Survey of progress

Neurological complications in AIDS

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Summary. Neurological complications in the acquired immunodeficiency syndrome (AIDS) are an important aspect of this new infectious disease and occur frequently. The existence of neurotropic variants of the human immunodeficiency virus (HIV), the causative agent of AIDS, is probable. Direct infection of the nervous system with HIV leads to a variety of HIV-induced neurological syndromes, the AIDS dementia complex being its most important representative. In addition, a large number of opportunistic infections and malignancies of the nervous system may complicate the disease. Major aspects of the clinical pictures, rational diagnostic approaches and treatment options of the most important sequels of HIV infection of the nervous system are discussed.

Introduction

Within a few years the acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) has become one of the most challenging and threatening problems for the medical profession, public health authorities and society at large [58]. When the first cases of AIDS were described in 1981 in the USA [19], nobody anticipated the coming of a new pandemic. More than 50,000 AIDS patients, some hundred of thousands of patients with pre-AIDS (i.e. the AIDS-related complex/ARC, persistent generalized lymphadenopathy/PGL or the lymphadenopathy syndrome/LAS), and some millions of people infected with the AIDS virus all over the world at present constitute an alarming situation [58]. The number of AIDS patients continues to double every 8–12 months in all countries concerned [13,58]. The disease shows three stages. Progression from the infection to pre-AIDS and from pre-AIDS to AIDS seems to occur in the majority of cases [13,58]. However, a latency period of many years may elapse after the infection before the disease breaks out, eventually leading to death in all full-blown AIDS cases [13,58]. Besides the well-known features of the disease, e.g. Pneumocystis carinii pneumonia or Kaposi's sarcoma, it has soon been recognized that 30%–40% of the AIDS patients develop neurological complaints [29,34,40,49,65,72,111]. Neuropathological examination at autopsy reveals nervous system involvement in more than 80% of the AIDS cases in the larger series [65,86,95]. In about 10%–20% of the patients neurological signs constitute the initial symptoms of the disease [34,65,72,111].

Since the spectrum of possible central nervous system (CNS) and peripheral nervous system (PNS) complications is very variable in these patients, in the future HIV infection and its secondary complications, i.e. numerous opportunistic infections and certain malignancies, will have to be considered in the differential diagnosis of virtually all neurological syndromes (Fig. 1) [12,34,39,40,42,43,65,72,111].

Because the disease is mainly transmitted sexually, most AIDS patients are young or middle-aged, corresponding to the high rate of sexual activity in these groups [34,58]. So far, some of the special risk factors for the HIV infection, such as male homo- or bisexuality, i.v. drug abuse, blood transfusions or haemophilia have sometimes helped the physician to establish the diagnosis. In the next few years, however, these risk factors will lose some of their importance when the heterosexual community is included in the infected population [34,42,43,58]. This development can already be clearly anticipated in the USA and in European countries and has characterized the epidemiological situation in African countries from the beginning, owing to the different promiscuous heterosexual practices in those countries [58].

The poor prognosis of the disease, the present lack of effective treatment of vaccination, and the rapid evolution of the pandemic will confront the clinician with a variety of diagnostic and therapeutic problems arising from the neurological complications of the retroviral infection. This review is intended to describe the major clinically relevant aspects of HIV-induced (primary or secondary) nervous system complications (Table 1).

Neurotropism of HIV

When the retrovirus HIV was discovered in 1983 in France (lymphadenopathy-associated virus/LAV) [3] and in 1984 in the USA (human T-cell lymphotropic virus type III/HTLV III) [48], it was first considered to be an exclusively lymphotropic virus, since it caused immunological problems consistent with the infection and gradual destruction of the so-called CD4+ lymphocytes of the host. When CNS and PNS complications in AIDS patients occurred that could not be explained by opportunistic infections or malignancies, a neurotropism of the HIV was suspected. Isolation of the retrovirus from the brain, spinal cord, peripheral nerves and cerebrospinal fluid...
(CSF) provided substantial support for the theory that HIV is neurotropic as well as lymphotropic [1, 10, 15, 36, 46, 50, 51, 55, 56, 59, 67, 75, 102, 104, 110, 116, 121]. Examination of the antigenic properties revealed common surface antigens of the CD4⁺ lymphocytes and neural tissues [15, 79]. Additionally, similarities were demonstrated in the nucleic acids of AIDS and the visna virus; visna is another “slow virus” that causes chronic encephalopathy in sheep [110, 113]. Therefore, the question arose as to whether or not the neurotropism of the HIV is associated with special HIV variants with neurotropic properties acquired by mutation. CSF samples of AIDS patients with neurological dysfunction contained HIV variants with significant differences in reverse transcriptase activity and cytopathic effects in cell cultures when compared with HIV from the blood of the same patient [10, 51, 104]. These findings are important arguments for the hypothesis that neurotropic variants of HIV do indeed exist. This raises the additional question of whether those variants occur by mutation within the infected individual, which seems to happen frequently in retroviruses [21], or whether they are acquired by the infection with an already mutated HIV with neurotropic properties [10, 104]. Additional genetic analysis of blood and CSF HIV variants will be necessary to clarify these questions.

Neurotropism of HIV does not automatically mean that the neuron itself is the target cell for the virus. On the contrary, monocytes and macrophages and macrophage-derived microglia have been detected as favourite target cells within the CNS [14, 36, 46, 50, 51, 67, 116, 121]. Examination of the surface antigens of the infected macrophages have shown that they originate from circulating blood monocytes and macrophages that have entered the CNS [14]. This makes it highly probable that the infected monocytes or macrophages may serve as a vehicle for the HIV to cross the blood-brain barrier [67]. This form of intracellular transport across the blood-brain barrier seems to be possible at any time in the course of the disease, resulting in early, concomitant or late complications in the nervous system [1, 17, 55, 56].

It is not yet clear whether infection of the nervous system by the HIV automatically means the immediate outbreak of acute or chronic AIDS encephalitis, or whether the virus lies dormant in the nervous tissue without causing damage for a longer or perhaps indefinite period of time [55]. However, it should be taken into account that CNS infection with HIV constitutes a considerable virus reservoir, and experiments have demonstrated the persistent viability of the HIV in the brains of AIDS patients [47, 50, 51, 67]. If in the future effective chemotherapy is available to combat the HIV infection, the drug would have to penetrate the CNS in order to avoid the disease persisting in the CNS with the possibility of an “endogenous reinfection” via recirculation infected monocytes or macrophages from the brain [39, 67]. 3’Azido-3’deoxythymidine (AZT), the first anti-HIV drug available for clinical trials, seems at least partially to fulfil this condition, as can penetrate the blood-brain barrier, albeit to a variable degree [123].

**HIV-induced disorders of the nervous system**

**Acute HIV meningoencephalitis**

The most acute form of CNS complication of the HIV infection is acute meningoencephalitis, which can occur at the time of the infection [17, 18, 34, 59]. In these cases HIV meningoencephalitis precedes or coincides with seroconversion [18, 34, 59]. Various cases have been reported with an acute onset of mental dysfunction and deterioration of consciousness, which can lead to transient coma, often accompanied by grand mal seizures [18, 34]. Lumbar puncture shows non-specific inflammatory changes of the CSF; CT scans are normal and the EEG deteriorates along with the loss of consciousness [18, 34]. This form of acute meningoencephalitis seems to be rather rare in comparison to the number of HIV-infected persons,