

Recurrent cerebral infarcts as the first manifestation of infection with the HIV virus

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Abstract

There is an increased risk of stroke in patients with HIV infection. One of the mechanisms is production of anticardiolipin (aCL) antibodies, induced by the virus. Many studies have documented a high incidence of aCL antibodies in patients with HIV infection and the increased risk of stroke, although there is no such correlation with other viruses that also stimulate production of aCL antibodies. Probably the HIV virus also stimulates production of other serum proteins, which together with aCL antibodies make procoagulation complexes, similar to the primary anticardiolipin syndrome. We present a case of a 40-year-old patient, hospitalized three times in our department because of recurrent ischemic strokes. Diagnostic tests revealed a high titre of anticardiolipin antibodies and the early stage of HIV infection. Recurrent ischemic strokes were the first manifestation of HIV infection in this patient.

Key words: stroke, HIV, antiphospholipid antibody

Introduction

There is an increased risk of stroke in patients with HIV infection. The incidence of stroke in HIV/AIDS (+) patients is approximately 2-7% but a prevalence of 40% has been observed in autopsy studies [1,6]. The majority of strokes in AIDS patients are ischemic, only about 1% is hemorrhagic [9]. Cerebrovascular changes are usually a complication of HIV infection but may be also caused by typical stroke risk factors for the general population. Strokes of vascular origin are usually the results of vasculitis associated with opportunistic infections: bacterial

(syphilis, tuberculosis), viral (cytomegalovirus, herpes), fungal (cryptococcosis, aspergillosis, candidiasis), and parasitic (toxoplasmosis). They may be also a complication of radiotherapy used in the treatment of the central nervous system lymphoma [4]. The causes of embolic strokes are most often bacterial and marantic endocarditis. Cachexia and dehydration present at the final stages of the disease can lead to global hypotension and „watershed” infarctions. In addition, protease inhibitors used in the treatment of AIDS cause metabolic disturbances and speed up the development of arteriosclerosis [8].

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Hemorrhagic strokes are caused by intraparenchymal mass lesion, e.g. neoplasm like Kaposi's sarcoma or by mycotic aneurysms forming in the course of bacterial endocarditis [9].

The above listed causes of stroke appear in the advanced stages of AIDS, but even in the initial stage of the infection there is an increased risk of vascular changes. It is probably the result of changed B-lymphocytes function arising after HIV infection. They start production of faulty antibodies such as antiphospholipid antibodies (APLA), which are the stroke risks factors [7].

The study of HIV /AIDS positive patients who experienced incidents of the central nervous system ischemia and with no evidence of secondary infections or neoplasm, showed that 75% of those patients had anticardiolipin (aCL) antibodies as well as antibodies against B2 glycoprotein, protein S and protein C, which is significantly more often than in infected patients without a stroke [4]. 80% of HIV patients with cerebral perfusion abnormalities seen in HMPAO-SPECT had aCL antibodies [10].

Antiphospholipid antibodies, especially anticardiolipin antibodies and lupus anticoagulant are immunoglobulins directed against negatively charged phospholipids and serum proteins associated with phospholipids: B2 glycoprotein, thrombomodulin, protein S and C [12]. The interaction between aCL antibodies, B2 glycoprotein and other serum proteins reduces their anticoagulation effect. Moreover, the antibodies reduce the inhibitory action of B2 glycoprotein on procoagulant factor X and through the reaction with cell membrane phospholipids, they activate thrombocytes and damage vascular endothelium. In effect, they cause venous and arterial thrombosis. They give incorrect results in phospholipid dependent laboratory tests: prolonged activated partial thromboplastin time and false positive VDRL, but these tests are sensitive only to 30% of APLA. The most reliable method to detect these antibodies is immunological test ELISA [13].

The occurrence of aCL antibodies together with one or more clinical symptoms such as: venous or arterial thrombosis, recurrent miscarriages and thrombocytopenia are called an APLA syndrome. Frequent neurological disturbances found in this syndrome are migraines, epileptic attacks, choreoatetosis, Guillain-Barre syndrome. The APLA syndrome may also cause skin necrosis, livedo reticular, Raynaud's phenomenon, hemolytic anemia and heart valves destruction [3].

The most common manifestation of arterial thrombosis is ischemic stroke, usually related to the territory supplied by the large or medium artery branch, and as a rule proceeded by episodes of transient ischemic attacks [3,14]. Strokes usually do not cause a large neurological deficit, however they are characterized by a high reoccurrence level of 14-20% per year. In the course of the illness also small penetrating arteries become damaged. This leads to lacunar strokes and can cause multi-infarct dementia [14]. The incidence of cerebrovascular events increases if other risk factors coexist, especially nicotine and hiperlipidaemia

APLA syndrome can be primary or secondary to other diseases such as: SLE, Sjögren syndrome, sclerodermia. It can be also induced by medications such as phenothiazines, procainamid, phenytoin and oral contraceptives, or accompanying infections: commonly HIV, but also syphilis, Lyme disease, mononucleosis [3,11].

Case report

We want to describe a case of a patient, whose first signs of HIV infection were repeated episodes of cerebrovascular events and who had a high level of aCL antibodies.

The patient, a 47-year-old soldier, for the first time came to our department in 1999 with difficulties in speech understanding and weakness of the right limbs. The symptoms lasted about half an hour and resolved before the patient was admitted to the hospital. Apart from cigarette smoking he had no risk factors for stroke. His family history did not supply any relevant information. In laboratory tests he had transaminase level twice above the norm, slight trombocytopenia, other results were within limits. Computer tomography (CT), echocardiography and ECG were normal. EEG showed insignificant changes (theta waves) in both temporal regions. The diagnosis of transient ischemic attack was made at that time. The patient was discharged from hospital and received acetylsalicylic acid as prophylactic treatment.

After 3 years, in August 2003, the patient was admitted again to the neurological department with repeated aphasia and weakness of the right limbs. He also complained of dizziness, problems with balance and severe migraines, which had commenced two years previously. He suffered from mood changes, insomnia, and often became aggressive. He was under

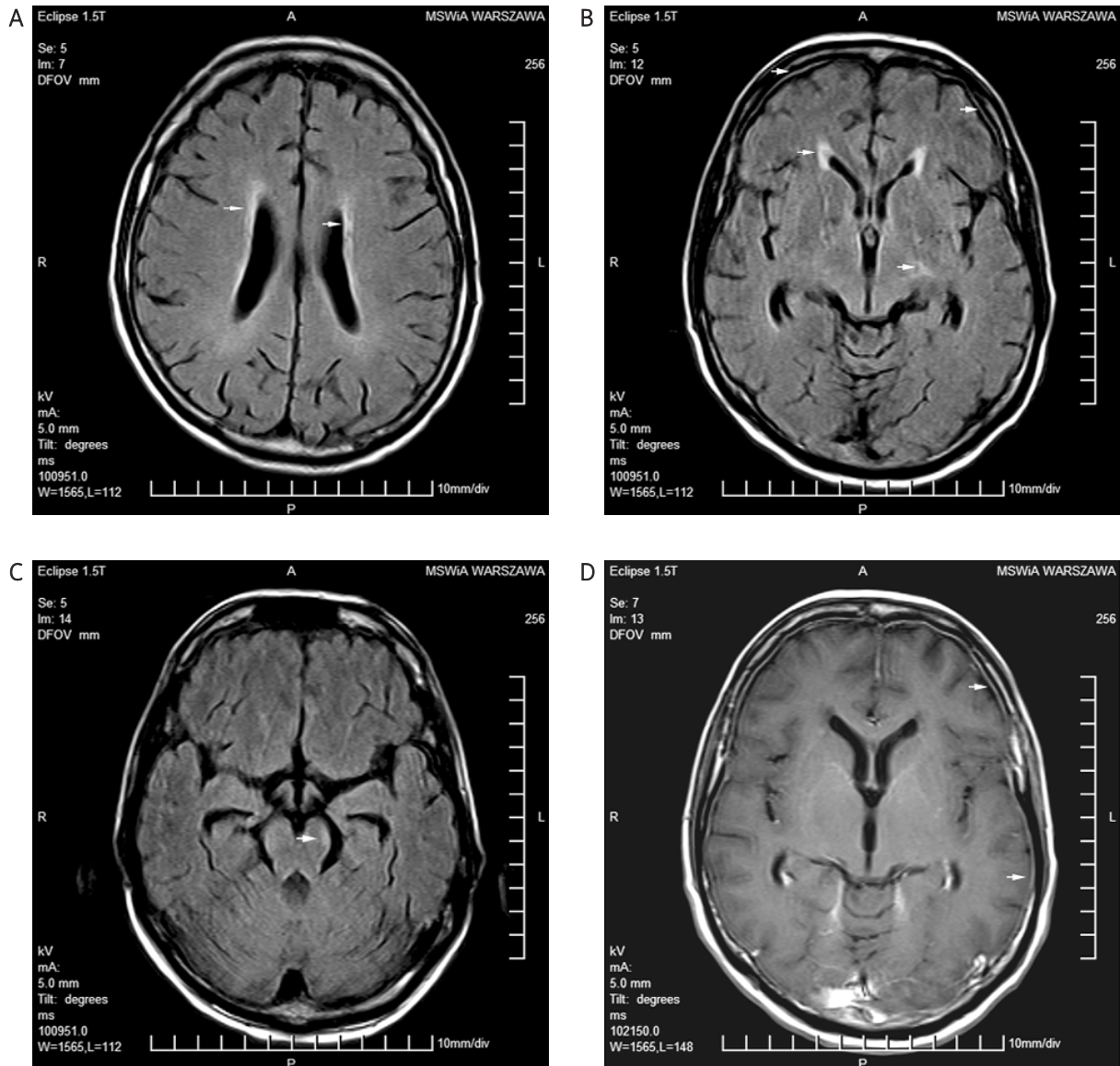


Fig. 1 A, B, C, D. MRI examination, FLAIR (A, B, C) and T1 weighted after contrast administration images (D) revealed:

- hyperintensive areas in the periventricular and semioval centers white matter, suggesting its damage (A, B);
- a small lacune surrounded by zone of gliosis (B) located at the basal part of the posterior crus of the left internal capsule, as in developed small infarct;
- hyperintensive lesion in left cerebral peduncle (C) – for further differentiation;
- thickening of meninges (B) and its strong contrast enhancement (D) – morphological signs of meningitis

psychiatric care and was given antidepressant treatment, however his condition did not improve. On neurological examination he had mild right pyramidal syndrome and bilateral cerebellar signs. Laboratory findings showed, as previously, thrombocytopenia and

an increased level of transaminase. Brain CT and USG –Doppler of carotid arteries were normal. MRI examination revealed on T2 and FLAIR imaging hyperintensive lesions in the periventricular white matter. These abnormalities were non-specific, and the

patient was advised to return for control MRI scan in six months. The patient was discharged from hospital and given ticlopidyne as prophylactic treatment.

Two months later the patient was admitted again to the hospital because of progression of the neurological deficit. On examination he had aphasia and spastic moderate right hemiparesis, bilateral cerebellar syndrome, numbness of legs and loss of ankle jerks. The patient's wife complained of his emotional instability and progressive behavioral changes. The patient also suffered from insomnia and memory loss. Our psychiatric consultant diagnosed depressive syndrome and disturbances of the cognitive function, mainly memory and attention.

CT examination showed periventricular hypointensive changes of vascular origin. Brain MRI revealed damage of the white matter in the periventricular region and centrum semiovale, more extensive than on the previous examination (Fig. 1A, B). There were also small lacunas, hyperintensive on T2 and FLAIR images, located in the left putamen and cerebral pedunculus (Fig. 1C). Moreover, FLAIR and post-contrast T1 images revealed thickening of leptomeninges, which suggested meningitis (Fig. 1D). The electromyography examination was performed because the suspicion of polyneuropathy revealed sensorimotor neuropathy with mixed axonal and demyelinating features. Examination of cerebrospinal fluid (CSF) showed an inflammatory process with lymphocytic pleocytosis 76 cells/mm³ and elevated protein level to 183 mg%. The proteinogram of serum and CSF showed features of a chronic inflammatory process: hypoalbuminemia and polyclonal hypergammaglobulinemia. Autoimmunological tests revealed increased levels of anticardiolipin and antiphosphoserine antibodies.

Antinuclear antibodies and anticoagulant tests were negative. Further diagnostics tests to detect the cause of infection revealed positive HIV antibodies in duo test. Other results for syphilis (VDRL, Fta), tuberculosis, borreliosis, Hbs were negative. The patient denied that he had had any behavioral risks associated with HIV infection. His wife was HIV negative.

The patient was sent to the infectious diseases hospital where HIV infection was confirmed by the PCR method. Immunological Western blot test revealed antigens p24, gp41, gp160, gp120 and the level of Cd4/Cd8 was 0.68. The patient also had IgG antibodies against toxoplasmosis, cytomegalovirus and HCV.

During the hospitalisation the patient had an epileptic attack and received anticonvulsant treatment. He was discharged from hospital without antiviral drugs because of the low level of virus RNA.

Discussion

The presented young patient suffered from recurrent strokes during a short time period. Besides cigarette smoking he had not any typical risk factors for cerebrovascular diseases. In routine laboratory tests he had only a mild increased level of transaminases and hypoprothrombinemia. More detailed diagnostic tests revealed a high level of anticardiolipin antibodies. Brain MRI examination showed diffuse changes in white matter and leptomeningeal and parenchyma enhancement. Changes in CSF were characteristic for a lymphocytic inflammation and microbiological tests detected an HIV infection.

We diagnosed recurrent ischemic strokes in the patient with HIV infection and secondary antiphospholipid syndrome. Repeated ischemic events, without severe neurological deficit, strong migraines, epileptic attacks and progressive global dysfunction of CNS: were characteristic for aCL syndrom. Multiple vascular changes in the gray and white matter of the brain seen on MRI examination supported the diagnosis.

Antiphospholipid antibodies can be associated with different infectious diseases: borreliosis, syphilis, viral infections. In these infections aCL antibodies act directly against phospholipids and they do not increase the risk of cerebrovascular events [5]. In primary aCL syndrome or associated with autoimmunological diseases ACL antibodies react with phospholipids in association with other present antibodies: against B2 glycoprotein and protein C, protein S and in such complexes they have procoagulation effects [2,12,14]. Also in an HIV infection with aCL antibodies there is an increased risk of thrombotic changes, which can lead to strokes, multiple osteonecrosis, and acute ischemia of lower extremities. There are also cases of catastrophic aCL syndrome with multiple thrombosis of small and large vessels and dysfunction of many organs.

HIV virus, besides aCL antibodies, also stimulates production of antibodies against B2 glycoprotein, serum C and S, similar to primary aCL syndrome [7].

Patients with an HIV infection who have aCL antibodies, as a prophylactic treatment against

cerebrovascular events should receive antiplatelet agents, but if venous or arterial thrombosis occur they should be treated with anticoagulants with INR 2-3.

The presented case shows that in diagnosis of cerebrovascular events associated with aCL antibodies, especially in young patients, one should remember about the possibility of secondary ALS syndrome, not only to autoimmune diseases but also to infection, most frequently HIV.

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