Patogeneza complicațiilor cardiace determinate de HIV
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Pathogenesis of HIV-related cardiac complications identified a high-risk population, which required early therapy.

A wide variety of possible etiological agents were postulated in HIV related cardiac complications like: myocardial infection with HIV itself, autoimmune response to viral infection, opportunistic infections, other viral infections, nutritional deficiencies, prolonged immunosuppression, cardiotoxicity of antiretroviral therapy.

Pathogenesis of myocardial disability in HIV infection/AIDS

AIDS is characterized by the severe acquired immunosuppression, which leads to a great number of infections or malignancy; it also leads to irreversible and progressive multiorgan dysfunction.

The prevalence of cardiac disability is 28-73% in HIV infected individuals (Kaul et al., 1991). Pathogenesis of cardiac complications is not yet fully known; there are many theories concerning triggering mechanism. Some theories suggest the direct action of HIV on the myocardial tissue, without specifying the mechanism of this action.

Some authors suggest the autoimmune disability due to T-helper lymphocytes, followed by hypergammaglobulinaemia; that leads to systemic inflammatory response, which affects the
myocytes, followed by a negative inotropic effect (Acierno, 1989; Herskowitz et al., 1993).

On the other hand, cardiac autoantibodies were detected in patients’ blood, as a result of HIV-induced synthesis of proteins similar to those in the myocytes membrane. The membrane proteins are identified as antigens causing an autoimmune process followed by structural disability of the myocytes.

HIV may persist in receiver cells of the myocardium and cortex, even after antiretroviral therapy. Receiver cells can maintain HIV-1 for long periods and they may chronically release the cytotoxic cytokines (tumor necrosis factor α, IL-6, endothelin-1), leading to the appearance and development of cells injuries, despite the specific therapy (HAART).

The speculative pathogenesis mechanism, which might be possible and could inspire new clinical studies in order to prove its veracity, is the following: the HIV-1 or other virus infection of dendrites, CD4 lymphocytes, myocytes or neurons, may be responsible for the release of the cytotoxic cytokines (TNFα, IL-1, IL-6) and these cytokines will activate the induced NO-synthase. It was proved that HIV-related GP120 increases the synthesis of NO activating nuclear transcription factor (NF-kappa β) into mouse cells; this process is activated by MAP kinase p38. Other studies are necessary to confirm this possible mechanism of cardiac injury.

The increase of TNFα levels and induced NO-synthase levels was also found in HIV-negative patients with dilated cardiomyopathy.

The increase of IL-6 levels, a multifunctional cytokine, was reported for a limited number of patients with evidence of myocarditis or borderline myocarditis. Although the role of IL-6 in murine myocarditis is still unclear, it is known that IL-6 plays an important part in triggering immune response and viral replication.

Levels of TNFα and induced NO-synthase were higher in myocytes from the HIV-infected patients with dilated cardiomyopathy in comparison with the levels from HIV-negative patients with idiopathic dilated cardiomyopathy. Levels of both markers varied inversely with CD4 count; particularly, the level of induced NO-synthase is correlated with mortality and it was increased in patients with viral co-infections (cytomegalovirus and Coxsackie virus group B).

The interaction between cytotoxic T lymphocytes and the complex Fas/Fas (receptor-ligand) in target cells, may cause mitochondrial injuries followed by pro-apoptotic mitochondrial factors release (cytochrome C, apoptosis induction factor - AIF). The same mitochondrial injuries may be caused by the reactive species of oxygen released through lymphocytes and monocytes activation.

Hypergammaglobulinaemia, high levels of circulating immune complex and different type of autoantibodies were identified in HIV-infected patients blood; that usually has a negative prognosis.

Although the importance of some autoantibodies is not clear (antineutrophil, anticytoplasm, antiphospholipid), it is possible that unidentified autoimmune processes may appear. The reaction between autoantigens and major histocompatibility complex in dendrites, phagocytes, myocytes (MHC I) and B lymphocytes (MHC II), leads to the synthesis of autoantibodies (anti α myosine); these autoantibodies are responsible for the direct cell injury.

Central nervous system injuries, especially of the autonomic nervous system, may amplify functional and structural disability of myocytes, by increasing sympathetic tonus and by the releasing of the catecholamines, followed by the down regulation of β adrenoreceptors.

From histopathological point of view, myocarditis is the most studied of the possible causes of dilated cardiomyopathy in AIDS. HIV virions seem to infect myocardiocytes in patchy distribution and no clear association was made between the infection and functional disability.

We do not know exactly how the viruses reach cells without receptors for CD4, like myocardiocytes. Receiver cells (for examples dendrites) may play an important part in pathogenesis; they may interfere in the interaction between the virus and myocardiocytes, and also in the multifunctional cytokines activation.

Some authors suggested that nutritional deficiencies have a negative inotropic effect; for example, it was mentioned that extra selenium intake improves the myocardium contractility.

Autoimmunity and myocardial complications in AIDS

Some authors suggested that different types of autoimmune process might appear in AIDS, in patients predisposed to autoimmune diseases through the presence of Human Leukocyte Antigens or the non-HLA genes.

Some common viruses induce or only facilitate cardiac autoimmune process in HIV-infected patient. For example, viruses with cardiac affinity can modify the myocytes antigens or only hidden epitopes placed on the cell membrane, leading to
an aberrant autoimmune response against autoantigenic endogenous peptides associated with MHC. The expression of myocytes antigens may be responsible for the chronic inflammation and for the microscopic injuries in some cases of myocarditis, although the mechanism is not yet fully known. Nevertheless, this hypothesis was demonstrated through experimental studies on animals in case of myocarditis with cytomegalovirus and coxsackie virus group B (Herskowitz et al., 1992; Herskowitz et al., 1994).

The antigens of MHC I are not represented in the normal myocytes or in dilated cardiomyopathy, but the antigen impregnation of sarcolemma in HIV-negative patients with myocarditis and dilated cardiomyopathy has been demonstrated by the use of immunoperoxidase method. Moreover, a significant number of CD8 and CD4 lymphocytes in association with the increase of MHC I antigens expression was found in apparently normal histological tissue through endomyocardial biopsy from HIV-infected patients with heart failure (Herskowitz et al., 1994).

These immunohistochemical results were identical with the results from HIV-infected patients with heart failure and histological evidence of myocarditis, showing that histological methods are not sufficiently to exclude the presence of myocarditis in AIDS patients.

Cardiac autoantibodies were detected through immunofluorescent methods in 30% of HIV-infected individuals with cardiomyopathy and in 20% of their asymptomatic relatives. Anti α myosine autoantibodies are the most cardiospecific antibodies and their presence in dilated cardiomyopathy was demonstrated through ELISA (Goldman et al., 1995).

Experimental models have also demonstrated the association between α myosine and autoimmune cardiac complications: some mice may develop dilated cardiomyopathy with anti-α myosine antibodies after immunization with α myosine or Coxsackie virus group B infection (Neu et al., 1987).

Not only α myosine is involved in the pathogenesis of dilated cardiomyopathy. β myosine involvement was shown through a minor study, by Herskowitz and his colleagues; they identified by the immunofluorescent method the presence of cardiac β myosine autoantibodies in patients with dilated cardiomyopathy and evidence of active myocarditis, and the absence of these autoantibodies in HIV-infected individuals without cardiac complications. For the first group of patients, it was found by ELISA that anti β myosine antibodies are cross interacting with skeletal muscle and myocondrial adenosine-nucleotid translocator (Herskowitz et al., 1989).

The incidence and clinical importance of specific cardiac autoantibodies were studied on 74 HIV-infected patients (Currie et al., 1998). 28 of these patients had echocardiographic evidence of myocarditis, 16 of them left ventricular dysfunction and 12 of them suffered from dilated cardiomyopathy. The second group, HIV-negative control group, included 52 patients with low risk of infection and 14 i.v. drug users, all of them with no echocardiographic evidence of cardiac dysfunction. Specific cardiac autoantibodies detected by immunofluorescent methods were frequently found in patients with myocardial complications, especially in HIV-infected patients. High levels of cardiac autoantibodies (anti α myosine) were detected through ELISA in HIV-infected individuals with myocardial dysfunction as compared to those without myocardial dysfunction or those from the control group.

Besides that, the medium level of anti α myosine autoantibodies was higher in HIV-infected individuals as compared to HIV-negative individuals; the highest level of these antibodies was in HIV-infected patients with cardiac complications. So, once again, the involvement of autoimmunity in HIV-related cardiac complications is documented. More than that, these autoantibodies were not found in the blood of the HIV-negative i.v. drug users, demonstrating that the autoantibodies are not consequence of certain type of lifestyle, but the consequence of HIV infection itself.

Therefore, it is possible that in the future, these autoantibodies will be used as biological markers for active cardiac injury in HIV infected patients.

At present, we certainly know that interstitial cells of the myocardium structure may be infected with HIV, but there are few data regarding the presence of HIV in the myocardial cells (Wu et al., 1992).

The contamination with own infected plasma cells leads to a difficult interpretation of the PCR and a difficult examination of cell cultures. The immunohistochemical studies did not bring any evidence about the cardiac expression of GP120 or p24 antigens (Rodriguez et al., 1991).

The presence of a least one gene part of HIV-1 was proved through PCR in endomyocardial samples from 15 HIV-infected patients, 5 of them suffering from cardiac disease.

Although these results are not correlated with clinical and histological evidences of cardiac dysfunction, the increased number of interstitial
dendrite cells was demonstrated in HIV-infected individuals with heart failure.

Although in vitro studies showed that HIV cannot penetrate scheletal muscle cells (Clapham et al., 1989), there is recent data about the development of new fetal myocardial cells; this fact suggests that despite the absence of CD4 receptors on the myocardial cells, HIV-1 could be introduced in cells by means of specific receptor Fc. Therefore, the opinion that HIV plays an important direct part in pathogenesis of myocardial complications is still plausible.

HIV could injure myocardial cells by means of some innocent markers of destruction; this hypothesis suggests that proteolytic enzymes released in the interstice after viral replication attack some cells; this attack is important especially in myocardium, where a great number of interstitial infected cells were described in HIV-infected individuals with evidence of myocarditis (Ho et al., 1987).

Some authors suggest that HIV infection may increase the production of abnormal interferon; this interferon stimulates the production of TNFα or IL, which induce an autoimmune destructive process (Skurkovich et al., 1994).

In conclusion, the mechanisms involved in the appearance of cardiac complications in AIDS or HIV-infection are not fully known. The participation of own abnormal immune system and the interaction with other possible induced factors is important in this process (for example co-infections). There is evidence that demonstrate the participation of myocardial tissue to its own destruction after triggering immune and autoimmune response which lead to cytotoxic cytokines release. Probably, the next research will discover unknown parts of this process.

Bibliografie