Dilated cardiomyopathy (DCM) is a primary myocardial disease, characterized by uni- or biventricular dilation associated with a generally progressive contractile dysfunction. It is predominantly diagnosed in the advanced stage, in which it manifests itself by cardiomegaly and heart failure, causing significant morbidity and mortality. Less frequently, it is identified in the initial stage, in which the congestive signals are absent but ventricular dilation and dysfunction in a mild or moderate degree are evident.

At first, DCM was considered a disease of obscure etiology. Several decades after being identified as an entity, its complex pathogenesis has gradually become better understood. Systematic studies generated in immunology, genetics, and cellular and molecular biology have contributed to the understanding of the disease mechanism. However, the heterogeneous character of DCM, coupled with the multiplicity of pathologic processes involved, has made this task difficult.

DCM is currently understood as a multifactorial disease, in which viral infections, immunologic mechanisms and genetic factors, acting individually or together, result in a definitive myocardial lesion (fig. 1).

Role of viral infection

Clinical and experimental evidence suggest the participation of a viral infection in the cellular injury process. Based on this concept, viral myocarditis is considered a precursor of DCM, leading to definitive heart disease in susceptible individuals. The concept of an evolutionary sequence is based on indirect clinical evidence and conclusions from studies developed in experimental models.

Coxackievirus B, from the Enteroviridae family, is considered the main etiologic agent of human myocarditis except in the endemic areas of Chagas’ disease. These viruses are related to lymphocytic myocarditis, which is a process characterized by diffuse cellular infiltration associated with myocytolysis, but in which the microorganism is not usually identified through conventional techniques. If viral participation in myocarditis is difficult to prove, viral action in DCM may still be considered controversial.

Longitudinal studies of a small series of patients demonstrate an evolution to DCM in 40 to 52% of the cases with a histopathologic diagnosis of lymphocytic myocarditis. However, the causal relationship between enterovirus infections and further development of cardiomyopathy is difficult to confirm because of the virus’ endemic characteristics and the frequent subclinical character of the inflammatory manifestations in the acute phase.

Serology of enterovirus infections is equally complex. Neutralizing antibodies to coxsackievirus B are detected at higher levels in DCM patients than in controls. The fact that most of the population has had contact with the virus, and the possibility of antibody levels remaining high after the acute phase of infection jeopardizes the evaluation of these results. Coxackie B-specific immunoglobulin M is identified in patients with recent diagnosis and end-stage forms. Although this immunoglobulin is found more frequently in the DCM group than in nonselected controls, no difference is seen when serologic data are compared with that obtained from relatives sharing the same domicile. Sequential evaluation of serum specimens revealed antibodies persisting in some cases, as well as late seroconversion after reactions become negative in other cases. Enteroviruses are not commonly isolated from myocardial cells of adult patients with myocarditis and DCM through conventional methods. The advent of new techniques of molecular biology based upon nucleic acid hybridization, made enteroviral RNA detection possible in up to 43% and 47% of the samples containing myocardial tissue of patients with DCM and myocarditis, respectively. Later determinations using the polymerase chain reaction (PCR) technique, more sensitive and specific, observed the presence of enteroviral genomes in 0% to 67% of the biopsies evaluated. Although significantly high numbers were reported, a similar proportion of enterovirus RNA was also seen in the DCM group in relation to controls. Negative results were also obtained by some researchers. However, meta-analysis of data from several studies that used PCR or in situ hybridization suggests a
possible association between enterovirus infections and DCM. Interpretation of these data should take into account methodological differences related to the technique applied and selection of patients and control groups. Small outbreaks of epidemics caused by enteroviruses may cause results to become positive in normal controls exposed to the same environmental factors, considering the cardio-tropic characteristics of these agents.

The presence of entroviral genomes combined with the persistence of serologic reactions suggests the possibility of the virus remaining in the myocardium after the acute phase, with no evidence of protein synthesis but nonetheless interference with cellular functions. This hypothesis becomes questionable because the entroviral RNA proportion usually detected through PCR in these hearts is small and localized. On the other hand, experimental myocarditis models show that some coxsackievirus B-3 strains have greater cardiovirulence. It is predicted that methods will be developed in the future that will be able to distinguish whether or not the identified genomes are related to strains with greater pathogenic potential.

Activation of immunologic mechanisms

It is estimated that, in one third of the cases, DCM is an autoimmune disease. Immunologic organ-specific reactions depend on genetic predisposition and are modulated by environmental factors. Enterovirus infections are thought to play a fundamental role in triggering autoimmunity in this disease. In an initial step, the virus may cause myocytolytic necrosis by direct action, depending on its capacity for intracellular replication. As this process evolves, activation of cytotoxic T lymphocytes occurs, which intensifies the injury of infected and intact cells during lysis. Persistence of infection could result in exacerbation of the cellular and humoral immunologic response, which would perpetuate aggression against myocytes. Autoimmune reaction would result from molecular mimicry between viral and host proteins or from neoantigen expression. Other factors may be responsible for triggering an autoimmune process, such as gestation and alcoholism.

Immunoregulatory disorders are seen in DCM. A decrease in the activity of natural killer cells and reduction of the suppressor function of T lymphocytes may indicate greater susceptibility to viral infections. Experimental models of viral and autoimmune myocarditis show the decisive participation of cellular immunity in the myocardial injury process through T lymphocyte activation and cytokine release. In DCM, a correlation of the expression of perforin and T cell intracellular antigen-1 with the degree of interstitial fibrosis revealed at endomyocardial biopsy was observed.

Autoantibodies to cardiac proteins are identified in 30 to 40% of DCM cases. Organ-specific autoantibodies, which interact with beta-adrenergic receptors, cholineric muscarinic receptors, mitochondrial antigens and alpha and beta cardiac myosin heavy chains, have already been described elsewhere. The clinical importance of autoantibodies and their pathogenic meaning are not fully understood, because they are usually identified in an evolutionary phase, in which the disease is established. It is possible that not all of them have the same clinical meaning. Negative results obtained in most of the patients could be justified by the fact that, similarly to other autoimmune processes, the autoantibodies become undetectable as the disease progresses.

There is no confirmation in regard to the ability of autoantibodies producing myocytolysis. They may interfere with cellular functions, as previously shown for beta-adrenergic receptors and calcium channels, by cross-reaction with autoantibodies to ADP/ATP carriers. Although there may be a correlation between disease severity and autoantibody presence, the autoantibodies may constitute mere cellular lesion markers. Their detection in 20% of asymptomatic individuals, 1st-degree relatives of DCM patients, indicates greater propensity to the disease in this subgroup.

Other evidence suggests the participation of two immunologic mechanisms in DCM: 1) presence of abnormal serologic concentrations of interleukin-2 and interleukin-10, and 2) abnormal expression of MHC class II antigens in endothelial cells.

Genetic factors and familiar forms

Recent studies introduced the concept that the development of DCM depends on genetic factors, which modulate sensitivity to viral infections and subsequent activation of immunologic reactions. Multiple genes may be involved in this process. Myocardial lesion depends on the interaction between genetic and environmental factors. Clinical and experimental studies suggest the association...
with HLA genes, which modulate the immunologic response, and the genes of T cell receptors. HLA genes regulate the immunologic system and the predisposition to autoimmune disease, through the modulation of T cell receptors, and the selection and presentation of antigenic peptides. A higher frequency of class II HLA antigens, DR4 and, possibly, DQw-4 loci, is identified in DCM patients when compared with controls, even though a further analysis restricted to patients in a heart transplant program did not confirm these results. Elevation of HLA-specific haplotypes is seen in the subgroup with deficiency in natural killer cells. Association of HLA-D alleles with autoantibodies to beta-adrenergic receptors is also referred to. These findings indicate that the disease development may be related to immunologic response and genes controlling this process.

Studies performed during the past decade to determine the frequency of familial forms of DCM reveal that this entity, initially interpreted as an acquired process, has a genetic basis in a significant number of patients. In preliminary investigations, familial forms were sporadically identified. Further, prospective analyses reveal an increasing prevalence of these forms, corresponding to 20% to 35% of the cases. These figures may be underestimated, considering the difficulty in evaluating all members of an affected family and the reduced gene penetrance, which makes the carriers of the disease look apparently healthy.

In a recent prospective evaluation of 200 I1-degree relatives of 100 patients, McKenna et al. identified familial nature and tendency in 25% and 45% of the cases, respectively. HLA antigen was detected in 2/3 of the affected families and a greater prevalence of this antigen was noted in familial forms when compared to nonfamilial ones.

DCM has several forms of genetic transmission. Keeling et al., in a prospective study of 236 individuals from 40 affected families, identified the predominance of autosomal dominant inheritance with incomplete penetrance. Early forms of the disease in asymptomatic members of the families were observed: 18% exhibited a slight increase of the left ventricle and 4% exhibited reduction in the fractional shortening when compared with controls. Other inherited forms are recognized: autosomal recessive, X chromosome-linked and mitochondrial.

From the genetic viewpoint, DCM also has heterogeneous characteristics. Distinct genetic mutations produce multiple phenotypes, which determine similar clinical, histopathologic and hemodynamic manifestations. Familial forms are, however, diagnosed in earlier ages than sporadic ones. It is estimated that 20% of the I1-degree relatives have a risk of developing the disease at more advanced ages, as gene penetrance is related to age range.

Lately, the progress made in genetics and molecular biology has allowed great advances in the study of the familial forms of the disease. The autosomal dominant form manifests itself in the 2nd or 3rd decade of life, with ventricular dilation and dysfunction, expressed by heart failure or arrhythmias. The first genetic locus was identified in chromosome 9q13-q22. Later, a second locus was described in chromosome 1q32. Forms associated with mitral valve prolapse were mapped to the short arm of chromosome 10. These chromosomal regions are related to genes modulating regulatory and cytoskeletal proteins.

Rare forms, characterized by conduction system of the disease of the heart beginning in the 2nd or 3rd decade of life, followed by ventricular dilation and dysfunction some years after, are also transmitted by autosomal dominant inheritance through genes mapped to the centromere of chromosome 1 and to the short arm of chromosome 3. Association of DCM with complex diseases that affect the mitochondrial DNA and are transmitted by maternal inheritance has also been described.

So far, only two types of genes related to DCM have been identified: the 1st encodes dystrophin and associated muscular proteins, among them LIM, and the 2nd encodes transcription factors regulating gene expression of myocardial cell genes.

Dystrophin is a protein present in the sarcolemma; it establishes the linkage of the cytoskeleton to the extracellular matrix. Anomalies affecting the gene coding this substance cause Duchenne's dystrophy and Becker type muscular dystrophy. In rare cases, mutations involving this gene produce myocytolysis and cardiomyopathy development. In males, the disease develops during adolescence and evolves quickly, but in females it develops later and with a slow progression. These patients do not usually have neuromuscular compromise but lack dystrophin in the myocardium and have generally high serum levels of creatine kinase. Inheritance is linked to the X chromosome and can be dominant or recessive. Sporadic cases are reported. Prevalence of disorders involving dystrophin in DCM patients is still unknown.

Mutations involving the gene encoding the muscle LIM protein produce severe cardiomyopathy in animal models. This protein is related to cellular maintenance and viability.

Identification of genetically transmitted DCM forms is of fundamental clinical importance. Systematic evaluation of affected families may establish the actual prevalence of familial forms and allow early diagnosis of the disease. The clinical meaning and evolutionary potential of early manifestations, such as conduction disturbances, arrhythmias, incipient ventricular dilation and dysfunction, can be thus cleared up, as well as the effect of early pharmacological intervention.

Individualization of affected genes and their respective mutations represents the next step to the elucidation of genetic and molecular bases of familial forms of DCM. Applying techniques developed under the orientation of these concepts may make possible the pre-clinical diagnosis in patients who still do not exhibit the disease phenotype. Genetic therapy may allow, in the future, the correction of molecular disorders through the substitution of anomalous structural proteins.

In conclusion, several processes participate in DCM.
pathogenesis, justifying its multifactorial character. Elucidation of cellular and biomolecular mechanisms responsible for myocardial dysfunction will help with the introduction of diagnostic methods and therapeutic modalities that will disrupt the development and evolution of this disease.

References