Cardiovascular diseases associated with HIV infection and their management

Choroby sercowo-naczyniowe związane z zakażeniem wirusem HIV: diagnostyka, profilaktyka, leczenie

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INTRODUCTION

Human immunodeficiency virus (HIV) was isolated by Luc Montagnier and his co-workers in 1983 in the Pasteur Institute (Nobel Prize in 2008 for Physiology or Medicine), and soon after by Robert Gallo's group in the USA in 1984. This virus is widespread worldwide nowadays. In 1986, in France, another type of virus (HIV-2) was isolated. This is more akin to Simian immunodeficiency virus (SIV), originating from the sooty mangabey monkey *Cercocebus atys*, which occurs in west Africa. Both types of virus can cause acquired immune deficiency syndrome (AIDS).

THE EPIDEMIOLOGY OF AIDS

It is estimated that in 2010 about 34 million people were living with an HIV infection worldwide (30.1 million adults — both sexes equally). The largest numbers of HIV patients, 22.9 million, lived in sub-Saharan Africa, about 4 million lived in southern and south-eastern Asia and Latin America, and 1.5 million lived in Eastern Europe. Approximately 2.7 million people were infected worldwide in 2010. According to the Polish National Institute of Public Health — National Institute of Hygiene, from 1985 (the beginning of the HIV epidemic) up to 31 December 2012, a total of 16,314 people were living with an HIV infection in Poland (including foreigners living in Poland); among them there were 5,946 intravenous drug users. 2,848 had been diagnosed with AIDS and 1,185 had died of the disease.

PATHOPHYSIOLOGY OF HIV INFECTION

HIV is a retrovirus, which belongs to the family of lentiviruses. Inside the capsid, there are a single-stranded RNA, reverse transcriptase and integrase. HIV is transmitted by sexual contact, blood or blood product transfusion, and vertically from an HIV-infected mother to the newborn (before or during the birth, and by breast-feeding). In adults, about 5–10 years pass between the primary infection and the occurrence of the first symptoms (Fig. 1).

HIV uses glycopeptide gp120 to attach to CD4 protein on helper lymphocytes, macrophages, monocytes, eosinophils, dendritic cells, microglia and oligodendroglia, T cell precursors in bone marrow and thymus. After the virus has penetrated into the cell (this process needs binding gp120 to CD4 and chemokine coreceptor), the viral single-stranded RNA genome is converted (reverse transcriptase) into a single-strand DNA, then a second complementary one is created, and subsequently integrated into a host chromosome by the viral integrase and cellular LEDGF/p75 factor. Available antiretroviral agents block the replication of the virus but they are unable to remove its genetic material from the host nucleus. HIV replication is very dynamic — every day 109 virions are produced and destroyed. During reverse transcription 1 to 10 errors are made on one genome/replication cycle [1, 2].

After the incubation period, AIDS develops progressively. In the course of the disease, there is a significant decrease of CD4+ T lymphocytes count. Opportunistic diseases and cancer usually appear when CD4+ T cell level is lower than 200/mm^3 or 15% (deep immunodeficiency).

HIV infection stages:

— Acute retroviral syndrome 'mononucleosis-like syndrome' — lasts for a few weeks after acquisition of the infection as a result of the spread of the virus with infection of the lymph nodes and occurs in approximately 40–90%

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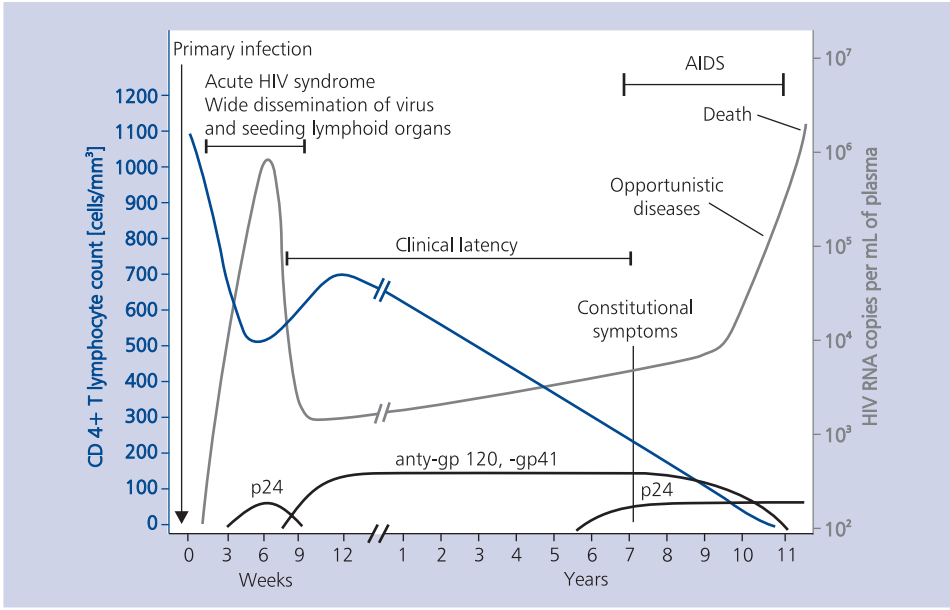

Figure 1. The natural course of HIV infection (based on Gąsiorowski et al. [1, 2])

of infected adults. Typical symptoms are: fever (96%), lymphadenopathy (74%), pharyngitis (70%), maculopapular rash (70%), and joint and muscle pain (54%); other symptoms are encountered in less than 15% of cases.

— Asymptomatic phase, chronic — possible occurrence: shingles, skin and mucous membrane diseases, fever > 1 month, diarrhoea > 3 months, peripheral neuropathy, pelvic inflammatory disease. During the chronic phase, organ damage, including cardiomyopathy, can occur.

— AIDS: opportunistic infections (such as Pneumocystis jioverci pneumonia, Cryptosporidiosis), Mycobacterium avium infection, recurrent severe bacterial infection, recurrent Salmonella bacteremia, recurrent pneumonia > 2 within 12 months; extrapulmonary tuberculosis, candidiasis of the oesophagus, bronchi, trachea, extrapulmonary histoplasmosis and cryptococcosis, inflammation of the oesophagus and ulcers associated with HSV infection, progressive multifocal leukoencephalopathy, cancer indicators (Kaposi's sarcoma, lymphoma, invasive cervical cancer), encephalopathy and wasting syndrome.

HIV antibodies appear in a few weeks after the infection (at least eight days, on average 14–60 days, with a maximum of 12 weeks). Diagnosis of HIV infection in adults is performed by an ELISA test (sensitivity > 98% and specificity 99%) three months after exposure and confirmed by Western blot (higher specificity with lower sensitivity). New — fourth generation ELISA tests identify not only the HIV antibodies but also a protein p24 and can detect infection much earlier. Polymerase chain reaction (PCR) detection of the virus is mainly used to diagnose vertical infections in children aged < 18 months due to the presence of the mother's antibodies (99–100% sensitivity and 100% specificity) [2].

IMPACT OF HIV INFECTION ON THE CARDIOVASCULAR SYSTEM

Patients with AIDS are at increased risk for cardiovascular (CV) diseases because of traditional CV risk factors that are commonly present. Hypercholesterolaemia/atherogenic dyslipidaemia, high blood pressure, and smoking are among them, also a proatherogenic diet, obesity, diabetes, low physical activity and, along with increasing survival of HIV-infected patients, unmodifiable factors like older age and male gender become important. It has been reported that a patient infected with HIV develops symptomatic atherosclerosis noticeably earlier; therefore HIV infection is considered an independent risk factor for CV disease along with other chronic inflammatory states. HIV-infected patients often have low total cholesterol and LDL-cholesterol as well as low HDL-cholesterol and increased triglycerides. Underlying mechanisms are varied and not fully elucidated. Low level of CD4+ lymphocytes T is associated with decreased apolipoprotein B [3]. LDL-cholesterol is smaller than normal [4] and harder to eliminate, and prone to oxidation (proatherogenic 'small dense LDL') [5].

Combined antiretroviral therapy results in increased LDL-cholesterol, and the predominance of small, dense LDL particles. Protease inhibitors may induce severe hypertriglyceridaemia with values of up to 1,000 mg/dL. Moreover, HIV-infected macrophages are more prone to develop atherosclerotic plaque. Highly active antiretroviral therapy (HAART) also increases blood pressure and insulin resistance, and this could contribute to the increased coronary artery disease

(CAD) risk. As a consequence, CAD risk may be doubled in patients treated with HAART compared to a non-infected cohort [6]. This risk may be especially prominent in young, male, heavy smokers with dyslipidaemia treated with HAART.

HIV-infected patients (adults and children) often have elevated inflammatory parameters in laboratory tests. Elevated D-dimer, interleukin-6, C-reactive protein are linked to the risk of CV diseases including heart failure [7]. It has been estimated that the sTNF-R1 increased in HIV-infected patients is related to a higher risk according to the Framingham Cardiac Risk score [8]. The ongoing inflammatory process, along with the use of antiretroviral drugs (combined antiretroviral therapy based on protease inhibitors — up to 30–90%), results in the development of insulin resistance and lipid disorders [9]. Insulin resistance may also be a result of abnormal redistribution of fat tissue i.e. an accumulation of visceral fat and fat loss on limbs in the course of infection and treatment (lipodystrophy) [10]. As a consequence of insulin resistance, lipid disorders often occur in HIV-induced metabolic syndrome (about 30–40% of children). These mechanisms and intensive antiretroviral therapy are responsible for up to a three-fold increase in the risk of incidental diabetes in a three year follow-up [11]. Moreover, in HIV infection, damage to the arterial wall occurs as a result of the virus itself, and also the antiviral therapy [12]. The cross-sectional study the Fat Redistribution and Metabolic Change in HIV Infection study, conducted worldwide, showed a significant increase of the intima-media complex of arterial wall in HIV+ patients, independent of the lipid profile abnormalities [13]. A European study on lipid disorders among HIV-infected children is being conducted in parallel with the Paediatric European Network Trial of AIDS.

HIV-infected patients often suffer from autonomic nerve system dysfunction manifested by inadequate heart rate, fainting, decreased sweating, diarrhoea, bladder dysfunction, and also erectile dysfunction [14].

CARDIOVASCULAR CLINICAL SYNDROMES ASSOCIATED WITH HIV INFECTION

Coronary artery disease

The commonly present metabolic risk factors and vascular changes described above result in a 75% increase of myocardial infarction risk in an HIV-infected group compared to the general population [15]. There is also a two-fold increase in CV risk (myocardial infarction, ischaemic heart disease, cerebral vascular events) in patients infected with HIV treated with antiretroviral therapy [16]. CAD occurs more frequently in patients treated with nucleoside reverse transcriptase inhibitors [17]. Myocardial infarction is more common in younger people with HIV. They also have less expressed typical symptoms of a heart attack. Retrospective observations in a cohort of young people infected with HIV, who had a heart attack, showed that despite more advanced coronary heart disease, their short-term prognosis was similar to the general population [18].

Cardiomyopathy associated with HIV infection

In about 30% of patients with deep immunosuppression (CD4+ < 100/mL) dilated cardiomyopathy is observed, although the size of the heart chambers only slightly exceeds the normal values. These changes are accompanied by a slight decrease of left ventricular ejection fraction (EF = 45–54%), mainly due to segmental hypokinesis [1, 19]. Left ventricular systolic dysfunction in patients with HIV infection, initially clinically silent, becomes gradually symptomatic (HIV-induced cardiomyopathy). The etiopathogenesis of left ventricular failure differs: it can be a consequence of virus infection [20], systemic and local inflammatory reactions [21], the presence of autoantibodies [20], or immunodeficiency-related infections. A viral load greater than 500 copies/mL is associated with more than a two-fold increase of heart failure risk [22].

In the course of cardiomyopathy, dilatation of the left ventricle often coexists with mild myocardial hypertrophy [23], typically observed in the region of the posterior wall or interventricular septum [19]. Disease aetiology is not fully understood. Animal models show that the induction of cardiac damage occurs by promoting the expression of induced nitric oxide synthase (iNOS) caused by tumour necrosis factor-α, interleukin-1 and interleukin-6 [24]. Cardiomyopathy can be aggravated by the use of nucleoside reverse transcriptase inhibitors therapy [25]. Isolated right ventricle dysfunction is also reported. Cardiac complications in children include dilated cardiomyopathy of the left ventricle and right ventricular hypertrophy [26].

Myocarditis and endocarditis

Myocarditis in the course of AIDS may develop due to different aetiologies: fungal (Candida, Histoplasma, Cryptococcus, Aspergillus), viral (herpes simplex, cytomegalovirus), bacterial, tuberculosis and toxoplasmosis. Also, HIV infection itself can cause myocarditis [27]. Autoimmune processes and AIDS indicator pathogens can lead to endocarditis. Non-bacterial thrombotic endocarditis is possible and can be associated with hypovitaminosis (vitamin C) and immune deficiency progress. Bacterial endocarditis usually develops in intravenous drug users (Staphylococcus aureus and Streptococcus viridans), and infection is located on the right heart valve (tricuspid valve) with subsequent lung abscesses. The HIV virus itself does not damage the endocardium, but endocarditis is due to the progressive decline of the CD4+ lymphocytes count.

The risk of arrhythmias and sudden cardiac death in HIV infection

Myocardial damage, autonomic neuropathy, and pharmacological treatment can cause cardiac arrhythmias. Antiretroviral drugs such as protease inhibitors (lopinavir and atazanavir) can cause QT prolongation and subsequent arrhythmias. Use of protease inhibitors may be associated with atrioventricular block and intraventricular conduction disturbances (left

bundle branch block) [28]. Pentamidine/pyrimethamine and trimethoprim/sulphamethoxazol that are used in the treatment of Pneumocystis jioverci infection can also prolong the QT interval. Systemic fungal therapy with amphotericin entails the risk of arrhythmias. QT prolongation is more evident in hypoxia and heart failure [29] and it can be threatened by subsequent polymorphic ventricular tachycardia (torsade de pointes). Gancyclovir may induce ventricular tachycardia [29].

Other abnormalities of the heart associated with HIV infection

In 20% of HIV-infected patients, pericardial effusion is detected by echocardiography, and the incidence increases in patients with fully symptomatic AIDS (CD4+ < 100/mL). In 4% of cases, the amount of fluid is large but cardiac tamponade is relatively rare [30]. Pericarditis in HIV infected patients may be a result of bacterial infections — the most common cause is tuberculosis. Pericardial effusion/pericarditis may be a sign of Kaposi's sarcoma [31] and lymphomas [32]. Tumours of the heart are possible; usually these are secondary malignancies (Kaposi's sarcoma, non-Hodgkin's lymphoma).

Abnormalities of cardiac development are observed in children born to mothers treated with antiretroviral therapy during pregnancy. Congenital heart abnormalities comprise small heart chambers, ventricular septum thinning, and the deterioration of left ventricular function (both systolic and diastolic) [33, 34].

In 0.5% of cases, pulmonary hypertension develops as a result of pulmonary artery damage associated with viral load. Three-year survival of these patients is approximately 70% [35].

Damage can also affect peripheral veins and arteries. Infection with HIV, cytomegalovirus or tuberculosis may increase the incidence of aortic aneurysm and cerebral aneurysms [36, 37] as a consequence. Increased level of plasminogen activator inhibitor type 1, heparin cofactor II, protein S, and D-dimers may promote venous thromboembolism, which is more common among HIV infected patients than in the general population [38].

STRATEGY OF CARDIOVASCULAR PREVENTION IN PATIENTS WITH HIV INFECTION

Lifestyle modification

It is mandatory for all high risk patients to stop smoking tobacco, a well-known CV risk factor. Proper diet and moderate physical activity contribute to the reduction of insulin resistance, lowering blood pressure, desirable blood lipid modification and as a consequence slow the progression of atherosclerosis. This is not different from the generally accepted recommendations for non-pharmacological risk reduction of CV disease [28, 39]. The increased risk of early atherosclerosis and its complications associated with HIV infection demands more vigorous implementation of CV prevention guidelines. It is necessary to check lipid profile after diagnosis of the disease and 3–6 months after initiation of antiretroviral therapy treatment. In children, lipid profile should be monitored routinely every six months. Additional regular sport activities are recommended, but strength sports (isometric) should be avoided. Parents are educated about healthy lifestyles and the principles of a low-fat (sometimes low-carb) diet, tailored to the needs of the developing child. Every three months the weight and height of children, waist circumference, body mass index, and blood pressure should be measured. Once a year, bone densitometry is recommended together with an assessment of fat distribution [39].

Pharmacological prevention

The recommendations do not differ notably from primary prevention in the general population. Due to the observed increased risk of CV complications in HIV-infected patients, statins are recommended, if total cholesterol > 190 mg/dL and/or LDL-cholesterol > 115 mg/dL. Caution is advised due to possible drug interactions i.e. simvastatin is contraindicated if protease inhibitors are used. Rosuvastatin, if used with lopinavir/ritonavir, needs caution [40]. It is recommended to use low-dose rosuvastatin, atorvastatin to avoid the increase of drug concentration induced by CYP3A4 inhibition by protease inhibitors. The additional anti-inflammatory effect of statins should be taken into account. Some figures suggest that statins may prolong life in HIV positive patients [41]. Fibrates should be started if triglycerides level is > 500 mg/dL [39, 42].

SUMMARY

HIV infection is associated with accelerated development of CV disease and can be a challenge for an infectious disease specialist involved in the care of HIV-infected patients. The most common CV complications include: premature CAD and myocardial infarction, myocarditis, and dilated cardiomyopathy. The proarrhythmic effects of some drugs used in antiretroviral therapy should also be taken into account. The efficacy of pharmacotherapy in controlling HIV infection results in a significant improvement in the life expectancy of patients infected. The new challenge in this group of patients involves ageing. In HIV positive patients, ageing is about ten years earlier than in the general population. This increases the likelihood of CV disease resulting not only from ageing but also as a consequence of HIV infection, its sequelae and antiretroviral therapy. Recommendations applying to CV prevention consist of lifestyle modification and pharmacotherapy, preferably with statins. The guidelines for the treatment of symptomatic CV disease do not differ from generally accepted standards.

Conflict of interest: *none declared*

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