Обзорные статьи

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Dilated cardiomyopathy: etiology, pathogenesis and diagnostic evaluation

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Cardiomyopathies constitute a group of diseases in which the dominant feature is direct involvement of the heart muscle itself. They are distinctive because they are *not* the result of pericardial, hypertensive, congenital, valvular, or ischemic diseases. Although the diagnosis of cardiomyopathy requires exclusion of these etiological factors, the features of cardiomyopathy are often sufficiently distinctive—both clinically and hemodynamically—to allow a definitive diagnosis to be made [60]. A variety of schemes have been proposed for classifying the cardiomyopathies. The most widely recognized classification is that promulgated jointly by the World Health Organization (WHO) and the International Society and Federation of Cardiology (ISFC) [50]. The following types of cardiomyopathies exist: ***dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, unclassified cardiomyopathy.*** In the WHO/ISFC classification, the cardiomyopathies are classified based on their predominant pathophysiological features; other diseases that affect the myocardium that are associated with a specific cardiac disorder or are part of a generalized systemic disorder are termed ***specific cardiomyopathies*** (in the previous WHO/ISFC classification, they were termed *specific heart muscle diseases*) [50].

Dilated cardiomyopathy(DCMP) is a group of cardiac diseases of unknown etiology with a primary damage of myocardium whithout atherosclerotic disturbances of coronary arteries [5]. It is characterized by cardiac enlargement and impaired systolic function of one or both ventricles. DCMP is characterized by dilation of all chambers of heart, but in some cases dilation is mostly one-sided [39]. Although it was formerly called congestive cardiomyopathy, the term dilated cardiomyopathy is now preferred because the earliest abnormality usually is ventricular enlargement and systolic contractile dysfunction, with the signs and symptoms of congestive heart failure often (but not invariably) developing later. In an occasional patient, the predominant finding is that of contractile dysfunction with only a mildly dilated left ventricle. In the WHO/ISFC classification scheme, this variant of DCMP is placed in the unclassified cardiomyopathy group. The incidence of DCM is reported to be 5 to 8 cases per 100,000 population per year and appears to be increasing, although the true figure likely is higher as a consequence of underreporting of mild or asymptomatic cases [12]. There are also some racial differences in incidence and survival of DCMP [15]. It occurs almost three times more frequently in blacks and males than in whites and females, and this difference does not appear to be related solely to differing degrees of hypertension, cigarette smoking, or alcohol use. Survival rate in blacks and males appears to be worse than in whites and females. Although the cause is not definable in many cases, more than 75 specific diseases of heart muscle can produce the clinical manifestations of DCMP. It is likely that this condition represents a final common pathway that is the end result of myocardial damage produced by a variety of cytotoxic, metabolic, immunological, familial, and infectious mechanisms. For example, some toxic substances may lead to severe cardiac dysfunction and may produce clinical findings identical to those present in idiopathic DCM.

Etiology and Pathogenesis

The exact cause(s) of DCMP still remains unclear. Interest has centered on some possible basic mechanisms of damage: familial and genetic factors; viral myocarditis and other cytotoxic insults; and immunological abnormalities. Familial linkage of DCMP occurs more commonly than often is appreciated. In 20% or more of patients, a first-degree relative also shows evidence of DCMP, suggesting that familial transmission is relatively frequent. Some asymptomatic relatives of patients with DCMP have subclinical left ventricular enlargement and/or dysfunction that may progress to overt symptomatic DMCP. Some authors find that in 25-30% of cases DCMP has familial character [48]. DCMP is genetically quite heterogeneous which determines heterogeneous phenotype in different patients. The most common inheritance is autosomal-dominant one. Less common is X-linked inheritance. Also autosomal-recessive and mitochondrial types exist. 8 mutant genes have been revealed as causes of DCMP, which encode the following cardiomyocyte proteins: dystrophin, taphasin, actin, desmin, laminin A and C, heavy chain of β-myosin, troponin. Mutation of some genes simultaneously cause myopathies of skeletal muscles. In 68% of inherited DCMP cases HLA DR4 genotype has been revealed, which allows to think about the possible roles of immune disorders in DCMP developing. Sarcomere protein encoding gene abnormalities are found in 10% of inherited DCMP cases. It is responsible for the early onset of the disease. In these cases diminished contractile ability of myocardium plays a substantial role in developing of cardiac failure.

There is an opinion that idiopathic dilated cardiomyopathy may be caused by viral infection. Wide speculation exists that an episode of subclinical viral myocarditis initiates an autoimmune reaction that culminates in the development of full-blown DCM. Some authors find that viral infection is responsible for about 50% of DCMP cases. Also it has been estimated that only about 15% of patients, with myocarditis progress to DCMP. In some patients who exhibit the clinical features of DCMP, endomyocardial biopsy reveals evidence of an inflammatory myocarditis. The reported frequency of evidence of an inflammatory infiltrate in DCM varieties widely and undoubtedly depends largely on patient selection and the criteria used for diagnosis; using rigorous criteria, only about 10% (or less) of patients with DCM have biopsy evidence of myocarditis. The main type of myocarditis that is considered to cause DCMP is chronic myocarditis [34]. Nevertheless, acute myocarditis also may cause DCMP, but much rarer than chronic type [3]. Viral myocarditis has poor clinical signs, therefore it is not diagnosed in time, and when DCMP develops, it is not mentioned in patient's history. Other evidence favoring the concept that DCMP is a postviral disorder includes the presence of high antibody viral titers, viral-specific RNA sequences, and apparent viral particles in patients with "idiopathic" DCMP [65]. On the other hand, the more rigorous technique of polymerase chain reaction generally has not confirmed the presence of viral remnants in the myocardium of most cardiomyopathy patients [13], although data are conflicting [20]. But there were no data about viral activity in those samples. Abnormalities of both humoral and cellular immunity have been found in patients with DCMP [46], although the findings have not been completely reproducible. There is speculation that antibodies might be the result of myocardial damage, rather than the cause. There appears to be an association with specific HLA Class II antigens (particularly DR4), suggesting that abnormalities of immunoregulation may play a role in DCMP [45] Circulating antimyocardial antibodies to a variety of antigens (including the myosin heavy chain, the β adrenoreceptor, the muscarinic receptor, laminin, and mitochondrial proteins) have been identified [53]. Additional evidence for the significance of circulating antimyocardial antibodies comes from the demonstration of short-term clinical improvement in the manifestations of heart failure in a small number of patients treated with immunoadsorption and elimination of anti-β_1-adrenergic receptor antibodies [16]. Abnormalities of various T cells, including cytotoxic T cells, suppressor T lymphocytes, and natural killer cells, have been found in some studies [9]. These immunological abnormalities may be the consequence of prior viral myocarditis. It has been postulated that viral components may be incorporated into the cardiac sarcolemma, only to serve as an antigenic source that directs the immune response to attack the myocardium. Nevertheless, the precise role of either humoral or cellular immunomodulation in the pathogenesis of DCMP remains unestablished [12]. A variety of proinflammatory cytokines such as tumor necrosis factor -α (and the related tumor necrosis factor -α converting enzyme) are expressed in DCMP and may play a role in producing contractile dysfunction; whether

viral infection, autoimmune abnormalities, or other factors induce their expression is unknown [7;52]. Similarly, the vasoconstrictor peptide endothelin is increased in decompensated DCMP and has been implicated as a cause of the heightened vascular tone that accompanies congestive heart failure [6].

A variety of other possible causes have been proposed, although none is accepted as the cause of DCMP. Thus, endocrinc abnormalities as well as the effects of chemicals or toxins have been suggested as possible etiological factors. It has been suggested that microvascular hyperreactivity (spasm) may lead to myocellular necrosis and scarring, with resultant heart failure, although this remains speculative [56]. Apoptosis, or programmed cell death, has been demonstrated in the hearts of patients with DCMP and arrhythmogenic right ventricular cardiomyopathy, although there is some controversy regarding the veracity of these findings in DCMP [33]. Even if true, the significance of this finding, and whether it is a primary or secondary event in the development of cardiomyopathy, remains unclear. From a clinical standpoint, the more important causes of nonidiopathic DCMP include alcohol and cocaine abuse, human immunodeficiency virus (HIV) infection [29], metabolic abnormalities, and the cardiotoxicity of anticancer drugs. Several abnormalities of the sympathetic nervous system have been demonstrated in DCMP, but they appear to be the result rather than the cause of the disease [62]. A reduction in density of membrane-associated β- adrenoreceptors is believed to be a consequence of the development of anti-β-adrenoreceptor autoantibodies. An alteration in the signal transmission pathway by which the β- adrenoreceptors stimulate the contractile apparatus (the G-protein system) has been found as well. Inhibition of this system is enhanced in DCMP patients, perhaps accounting for their depressed contractile function. An increase of the subunits of the inhibitory guanine nucleotide-binding protein (Gi) has been reported to occur in the membranes of myocytes from failing hearts [8]. This increase in Gi is associated with a striking reduction of basal adenylate cyclase activity and of the positive inotropic effects of isoproterenol and the phosphodiesterase inhibitor milrinone. These findings suggest that the increase of Gi might contribute to the reduced effects of endogenous catecholamines in DCMP [28]. The precise cause of contractile dysfunction at the cellular level in patients with DCM remains speculative. Although there are demonstrable abnormalities of cellular metabolism and calcium handling by cardiomyopathic tissue [31]. the significance of these findings is not yet clear [25].

Pathomorphology

This reveals enlargement and dilatation of all four cardiac chambers; the ventricles are more dilated than the atria. Although the thickness of the ventricular wall is increased in some cases, the degree of hypertrophy often is less than might be expected given the severe dilatation present. The development of left ventricular hypertrophy appears to have a protective or beneficial role in DCMP, presumably because it reduces systolic wall stress and thus protects against further cavity dilatation. The cardiac valves are intrinsically normal, and intracavitary thrombi, particularly in the ventricular apex, are common. The coronary arteries usually are normal. In DCMP heart chambers enlarge to such extent that some authors call it bull's heart (cor bovinum), or total cardiac aneurism (aneurysma totale cordis). There are not specific pathohistological features. Microscopic study reveals extensive areas of interstitial and perivascular fibrosis, particularly involving the left ventricular subendocardium. Small areas of necrosis and cellular infiltrate are seen on occasion, but these typically are not prominent features. There is marked variation in myocyte size; some myocardial cells are hypertrophied, and others are atrophied. No viruses or other etiological agents have been identified with any regularity in tissue from patients with DCMP [17].

Prognosis

Prognosis is unfavourable [4]. Pharmacothearapy in most cases is not effective, that is why heart transplantation is the only method in terminal stages of DCMP, but because of donor heart deficiency many patients die before the operation. A variety of clinical predictors of patients at enhanced risk of dying of DCMP have been identified, including the presence of a protodiastolic (S3) gallop, ventricular arrhythmias, advanced age, and specific endomyocardial biopsy features [19]. However, the predictive reliability of any single feature is not high [2], that is why it's difficult to predict the prognosis. However, greater ventricular enlargement and worse dysfunction tend to correlate with poorer prognosis [1]. There is a slight decrease in mortality during the last 25 years. There are several

causes for this–there is a new strategy of pharmacothearapy using ACE-inhibitors, β-blockers etc., electrostimlators are widely used to prevent arrhythmias. Nevertheless, even in these cases mortality remains enough high and the only radical method still remains heart transplantation [47]. Cardiopulmonary exercise testing also can provide prognostic information. Marked limitation of exercise capacity manifested by reduced maximal systemic oxygen uptake (especially when below 10 to 12 *ml/kg/min*) is a reliable predictor of mortality and is used widely as an indicator for consideration of cardiac transplantation [1]. It has been suggested that specific endomyocardial biopsy morphological findings (such as loss of intracellular myofilaments) may offer some predictive information regarding prognosis.

Diagnostic Evaluation

Possible Causes

In a large proportion of patients, the cause of the disease is unknown and DCMP is considered to be the final common phenotype of a hetcrogeneous group of disorders. However, a familial trait is present up to 50% of cases, indicating a major role of genetic factors. Furthermore, the risk of disease has been estimated as high as 20% in relatives of familial DCMP patients, which is significantly higher than in the normal population. Taking into account that DCMP can be clinically not evident due to its low penetrance (in particular in the young population), a reproducible and reliable method for the diagnosis of familial forms is critical in the management of the disease. In familial forms of DCMP it is essential to speak about family screening method. The screening method for familial DCMP is based on physical exam, electrocardiography, and echocardiography of first-degree relatives of affected subjects. The family screening should be followed-up every 2 to 3 years, in particular in unaffected relatives (in the absence of a molecular diagnosis), to exclude a late onset of the disease [57]. The initial diagnostic approach should exclude all potentially reversible causes of left ventricular dysfunction. Excess alcohol consumption has been reported in up to 40% of patients with IDC; obtaining a quantitative history of alcohol consumption is of paramount importance, since abstinence may result in a dramatic increase in the ejection fraction [21;23;66]. A recent viral illness, particularly one accompanied by myalgias or pericarditis, may suggest a role for myocarditis. Ischemic heart disease should be considered whenever coronary risk factors or chest pain on exertion is present. Chest pain occurs in about one third of patients and may suggest concomitant ischemic heart disease [12;49]. The demonstrated reduction in the vasodilator reserve of the coronary microvasculature in DCMP suggests that subendocardial ischemia may play a role in the genesis of chest pain that occurs despite angiographically normal coronary arteries [18]. Chest pain secondary to pulmonary embolism and abdominal pain secondary to congestive hepatomegaly are frequent in the late stages of illness. A complete family history may suggest a familial cardiomyopathy, but only echocardiography can rule out asymptomatic abnormalities in close relatives.

The History and Physical Examination

Symptoms usually develop gradually in patients with DCMP. Some patients are asymptomatic and yet have left ventricular dilatation for months or even years. This dilatation may be recognized clinically only later when symptoms develop or when routine chest roentgenography demonstrates cardiomegaly. A relatively small number of patients develop symptoms of heart failure for the first time after recovery from what appears to be a systemic viral infection. In still others, severe heart failure develops acutely during an episode of myocarditis; although some recovery occurs, chronic manifestations of diminished cardiac reserve persist and heart failure reappears months or years later. It is important to question the patient and family carefully about alcohol consumption, because as spoken above excessive alcohol consumption is a major cause of DCMP, and its cessation may result in substantial clinical improvement [14]. Although patients of any age may be affected, the disease is most common in middle age and is more frequent in men than in women. The most striking symptoms of DCMP are those of left ventricular failure. Fatigue and weakness due to diminished cardiac output are common. Right-sided heart failure is a late and ominous sign and is associated with a particularly poor prognosis.

The physical findings reflect the severity of the left ventricular dysfunction and range from subtle signs (for example, unexplained premature ventricular beats or asymptomatic cardiomegaly) to overt decompensated heart failure. Pulsus alternans is common when severe left ventricular failure is present. Cheyne-Stokes breathing may be present and is associated with a poor

prognosis [40]. The jugular veins are distended when right-sided heart failure appears, but on initial presentation most patients do not have evidence of this [12]. Prominent *a* and *v* waves may be visible. Grossly pulsatile jugular veins with prominent regurgitant waves indicate the presence of tricuspid valvular regurgitation; this is usually a late and often ominous finding. The liver may be engorged and pulsatile. Peripheral edema and ascites are present when right-sided heart failure is advanced. Other signs of right-sided-heart failure are initially present in fewer than 50% of patients [58]. The results of precordial palpation may initially be normal, but a diffuse, laterally displaced apical impulse is noted as left ventricular dilatation increases. The second heart sound (S_2) is usually normally split, although paradoxical splitting may be detected in the presence of left bundle branch block–an electrocardiographic (ECG) finding that is not unusual in DCMP. If pulmonary hypertension is present, the pulmonary component of S_2 may be accentuated and the splitting may be narrow. Presystolic gallop sounds (S_4) are almost universally present and often precede the development of overt congestive heart failure [12]. Ventricular gallops (S_3) are the rule once cardiac decompensation occurs, and a summation gallop is heard when there is concomitant tachycardia. Systolic murmurs due to atrioventricular regurgitation are common and reflect the extent of ventricular dilatation. These murmurs almost never exceed grade 2/6 in intensity and may have unusual features. The murmur of mitral regurgitation may not be holosystolic, and the usual inspiratory increase in the murmur of tricuspid regurgitation (Carvallo's sign) is frequently absent [10].

Paraclinical Findings

Laboratory tests. To identify potentially reversible causes of DCMP, several basic screening biochemical tests are indicated, including determination of levels of serum phosphorus (hypophosphatemia), serum calcium (hypocalcemia), and serum creatinine and urea nitrogen (uremia), thyroid function studies (hypothyroidism and hyperthyroidism), and iron studies (hemochromatosis). It is prudent to test for HIV as well, because this infection is an important and often unrecognized cause of congestive heart failure [29].

Cardiomegaly and pulmonary venous redistribution are generally seen on chest radiography, whereas interstitial or alveolar edema is uncommon.

Electrocardiography. The electrocardiogram is seldom normal but initially may show only nonspecific repolarization abnormalities. The ECG often shows sinus tachycardia when heart failure is present. Conduction abnormalities occur in over 80% of cases and include first-degree atrioventricular block, left bundle-branch block, left anterior hemiblock, and nonspecific interventricular conduction delays [51;66]. Right bundle-branch block is rare. Conduction abnormalities are more common in patients with long-standing symptoms, progress over time, and are markers of increasing interstitial fibrosis or myocytic hypertrophy [66]. Left ventricular hypertrophy, pathologic anterior QS waves, and poor R-wave progression are not infrequently observed. Anterior Q waves may be present when there is extensive left ventricular fibrosis, even without a discrete myocardial scar or evidence of coronary artery disease [12]. Atrial fibrillation, which is often poorly tolerated, develops in 20% of patients but has not been associated with a worse prognosis [14,21,22,30,37,38,42,60]. Ambulatory monitoring demonstrates the ubiquity of ventricular arrhythmias, with about half of monitored patients with DCMP exhibiting nonsustained ventricular tachycardia [12]. There is no consensus that complex or frequent ventricular arrhythmias predict sudden (presumably arrhythmic) death, although they do appear to predict *total* mortality [55]. Perhaps ventricular arrhythmias as detected on ambulatory monitoring are a marker for the extent of myocardial damage in DCMP and therefore are associated with sudden death without necessarily being its cause. In occasional cases, particularly in children, recurrent and/or incessant supraventricular or ventricular tachyarrhythmias may actually be the cause (rather than the result) of ventricular dysfunction [11;36]: In those cases, restoration of sinus rhythm or slowing of the heart rate may reverse the cardiomyopathy [41; 43]

Echocardiography. Echocardiography is the most useful initial diagnostic procedure. Two-dimensional and Doppler forms of echocardiography are useful in assessing the degree of impairment of left ventricular function and for excluding concomitant valvular or pericardial disease [44]. In addition to examining all four cardiac valves for evidence of structural or functional abnormalities, echocardiography allows evaluation of the size of the ventricular cavity and thickness of the ventricular walls. The findings may include left

ventricular dilatation, normal or reduced septal and free-wall thickness, and global hypokinesis [54]. Abnormal ventricular contractility is the sine qua non of IDC, and an ejection fraction below 45% is generally required for diagnosis [32;44]. Although global hypokinesis may be found, considerable variability in the extent of segmental wall-motion abnormalities is evident in up to 60% of patients because of altered regional-wall stress. Segmental rather than global hypokinesis may predict a more favorable outcome [24;26;64]. Atrial enlargement is also common but less pronounced than enlargement of the ventricles. Intracavitary thrombi are most frequently seen at the left ventricular apex. Although IDC is usually a diffuse process, we have observed left ventricular dysfunction without concomitant right ventricular involvement in 10 to 15 percent of our patients. This pattern should generally suggest ischemic heart disease rather than a primary myocardial process. Doppler study may detect clinically inaudible moderate mitral and tricuspid regurgitation [59]. Combining echocardiography with dobutamine infusion may identify patients with left ventricular dysfunction due to coronary artery disease by demonstrating provocable differences in regional wall motion and thus distinguish them from patients with idiopathic DCMP [63]. It has been suggested that thallium-201 imaging may be helpful in distinguishing left ventricular enlargement caused by DCMP from that caused by coronary artery disease [61], although there is not complete agreement on this point [12;24]. A pericardial effusion may be demonstrated on occasion.

Endomyocardial biopsy. Evaluation of some patients suspected of suffering from a cardiomyopathy has been facilitated by the use of endomyocardial biopsy [35]. Using a flexible bioptome, the clinician may obtain tissue samples from the right ventricle (and left ventricle when required) through a transvenous (or transarterial) approach with ease and safety. The availability of disposable transfemoral bioptomes has further facilitated endomyocardial biopsy. Two-dimensional echocardiography may help guide the placement of the bioptome and reduce or eliminate radiation exposure [27]. Endomyocardial biopsy results in a small tissue sample (average size 1 to 2 *mm*), and multiple samples (usually four or more) are required because pronounced topographical variations may be found within the myocardium. Which patients should be subjected to biopsy remains controversial, but there is general agreement that biopsy may be of benefit in certain specific situations. There is little debate as to its clinical utility in detecting infiltrative disorders of the myocardium and in monitoring for anthracycline cardiotoxicity and cardiac transplant rejection.

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Դիլիատացիոն կարդիոմիոպաթիա՝ էթիոլոգիան, պաթոգենեզը, ախտորոշումը

Ս.Վ. Շեկոյան, Ն.Ս. Վերանյան

Դիալատացիոն կարդիոմիոպաթիան անհայտ ծագման հիվանդություն է, որի հիմքում ընկած է սրտամկանի առաջնային ախտահարումն ու սրտի խոռոչների լայնացումը: Վերջին ժամանակներս դիտվում է դիլատացիոն կարդիոմիոպաթիայով հիվանդացության աճ: Դեպքերի մոտավորապես 20%-ի մոտ ժառանգականությունը ճանաչաբեռնված է, ինչը խոսում է հիվանդության զարգացման մեջ ժառանգական գործոնի էական դերի մասին: Հաշվի առնելով, որ այս հիվանդության ժամանակ զարգանում է հարաճող սրտային անբավարարություն, որը երբեմն պահանջում է սրտի փոխպատվաստում, և այն, որ Հայաստանի Հանրապետության որոշ տարածքներում այն ունի բարձր տարածվածություն, հեղինակները գտնում են, որ անհրաժեշտ է բարձրացնել բուժանձնակազմի զգոնությունը դիլատացիոն կարդիոմիոպաթիայի նկատմամբ՝ տալով մեծ նշանակություն հիվանդների հարազատների սկրինինգային հետազոտությանը:

Дилятационная кардиомиопатия: этиология, патогенез и диагностика

С.В.Шекоян, Н.С. Веранян

Дилятационная кардиомиопатия это заболевание неясной этиологии, в основе которого лежит первичное поражение миокарда и расширение полостей сердца. Наблюдается рост заболеваемости дилятационной кардиомиопатией. В 20% случаев наблюдается родственная связь между больными, что указывает на существенную роль наследственности в развитии дилятационной кардиомиопатии. Учитывая серьезный прогноз этой болезни, приводящий иногда к трансплантации сердца, и распространенность дилятационной кардиомиопатии в некоторых регионах Армении, авторы подчеркивают необходимость повышения бдительности медицинского персонала к этой проблеме, придавая большое значение скрининговому обследованию родственников больных.

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