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Plenary Session 8

Epidemiology/CSF virology & blood-brain-barrier

Chairpersons: N. Brockmeyer (Bochum, D)
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The epidemiology of HIV-associated neurological disease in the era of highly active antiretroviral therapy

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Highly active antiretroviral therapy (HAART) is effective in suppressing systemic HIV viral load and has decreased mortality rates in patients with HIV infection. HAART has also decreased the incidence of systemic opportunistic infections in AIDS patients. Many antiretroviral drugs, however, do not penetrate well into the central nervous system. Yet, multiple studies now suggest that the incidence rates of HIV-associated neurological disease and CNS opportunistic infections are decreasing. Since the introduction of HAART in 1996, the incidence of HIV dementia has decreased by approximately 50%. The median CD4 cell count for new cases of HIV dementia is increasing, but it remains as a complication of moderate-advanced immunosuppression. The incidence of HIV-associated sensory peripheral neuropathy has decreased although the incidence of antiretroviral drug induced toxic peripheral neuropathy has increased. However, as patients with AIDS live longer as a result of HAART, the prevalence of peripheral neuropathy in HIV seropositive patients may be increasing. The incidence rates of CNS opportunistic infections (cryptococcal mennigitis, toxoplasmosis, progressive multifocal leukoencephalopathy) and primary CNS lymphoma have decreased since the introduction of HAART. However, as patients develop increasing resistance mutations to antiretroviral drugs and with subsequent decline in CD4 cell counts, in the near future, the incidence of HIV associated neurological disease may begin to rise.

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CSF markers in AIDS dementia complex

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At present there are many potential CSF markers of AIDS dementia complex (ADC). This review will evaluate them in an organisational framework and assess the possibility that ADC has changed and how that will affect CSF markers. There are three broad categories: the effector of toxins (macrophages/microglia, HIV), the toxins, and their target. Examination of the effector has led to speculation concerning the importance of a subset of monocytes and whether there might be ADC specific mutations in gp120 or tat. In regard to the toxins per se it has yet to be determined whether one toxin is dominant or the initiator. Assessment of the target of the toxins originally focussed on neurons, but now the astrocyte is being assessed. Any evaluation of new CSF markers of ADC should however, include comparison to more classic ADC markers: CSF HIV RNA load, CSF beta2 microglobulin, neopterin, quinolinic acid, prostagladins and matrix metalloproteinases. But CSF markers of ADC should also be evaluated in the context of potential change to ADC in the era of HAART. It is becoming increasingly apparent that ADC in some HAART-treated patients may become inactive as supported by data from the abacavir ADC trial where most patients did not have evidence of active viral replication or immune activation. Such patients may have fixed deficits representing burnt out brain disease. However, there are several pieces of data from in vitro experiments and PET studies that point to the possibility of a chronic form of ADC. Finally, ADC may be complicated by other factors: brain mitochondrial toxicity from treatment, Alzheimer's disease, the cognitive deficit associated with testosterone deficiency and hepatitis C infection. There is an additional as yet theoretical confound that continued cognitive decline may occur as a result of the death of trophic support cells which maintain neurons and other trophic support cells potentially leading to a domino effect.

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CSF studies on HIV-1 associated opportunistic infections

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Central nevous system (CNS) infections have long represented a major threat in HIV-infected people. Following the introduction of potent antiretroviral combination therapies, their incidence has drastically declined in the western world. However, even patients showing a proper response to these therapies may develop CNS complications, such as progressive multifocal leukoencephalopathy (PML) or lymphoma. Furthermore, all of these disease are still observed in patients who do not respond to antiretrovirals or in the vast majority of patients affected by AIDS, who have no access to anti-HIV drugs. Cerebrospinal fluid (CSF) analysis is indispensable for the study of HIV-associated CNS infections. Starting one decade ago, the use of nucleic acid amplification techniques, in concert with traditional examinations, has greatly enhanced the possibility of diagnosing these diseases. Herpesvirus infections of the CNS, especially those caused by cytomegalovirus (CMV), PML, CNS tuberculosis

and other bacterial or fungal infections can now be specifically identified by detection of the respective genomes in CSF. Moreover, CNS localizations of lymphoma can be recognised by the presence in CSF of Epsten-Barr virus DNA. The use of these techniques has substantially reduced the time for diagnosis and in many cases avoided the use of invasive procedures. More recently, quantitative amplification techniques have also been introduced in clinical practice. These hold the advantage of providing an estimate of microbial replication at the time of diagnosis and during follow-up. Furthermore, nucleic acid sequencing has been applied at epidemiological or clinical purposes. Examples are represented by JCV genotyping or detection of mutations associated with resistance to antimicrobial drugs, such in the case of CMV or TB infections. Finally, a number of "immunological" markers, such as cytokines or other soluble molecules, may be found in elevated levels in certain diseases, e.g., monocyte chemotactic protein-1 in CMV encephalitis or sCD20 in CNS lymphomas, and thus provide precious information on the nature of a disease.

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Human immunodeficiency virus type 1 (HIV)-induced complement synthesis in astrocytes and neurons

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Complement is hypothesized to contribute to neurodegeneration in the pathogenesis of AIDS-associated neurological disorders. Our former results have shown that the human immunodeficiency virus HIV strongly induces the synthesis of complement factors C2 and C3 in astrocytes. This upregulation explains *in vivo* data showing elevated complement levels in the cerebrospinal fluid of patients with AIDS-associated neurological symptoms. Since inhibition of complement synthesis and activation in the brain may represent a putative therapeutic goal to prevent virus-induced damage, we analysed in detail the mechanisms of HIV-induced modulation of C3 expression.

Signal transduction studies revealed that adenylate cyclase activation with upregulation of cyclic AMP is the central signalling pathway to mediate that increase in C3 levels after HIV-infection. Furthermore, activity of protein kinase C is necessary for HIV-induction of C3 since inhibition of PKC by prolonged exposure to the phorbol ester TPA partly abolished the HIV effect. Beside the whole HIV virions the purified viral proteins Nef and gp41 are biologically active in upregulating C3, whereas Tat, gp120 and gp160 were not able to modulate C3 synthesis.

Further experiments revealed that neurons were also able to respond on incubation with HIV with increased C3 synthesis, although the precise pattern was slightly different from that in astrocytes. This strengthens the hypothesis that HIV-induced complement synthesis represents an important mechanism for the pathogenesis of AIDS in the brain. This work was supported by the Austrian FWF (Project P15375), the Österreichische Nationalbank (9374), the Ludwig-Boltzmann-Society, the BMAGS and the State of Tyrol.

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Human polyomavirus infection in peripheral blood

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Primary contact with the human polyomaviruses is followed by lifelong persistence of viral DNA in target organs including cells of the hematopoietic system. Under impairment of immune competence limited activation of virus infection can be followed by extended virus multiplication, prolonged dissemination of the virus to target organs and severe destruction of tissue. Although the virus load in persistently infected immunodeficient individuals appears to be enhanced, the question whether localization and dissemination of viral infection in the hematopoietic system is influenced by changes of immune competence is not yet answered.

The aim of our studies was to compare presence and dissemination of the human polyomaviruses in blood specimens of blood donors, immunocompetent individuals and risk group patients. Virus load was evaluated by molecular techniques resulting in a higher detection rate in risk group patients compared to that in immuno-competent individuals. In blood donors the amount of virus DNA was highly variable, and virus DNA in lymphoid subpopulations was individually distributed. The data confirm that immune impairment and activation of polyomavirus infection can be associated with an enhanced virus load in the blood. In addition, it can be assumed that presence of virus DNA is not only dependent on severe impairment of the immune system but appears also to be a natural event in persistent infection.