Dilated cardiomyopathy – new therapeutic approach

Cardiomiopatia dilatada – nova abordagem terapêutica

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Abstract

Inflammatory reaction has been associated with dilated cardiomyo pathy. In this context, cardiac autoantibodies and inflammatory cell infiltration have been studied during the last two decades towards the understanding of their origin and the underlying pathogenic mechanisms. Recent research has increasingly focused on the development of an etiological therapeutic approach.

Immunoadsorption has shown to improve clinical, echocardiographic, haemodynamic and laboratory parameters in patients with inflammatory dilated cardiomyopathy.

In this article we review recent literature concerning this subject, including classification, pathophysiological mechanisms and therapy.

Key words: Dilated Cardiomyopathy, Immunoadsorption, Cardiac Autoantibodies.

Resumo

A cardiomiopatia dilatada ocorre na presença de uma reacção inflamatória. Neste contexto, nas últimas duas décadas tem sido estudada a existência de auto-anticorpos cardíacos assim como o processo de infiltração cardíaca por células inflamatórias. Hoje em dia percebem-se melhor os mecanismos patogénicos subjacentes ao processo. Recentemente, o esforço de investigação nesta área centrou-se numa abordagem terapêutica em função da etiologia. O processo de remoção de auto-anticorpos circulantes pelo método da imunoadsorção tem demonstrado bons resultados clínicos, ecocardiográficos, hemodinâmicos e laboratoriais na cardiomiopatia dilatada. Neste artigo pretendeu-se rever o tema abordando a literatura recente sobre classificação da doença, mecanismos fisiopatológicos e terapêutica.

Palavras chave: Cardiomiopatia dilatada, imunoadsorção, auto--anticorpos cardíacos.

DEFINITION OF DILATED CARDIOMYOPATHY (DCM)

Dilated cardiomyopathy is characterized by the dilation of the left or both ventricles and systolic dysfunction with normal wall thickness, excluding other pathologies as valvular disease, hypertension, coronary disease and congenital heart disease that could explain such changes.[1,2,3] This disease constitutes a single class according to the World Health Organization (WHO)[1] and the European Society of Cardiology (ESC),[2] being included in the mixed primary cardiomyopathies according to the American Heart Association.[3]

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INFLAMMATORY DILATED CARDIOMYOPATHY (iDCM)

The importance of iDCM as a separate disease entity has only been recognized in recent years. According to the WHO[1], it can be classified as idiopathic, autoimmune or infectious, with the last two etiologies being nearly indistinguishable.

The study of the mechanisms involved in iDCM started in the 1980's, when the infiltration of lymphocytes was first demonstrated in endomyocardial biopsies.[4] Recent studies also indicate that cellular as well as humoral immune reactions contribute to the pathogenesis of iDCM.[5]

Autoantibodies against heart antigens were found in up to 80% of patients with DCM,[5,6,7] including those directed against myosin chains[8] or the first and second extracellular loops[7,9,10] of the β-adrenergic receptor.

These autoantibodies may be originated by cross reaction of antibodies against viral antigens,[11] due to their molecular mimicry to heart antigens,[5] in individuals with genetic predisposition,[6] supported by the detection of cardiotrophic viruses in up to 70% of patients suffering from iDCM of unknown cause.[12-14]

It was also proposed that these might be formed

from the exposure to intracellular antigens caused by cardiomyocyte necrosis,[15,16] based on the observation that these autoantibodies can also be found in patients recovering from myocardial infarction.[16]

The hypothesis of a genetic involvement in this disease should also be considered. Caforio et al.[17] isolated cardiac autoantibodies in 20% of symptom free relatives of patients with DCM but they were absent in asymptomatic individuals from the same household but genetically unrelated to already diagnosed DCM patients.

Due to reasons not fully understood yet, antibodies can only be isolated from the patients' blood samples during a short period of time, becoming undetectable as the disease progresses.[18] Thus, the absence of autoantibodies in DCM patients does not exclude inflammation as a cause of disease.[16]

The role of the autoantibodies in the pathogenesis of the disease is not well known yet, as they may initiate the disease,[19] contribute to its progression or serve as a marker.[5]

Regardless of their origin, autoantibodies compromise cardiomyocyte function,[20,21] cause hypertrophy and have a negative inotropic[22] and positive chronotropic[23] effect on rat cardiomyocytes. According to Matsui et al.,[19] rabbits that are immunized with β-adrenergic receptor peptide develop a cardiac morphology that resembles the one seen in DCM patients, which supports the initiating role of the autoantibody in the disease.

Although the pathogenic mechanisms involved in iDCM are still poorly defined, many studies documented significant clinical and functional improvement in patients with DCM after receiving immunologic therapy (immunoadsorption[9,22-30]).

As for cellular immunity, infiltration of T_c lymphocytes, natural killer cells and macrophages in the myocardium of patients with DCM has already been described by many authors[5]. Cardiomyocyte lysis and interstitial changes occur through direct (lymphocytic subpopulations), and indirect (cytokine action) cytotoxic effects. They are involved in myocardial remodeling processes that ultimately lead to the dilation of the heart chambers.[6]

In 2000 this new data lead to the redefinition of the histopathologic diagnosis criteria for iDCM[5], considering DCM as an inflammatory disease of the myocardium, along with myocarditis. According to these new criteria, the presence of at least 14 lymphocytes/mm^3 in an endomyocardial biopsy is considered a myocarditis diagnosis, deemed acute in the presence of edema and necrosis. The persistence of the cellular infiltrate in a second biopsy, in the absence of necrosis and edema is characteristic of chronic myocarditis or, if typical echocardiographic changes are present, dilated cardiomyopathy.[5]

THERAPY AND NEW THERAPEUTIC APPROACH

As in heart failure due to other causes, the aims of DCM therapy are the symptomatic improvement as well as control of disease progression.[31] The latest guidelines[32] for heart failure management are also applied to these patients. Heart transplant is indicated in patients with refractory severe heart failure.[32]

There is no consensus about the benefit/risk of anticoagulation therapy in these patients so far.[33]

An etiological therapeutic approach for iDCM has been investigated. Immunologic therapy is thought to reduce the inflammatory reaction affecting the myocardium. Immunoadsorption has become a promising therapeutic approach in the management of these patients.

IMMUNOADSORPTION

Immunoadsorption (IA) is an extracorporeal procedure designed to withdraw antibodies from plasma. It has been successfully used in the therapy of some autoimmune diseases such as *Myasthenia Gravis*.[6,7] The plasma resulting from an initial plasmapheresis is pumped through a column that contains an IgG fixing matrix. The immunoglobulines are adsorbed by this matrix and the IgG-free plasma is reinfused into the patient (reviewed in 6).

Several authors[7,9,23-30] studied the effect of this technique on symptomatic, echocardiographic and haemodynamic parameters in patients with CMD.

Dörffel et al.[7] performed immunoadsorption in nine DCM patients on five consecutive days. Patients were assessed before and after the procedure, showing significant decrease in blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure as well as significant symptomatic improvement. Müller et al.[9] designed a similar study and extended the patient evaluation to up to twelve months after immunoadsorption, accomplishing similar results.

Another therapeutic scheme was adopted by other authors.[23-30] Their patients underwent four immunoadsorption courses with one month intervals. At each

course, the patients received immunoadsorption therapy once daily during two to five consecutive days. Polyclonal IgG substitution was performed after each course, to decrease the risk of infection.

These authors achieved a significant improvement of some echocardiographic parameters (left chamber diameter decrease,[9,25] left ventricular ejection fraction increase[9,24-28]), hemodynamic parameters (stroke volume increase,[24,27,28] cardiac index increase,[23,24,26-28] systemic vascular resistance decrease[23.26]), laboratorial parameters (ntANP e ntBNP[25]) and also significant symptomatic improvement.[9,23,25,26,28,29] Both schemes are equally effective even six months after the first IA course, as shown by Staudt et al.[28]

Study design variations could provide further insights that may lead to new lines of investigation.

As IA is an invasive and expensive procedure, the identification of a marker that could predict patient responsiveness to therapy became an area of active research. Staudt et al.[23] isolated immunoglobulines from patients' blood samples prior to IA and tested their effect on the contractility of rat cardiomyocytes. Only the group of patients whose antibodies depressed the contractility of cardiomyocytes (cardiodepressant group) showed significant improvement after IA therapy.

IgG_3 plays an important role in the reversibility of this disease. Staudt[24,26] compared the results of adsorbing patients' serum either with columns with low affinity to IgG_3 (protein A column[24,26]) or columns with high affinity for all IgG subclasses (anti-IgG[26] or improved protein A[24]). Patients who received treatment with high-affinity IgG_3 columns showed significantly greater improvement of clinical, echocardiographic and hemodynamic parameters compared to patients who received treatment with low-affinity IgG_3 colums.[24,26]

Even though good results have been achieved, there are still some issues that remain unsolved. Policlonal IgG substitution was performed at most of the studies.[23-29] This procedure *per se* has been related to improvement of heart failure patients,[34,35] but Felix et al[30] evaluated the patients before polyclonal IgG substitution and concluded that patients benefited from IA alone.

The follow-up study with the longest duration lasted 36 months[29] after the first IA course. Thus, the long term benefit and adverse effects of IA therapy are still unknown. When applied to other autoimmune diseases, the procedure has to be repeated at regular intervals.

The individuals included in the studies constituted a small (maximal forty-five[23] patients) and homogenous population, with left ventricular ejection fraction lower than 35%.[23-29] Thus, the benefit of this procedure in patients in an earlier disease stage and better heart function remains unknown.

A large scaled multicentre study should be done to address these and other issues,[7,15,28] analyzing a more heterogenous population and evaluating them over a longer period of time.

Current data show that IA improves the clinical situation and the prognosis of some DCM patients and potentially delays the need for heart transplantation in patients in an advanced stage of the disease.[9]

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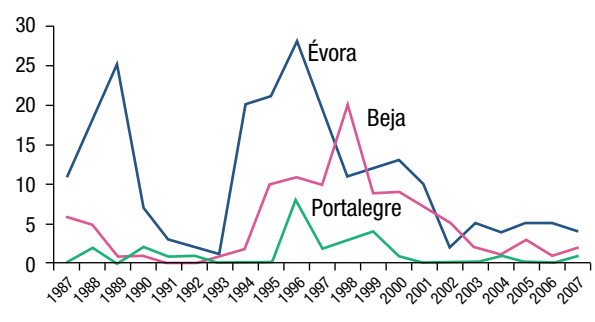
ERRATA

No trabalho de J. A. David de Morais – "*Progressão e declíneo da hidatidose humana em Portugal: análise histórico-epidemiológica*" – publicado no último número da nossa revista (Medicina Interna 2010;17(4):274-85), por lapso, a *Fig. 3* saiu truncada, facto que se lamenta. Assim, reemprime-se a *Fig.* em causa com a devida correcção (indicação dos respectivos distritos).



"Doenças de Declaração Obrigatória": casos de hidatidose no Alentejo por distritos e anos.

FIG. 3