ± 0.14	p = 0.023
LVEF, %	28.9 ± 8.0	28.1 ± 9.4	29.7 ± 6.5	p = NS
LVFS, %	14.0 ± 3.3	13.9 ± 1.9	14.2 ± 4.7	p = NS
$LVVcf^{-1}$	0.66 ± 0.23	0.63 ± 0.21	0.69 ± 0.25	p = NS
LVedP, mmHg.	20.3 ± 0.8	21.5 ± 6.6	19.1 ± 4.5	p = 0.013
LVedV, ml	162.6±36.3	166.2 ± 35.9	159.0 ± 36.7	p = NS
E/A	2.5 ± 1.0	2.6 ± 1.2	2.3 ± 0.9	p = NS

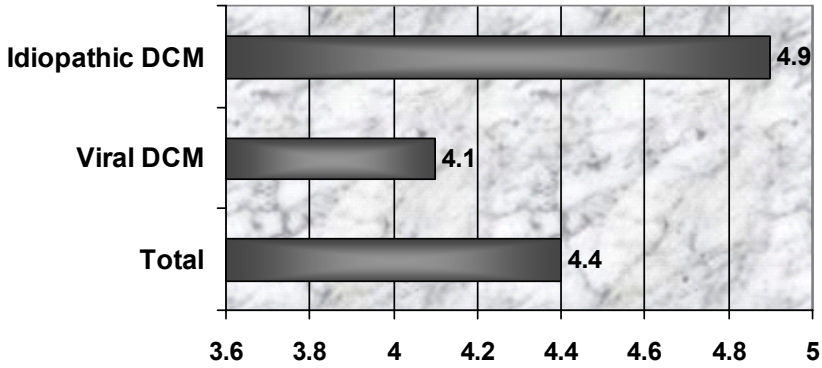

Fig. 2. Mean life-expectancy in patients with viral and idiopathic DCM (n=144).

left bundle branch block (LBBB) (22.1% vs 29.9%), atrioventricular block (19.5% vs 14.9%), QTc interval, QRS complex length and frequency of low-voltage ECG signs (Table 3).

Chest X-ray examination showed high rates of cardiomegaly and an increase in the cardiothoracic index up to 0.61±0.1 and 0.64±0.11, respectively.

Data of Doppler echocardiography (Table 4) showed significant dilation of heart chambers and pronounced systolic and diastolic dysfunctions. Mean left ventricular end diastolic diameter was 7.1±0.8cm; in gr.1 and gr.2 it was 7.3±0.8 and 6.9±0.8cm, respectively (p=0.003). Right ventricle diastolic diameter was 4.2±0.7cm and 4.3±0.8cm, respectively. In both groups mean indices of LVEF were <30%-28.1±9.4% and 29.7±6.5%, respectively. Mean values of left ventricle end-diastolic pressure and end-diastolic volume were elevated – 21.5±6.6mmHg and 19.1±4.5 mmHg (p=0.013), and 166.2±35.9mmHg and 159.0±36.7mmHg, respectively. Index of transmitral blood flow (E/A) was also significantly elevated – 2.4 (2.3±1.2 and 2.6±0.9, respectively).

Thus, we may say that at diagnosis of both viral and idiopathic DCM, their clinical manifestation is associated with severe complications and presence of several predictors of poor prognosis, which have adverse effect on life-expectancy and quality of life of patients with DCM.

Long-term prognosis of DCM and causes of death: We continued observations and compared the severity of the clinical course of the disease and DCM prognosis between the groups.

During a 5-year observation period 69 (47.9%) out of 144 patients enrolled in the study died, while 75 (52.1%) survived. Life-expectancy in patients with DCM was 4.4±2.5yrs; 4.1±2.4yrs and 4.9±2.8yrs, respectively for viral and idiopathic DCM groups (Fig 2).

One-year mortality rate was 10.4% and 7.5%; 3-year mortality rate was 33.8% and 26.9% and 5-year mortality rate was 53.2% and 41.8%, respectively for gr.1 and gr.2 (Fig 3). Total mortality rates were as follows: 1-year – 9.0%; 3-year – 30.6%; 5-year – 47.9% (Fig 3).

Survival rates were: 1-year – 89.6% and 92.5%; 3-year – 66.2% and 73.1%; 5-year – 46.8% and 58.2% for gr.1 and gr.2 respectively. Total survival index was: 1-year – 91.0%, 3-year – 69.4%, 5-year – 52.1%.

Thus, during 5-year period 47.9% of patients with DCM died, and DCM of viral etiology was characterized by the tendency to higher mortality rates, when compared to idiopathic DCM.

According to other authors as well, the survival of the patients is rather limited, although, 5-year mortality rates are very different and range from 37%-66%. [1, 5, 16, 17, 20, 22]. According to *V. Naumov (1995)*, 40% mortality occurred within the period of 1.5 years; *Y. Matsumura 2006* had different results [19]: 5-year mortality rate was only 19.1 %. According to *M. Grogan et al 1995* [21], there was no significant difference in 5-year survival rates of patients with Viral Myocarditis and with DCM - 56% vs 54%, respectively.

In the case of lethal outcomes we used existing medical reports and/or interviewed family members to define the cause of death, and found that the most common causes of DCM mortality are progressive heart failure (28 patients, 40.6%) and sudden death (26 patients, 37.7%). Then - thromboembolisms (9 patients, 13.1%), non-cardiac mortality (3 cases, 4.3%) and unknown death (3 cases, 4.3%). When groups were analyzed, we found that in gr.1 mortality due to progressive cardiovascular failure prevailed, while in gr.2 - sudden death was the most common cause. Thromboembolisms were a relatively rare cause of death. They comprised 14.6% and 10.7%, respectively (Table 5).

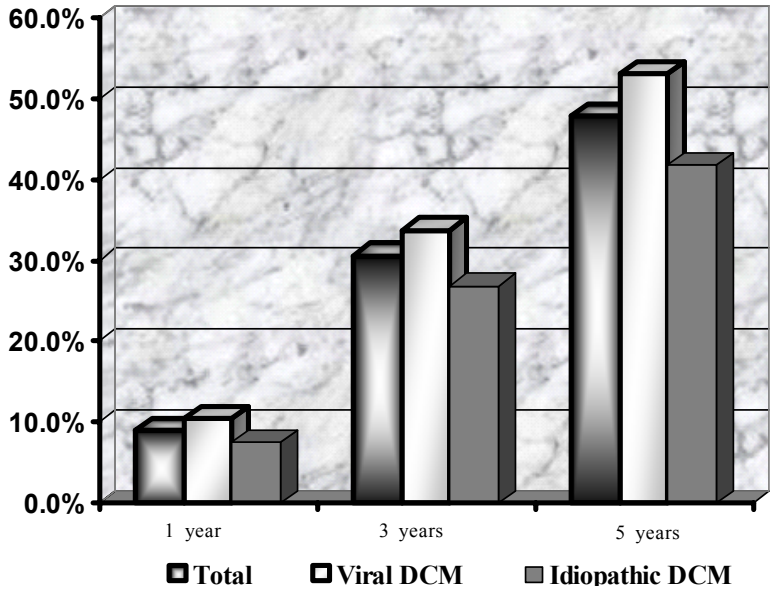

Fig. 3. 1, 3 and 5-year mortality rates in patients with Viral and Idiopathic DCM (n=144)

Table 5

Death causes in patients with viral and idiopathic DCM.

DEATH CAUSE	TOTAL		Viral DCM		Idiopathic DCM		OR (95%CI)
	n=69		n=41		n=28		
Progressive HF	28	40.6%	18	43.9%	10	35.7%	1.41(0.52-3.79)
Sudden death	26	37.7%	13	31.7%	13	46.4%	0.54(0.20-1.44)
Tromboembolism	9	13.1%	6	14.6%	3	10.7%	1.43(0.33-6.26)
Non-cardiac	3	4.3%	2	4.9%	1	3.6%	1.38(0.12-16.05)
Unknown	3	4.3%	2	4.9%	1	3.6%	1.38(0.12-16.05)

Conclusions

More than 1/2 of all DCM cases are of viral etiology, Coxsackie B virus is characterized by the highest cardiotropicity and is revealed most frequently, next comes Influenza A and Adenoviruses, while combinations of other viruses are observed less frequently.

Viral DCM is characterized by a higher severity of clinical manifestation, more rapid development of progressive heart failure and by higher mortality rates than idiopathic DCM.

The most common cause of viral DCM mortality is progressive heart failure, while in idiopathic DCM sudden death occupies the first position. In the whole DCM group progressive heart failure and sudden death (as mortality causes) are approximately equal, each amounting to around 40%.

ექსპერიმენტული მედიცინა

ვირუსული და იდიოპათიური დილატაციური კარდიომიოპათიის კლინიკური მანიფესტაცია და ხანგრძლივი პროგნოზი

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ჩვენი კვლევის ძირითადი მიზანი იყო კარდიომიოპათიების ყველაზე გავრცელებული და მძიმედ მიმდინარე ფორმების — ვირუსული და იდიოპათიური დილატაციური კარდიომიოპათიის – კლინიკური გამოვლენის თავისებურებათა და ხანგრძლივი პროგნოზის მაჩვენებლების შეფასება. კვლევაში ჩართულ იქნა 15-დან 68 წლამდე ასაკის 144 პაციენტი (საშუალო ასაკი – 43.8±12.0, 122 მამაკაცი და 22 ქალი) რომლებიც მკურნალობას გადიოდნენ თერაპიის ეროვნული ცენტრის კარდიომიოპათიებისა და გულის იშემიური დაავადების განყოფილებაში დკმ-ის დიაგნოზით 1991 წლიდან. პაციენტების ჩართვისას საკვლევ ჯგუფში ხორციელდებოდა დკმ-ის მკაცრი დიფერენცირება იშემიური, ალკოჰოლური და სხვა მეორადი კარდიომიოპათიებისგან. სტანდარტულ კლინიკურ და ბიოქიმიურ გამოკვლევებთან ერთად (რაც მოიცავდა დაავადების დეტალურ ანამნეზს) კარდიოტროპულ და ჰეპატოტროპულ ვირუსებზე ანტისხეულების გამოსავლენად გამოყენებულ იქნა სეროლოგიური კვლევა (იმუნოფერმენტული მეთოდი **ELISA**). სეროლოგიური კვლევის შედეგების გათვალისწინებით და ანამნეზურ და კლინიკურ მონაცემებზე დაყრდნობით პაციენტები დაყოფილ იქნენ 2 ჯგუფად: I ჯგუფი — პაციენტები ვირუსული ეტიოლოგიის დკმ-ით; II ჯგუფი — პაციენტები იდიოპათიური დკმ-ით.

კვლევაში ჩართული დკმ-ის დიაგნოზის მქონე 144 პაციენტიდან 77 (53.5%) პაციენტს ანამნეზში მწვავე რესპირატორულ ინფექციასთან ერთად გამოუვლინდა დადებითი სეროლოგიური რეაქცია კარდიოტროპული ვირუსების მიმართ, რის შედეგადაც I ჯგუფში გაერთიანდა 77 პაციენტი ვირუსული ეტიოლოგიის დკმ-ით, ხოლო II ჯგუფში — 67 (46.5%) პაციენტი იდიოპათიური დკმ-ით. 144 პაციენტიდან 5 წლის განმავლობაში დაილუპა 69 (47.9%) პაციენტი, ხოლო 75 (52.1%) გადარჩა. საშუალო სიცოცხლის ხანგრძლივობამ ვირუსული და იდიოპათიური დკმ-ის ჯგუფებში შეადგინა შესაბამისად 4,1±2,0 და 4,9±2,8 წელი. 3-წლიანმა ლეტალობამ შეადგინა 33.8% და 26.9%, ხოლო 5-წლიანმა ლეტალობამ — 53.2% და 41.8% შესაბამისად. ლეტალობის ყველაზე ხშირი მიზეზები იყო გსლ მზარდი უკმარისობა და უეცარი სიკვდილი (I ჯგუფი - 43.9% და 31.7%, II ჯგუფი – 35.7% და 46.4% შესაბამისად).

მიღებული შედეგების საფუძველზე შეიძლება დავასკვნათ, რომ დკმ-ის შემთხვევათა ნახევარს აქვს ვირუსული ეტიოლოგია, ყველაზე ხშირად გამოვლინდება და მაღალი კარდიოტროპულობით ხასიათდება კოქსაკიBB ვირუსი. ვირუსული დკმ ხასიათდება უფრო მძიმედ გამოხატული კლინიკური მანიფესტაციით, პროგრესირებადი გულის უკმარისობის უფრო სწრაფი განვითარებით და ლეტალობის მაჩვენებლების უფრო მაღალი დონით, ვიდრე იდიოპათიური დკმ.

დილატაციური კარდიომიოპათიების სტრუქტურაში ვირუსული ეტიოლოგიის კარდიომიოპათიის მაღალი ხვედრითი წილისა და ლეტალობის მაღალი მაჩვენებლებიდან გამომდინარე აუცილებლად მიგვაჩნია ქვემწვავე და ქრონიკული ვირუსული მიოკარდიტების დროული დიაგნოსტირება და მათი ადეკვატური მკურნალობა, რათა თავიდან იქნას აცილებული დილატაციურ კარდიომიოპათიად მათი შესაძლო ტრანსფორმაცია.

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Received June, 2008