EXPRESSION OF MAJOR HISTOCOMpatibility COMPLEX (MHC) CLASS II AND CYTOKINES IN BRAINS OF ASYMPTOMATIC AND ASYMPTOMATIC HIV-1 POSITIVE PATIENTS: CORRELATION WITH DETECTION OF HIV-1 DNA

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Among the mechanisms proposed to explain the pathogenesis of HIV encephalitis, a cytokine-mediated action has found most favour. Elevated expression of various cytokines, thought to be neurotoxic, has been found in AIDS patients. As a previous study had demonstrated the presence of HIV proviral DNA in brain of HIV positive non-AIDS patients, we undertook this investigation by morphological, immunohistochemical and PCR methods to detect in brains of the same group of individuals the expression of MHC II, the presence of HIV-1 proviral DNA and of the cytokines TNF-a, IL-1a, interleukin-1, interleukin-6.

The study included 36 asymptomatic HIV-1 positive patients and results were compared with those of AIDS patients either affected by HIV encephalitis (n=8) or except from neuropathological changes (n=10) and with normal controls (n=5). Results show that: HIV proviral DNA could be detected by PCR in 17/36 brains from HIV positive pre-AIDS cases; most (13/17) of PCR positive brains showed minimal to severe expression of MHC II; cytokines could be detected predominantly within white matter at this early stage. Results demonstrated that the state of immune activation is already present at the pre-AIDS stage and suggest that cytokines may already trigger the cascade of events leading to brain damage.

PROGRAMMED CELL DEATH IN BRAINS OF HIV-1 POSITIVE AIDS AND PRE-AIDS INDIVIDUALS

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Neuropathological studies revealed that brains of HIV-1 infected AIDS patients show typical encephalitis and neuronal loss. More recently, this neuronal cell loss has been thought to take place via programmed cell death (apoptosis) which has been demonstrated by in situ end labelling (ISEL) technique.

In this study we investigated 54 brains of HIV-1 positive patients by ISEL technique. Our aim was to ascertain whether the process of apoptosis was also present in brains at the asymptomatic stage. Of these, 10 were HIV encephalitis (HIVE), 8 were AIDS without neuropathological disorders and 36 belonged to HIV-1 positive pre-AIDS patients.

Apoptotic cells were detected in 6/10 HIVE, 1/8 AIDS without central nervous system (CNS) disease and 4/36 asymptomatic individuals. The difference between AIDS and pre-AIDS cases was that, in the latter, apoptotic cells were found in the white matter in all 4 cases whilst only 2/4 showed apoptotic neurons. The presence of apoptotic cells in a number, albeit small, of brains of HIV-1 positive pre-AIDS individuals, combined with abnormalities previously described in the same group of patients gives further support to the opinion that brain damage is already taking place during the early stages of HIV infection.

DETECTION OF EBV DNA IN CSF AND ITS CORRELATION WITH NEUROLOGICAL DISEASE IN HIV-INFECTED INDIVIDUALS

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Cerebrospinal fluid (CSF) was examined for the presence of EBV DNA in 89 HIV-infected individuals undergoing diagnostic lumbar puncture (LP). A nested polymerase chain reaction was used with primers located in the internal repeats of the EBV genome. Results were correlated with clinical, radiological and histological diagnoses. Seventeen patients had a diagnosis of lymphoma (7 CNS lymphoma, 2 CNS and systemic lymphoma, 8 systemic lymphoma). EBV DNA was detected in the CSF supernatant from 18 patients, including all 7 patients with CNS lymphoma, both patients with CNS and systemic lymphoma and 9 patients with no lymphoma at the time of LP. A further patient with systemic lymphoma had detectable EBV DNA in the CSF cellular pellet. Two patients with detectable EBV DNA in CSF but no lymphoma at the time of LP subsequently developed systemic and CNS lymphomas 15 and 19 weeks later. In summary, a diagnosis of CNS lymphoma was strongly associated with the presence of CSF EBV DNA. However, not all patients with detectable CSF EBV DNA had evidence of lymphoma emphasizing the need for caution when interpreting a positive result. This latter group of patients, may however, be at risk of developing lymphoma.

MUSCLE INVOLVEMENT IN HIV-INFECTED PATIENTS IS ASSOCIATED WITH MARKED Selenium deficiency

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Objective: To evaluate the possible implication of selenium and vitamin E deficiencies in the occurrence of muscle involvement during HIV infection.

Background: Oxidative stress is implicated in tissue damage during HIV infection. Micronutrient deficiencies have long been recognized in HIV infected patients and involve vitamins and trace-elements such as zinc, iron, and selenium. Selenium is a component of glutathione peroxidase, a major redox agent.

Selenium deficiency, alone or in association with a deficiency in vitamins E, another antioxidant, is known to induce a skeletal muscle disorder manifesting by pain and proximal weakness (J Parent Er Nutr 1985; 9:59-60; Am J Clin Nutr 1996; 43:549-54).

Methods: We studied serum levels of selenium and vitamin E (alpha-tocopherol) in 20 patients with muscular symptoms and 20 patients matched for CD4 count without muscular symptoms. Myopathic patients had zidovudine myopathy (8 patients), HIV polymyositis (6 patients), HIV-wasting syndrome (1 patient), and myopathies of unknown origin (5 patients).

Results: Selenium status (mean ± SE: 0.51 μmol/L ± 0.04 vs. 0.69 ± 0.05, Student's paired t test: P = 0.005, but not vitamin E status (21.1 μmol/L ± 2.0 vs. 21.6 ± 1.2, NS) was significantly impaired in patients with muscular symptoms. There was no correlation between selenium levels and the type of myopathy.

Conclusion. Since it is likely that selenium deficiency is not secondary to muscle damage, these results suggest that selenium deficiency might act as a cofactor of muscle involvement in HIV-infected patients, conceivably allowing oxidative stress in muscle tissue.
SWITCHING FROM ZIDOVUDINE (AZT) TO DIDANOSONE (DDI) ALSO PROTECTS FROM HIV ENCEPHALITIS

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Productive HIV infection of the central nervous system (CNS) results in HIV-specific lesions, generally termed HIV encephalitis (HIVE), which usually contains multinucleated giant cells (MGCs). It has been demonstrated that AZT markedly reduces the incidence of HIV encephalitis (Gray, et al. AIDS 1994; 8: 489-93). In order to evaluate, on neuropathological grounds, whether switching from AZT to another antiretroviral drug, such as ddi, may be also effective to prevent from HIVE, we examined systematically the CNS of 263 AIDS patients who died between 1982 and December 1994. Antiretroviral treatment was retrospectively reviewed without knowledge of the neuropathological diagnosis: 115 patients (group I) had never been treated by AZT, 93 (group II) had received AZT for over 3 months and continuously until death, 33 patients (group III) had their AZT treatment terminated 1 month or more before death without substitution therapy, and 22 patients (group IV) had stopped AZT and received ddi as substitute for at least 3 months before death.

The prevalences of MGCs and of HIVE were significantly lower in patients treated until death by an antiretroviral drug (group II: MGCs = 17%, HIVE = 14%), group IV: MGCs = 14%, HIVE = 5%) than in untreated patients (group I: MGCs = 42%, HIVE = 39%) (p < 0.001). In patients whose AZT treatment was interrupted without substitution therapy (group III), the prevalence of HIV-induced brain lesions increased again to a level comparable of that of untreated patients (MGCs = 42%, HIVE = 27%). Lastly, substitution treatment by ddi appears as effective as AZT in preventing HIV encephalitis.

These observations support the clinical report that interrupting AZT treatment may lead to acute exacerbation of HIV-induced brain disease, probably because increased HIV replication, and suggest that substitution treatment with ddl may also prevent from HIV replication within the CNS.

DECREASED EXPRESSION OF AMPA RECEPTOR MESSENGER RNA AND PROTEIN IN AIDS

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HIV infection can cause extensive neuronal loss and clinically a severe dementia. The cause of this neurotoxicity is not known as neurons are not infected, but disturbance of glutamate-linked calcium entry has been implicated. In this study we have examined this hypothesis by investigating the mRNA and protein expression of glutamate AMPA receptors in the cerebellum of nine control and eighteen individuals who died of AIDS.

In situ hybridisation was performed for both the mRNA of AMPA receptors GluR-A, -B and -C together with their flip and flop isoforms by a radiolabelled probe, and the structural protein actin using a digoxigenin labelled probe. Immunohistochemistry was carried out for the GluR-A receptor, GFAP, and gss4. Evaluation of mRNA levels in the granular layer of the cerebellum was by autoradiographic analysis, while microautoradiograms were employed for estimation of Purkinje cells density (Hall, et al. Neuropath. Appl Neurobiol 1975; 1: 267-292). Semi-quantitative analysis of staining for GFAP and gss4 was also carried out.

Clinical neuropathological examination did not reveal evidence of lichenatia in any of the cerebella. In the granular cell layer there was no difference in the mRNA levels of either the flip or flop isoforms of any of the AMPA receptors examined. However, there was a significant (p = 0.00001) 56% reduction in the number of Purkinje cells expressing mRNA for GluR-A flop, and this was accompanied by a 50% reduction in the protein expression. There was no corresponding decrease in the levels of mRNA for A or C actin or the total number of Purkinje cells.

Despite the lack of neuronal infection, this study has demonstrated that HIV results in significant changes in glutamate AMPA receptor expression, which may alter current characteristics. While Purkinje cells are relatively resistant to loss, this observed alteration may contribute to the neurotoxic process in other vulnerable brain regions.

A NEUROCHEMICAL AND NEUROANATOMICAL CORRELATE OF HIV-1 ENCEPHALOPATHY

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Diminished intellectual function and motor impairment (HIV-1 encephalopathy) commonly occur in HIV-1 infected children. The cause appears to be the immunodeficiency virus itself, rather than other opportunistic pathogens. The exact mechanism(s) by which virus affects brain function is not clear. To identify alterations in cortical neurons that might explain this brain dysfunction, we examined peptide neurotransmitter expression in the frontal cortex of HIV-1 infected children, with and without HIV-1 encephalitis, as well as with and without HIV-1 encephalopathy. A 2-fold higher number of preproenkephalin mRNA positive interneurons were present in layer IV-VI and subcortical white matter (SWM) in HIV-1 infected children with HIV-1 encephalopathy. This alteration was confirmed to layer IV and SWM in children with HIV-1 encephalopathy. Cortical laminae (layers IV-VI) and SWM having this neuronal alteration, connect to subcortical areas (basal ganglia, thalamus) that have an increase in metabolic activity and contain the highest amounts of viral antigen. Of these cortical laminae, layer IV receives the most synaptic input from the medio-dorsal nucleus of the thalamus, via the SWM which projects to the thalamus. Two mechanisms by which the virus elicits the up-regulation of [P]IF mRNA via alterations in trans-synaptic activity and cytokine (IL-1, TNFα) release. Altered function of somatostatinergic interneurons likely contributes to HIV-1 encephalopathy.

Peripheral neuropathies in the Diffuse Infiltrative Lymphocytosis Syndrome are associated with abundant HIV in nerve tissue

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Objective: To describe neurological, nerve biopsy and virological findings in 12 patients with DILS (Ieusu et al, Ann Intern Med 1990; 112: 2-10). Background: A subset of HIV-infected patients develop persistent CD8 hyperactivation and a syndrome resembling Sjögren's syndrome, associated with multiscleral infiltration involving salivary glands, lungs, kidneys and gut. Peripheral nerve involvement was seldom reported. Patients with DILS tend to have more preserved CD4 cell count, less opportunistic infection and longer survival times than other HIV-infected patients.

Methods: Twelve HIV-infected patients were included according to the following criteria: circulating CD8 cell count > 1200/mm3, abundant CD8 T-cell tissue infiltration in at least three different organs or tissues, and clinical evidence of peripheral neuropathy. Eight patients had CD4 cell count > 200/mm3.

Results. All patients had sicca syndrome and multiscleral involvement. The neuropathy was acute or subacute, painful, symmetrical (8/12) or not (4/12), and usually axonal (10/12). Nerve biopsy showed marked angiocoenic CD8 infiltrates without mural necrosis, mimicking lymphoma (12/12), and abundant expression of HIV p24 protein in macrophages (12/12). Provirus was detected by PCR in nerve homogenates. End-point dilution studies revealed that HIV was present in much higher abundance in DILS than in other types of HIV-neuropathies. 6/6 patients improved with zidovudine and 4/5 with steroid therapy.

Conclusion. DILS may be associated with a treatable neuropathy. Abundant CD8 infiltration and abundant expression of HIV proteins and genomes in nerve is consistent with an antigen-driven expansion of CD8 T cells directed toward HIV.
NEURONAL APOPTOSIS IN HIV INFECTION. AN IN VIVO AND IN VITRO STUDY.

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Productive infection of the CNS by HIV causes predominant involvement of the white matter and basal ganglia. Involvement of the cerebral cortex with neuronal loss was also described in AIDS cases but not in asymptomatic HIV-positive patients [Evertz et al. J Neurovirol Exp Neurol 1993:52:561-566]. The mechanism of neuronal damages is unknown. In an attempt to demonstrate that neuronal loss in AIDS may be due to an apoptotic process, we examined the cerebral cortex from 16 patients who died from AIDS using 2 different methods to demonstrate DNA fragmentation: in situ end labelling and gel electrophoresis of DNA. None of the patients had cerebral opportunistic infection or tumor. Six patients had no significant neuropathological changes, 10 patients had variable cerebral atrophy and 5 also had productive HIV infection of the brain. These were compared with 12 HIV-positive asymptomatic cases, 9 seronegative asymptomatic controls, and 2 seronegative patients with Alzheimer's disease. We demonstrated neuronal apoptosis in the cortex in all AIDS cases, as well as in the Alzheimer's cases. Occasional apoptotic neurons were found in two asymptomatic HIV-positive patients. Apoptosis was not observed in seronegative asymptomatic controls. Neuronal apoptosis was more severe in corticobasal, and did not directly correlate with productive HIV infection making an indirect mechanism of neuronal damage likely. Consistent findings were obtained in primary cultures of human embryonic spinal cord and cortex and in cultures enriched in astrocytes and microglia [Tartis et al. Ann Neurol 1992:32:11-17]. Infection by HIV induced frequent apoptosis. DNA fragmentation involved astrocytes, microglial cells and neurons. No apoptotic cell was identified in non infected control cultures. Only occasional apoptotic cells were detected in cultures treated by TNFa (200 nM) for 18h. Primary embryonic CNS cultures may represent an useful tool to investigate the mechanisms involved in HIV-induced neuronal damage.
**BCL-2 EXPRESSION IN PRIMARY CENTRAL NERVOUS SYSTEM NON HODGKIN LYMPHOMAS (CNS-NHL)**

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Primary CNS-NHL are very frequently associated with EBV in AIDS. A proposed mechanism for EBV effect is through transactivation of BCL-2 proto-oncogene by LMP-1, whose co-expression has been shown in post-mortem AIDS-related brain lymphomas (1).

We report a comparative series of 17 primary CNS-NHL in 11 HIV (+) and 6 HIV (-). Immuno-histochemistry was performed on paraffin sections, with monoclonal antibodies against BCL-2 and LMP-1.

All HIV (+) patients expressed BCL-2 and 10 LMP-1; among HIV (-), 3 expressed BCL-2 and one LMP-1, with no co-expression. There was no correlation between intensity of LMP-1 and BCL-2 expression and age, sex or NHL type.

Activation of BCL-2 is an important event in immortalization of B cells lines through its anti-apoptotic action. LMP-1 is a potent inductor of BCL-2 which appears as an important factor in HIV CNS-NHL. Our study sustains this hypothesis in HIV (+), as there is a correlation between LMP-1 and BCL-2 expression. In HIV (-) patients BCL-2 activation does not parallel LMP-1, nor does it in HIV (+) systemic NHL (3), indicating that other factors for BCL-2 activation could be important in these cases.

(1: Camilleri-Brotte and al., Blood 1993)

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**EXPRESSION OF TUMOR NECROSIS FACTOR (TNF) - α IN AIDS DEMENTIA COMPLEX**

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TNF-α immunohistochemistry was performed in the frontal cortex, white matter, and basal ganglia of 12 AIDS patients, without focal brain lesion, and 6 controls. The cognitive functions of AIDS patients had been prospectively assessed with the Mini Mental State (MMS) evaluation. Perivascular macrophages, ramified microglia and endothelial cells were labelled. Astrocytes were negative in spite of their close contact with TNF-α positive cells. The density of TNF-α positive cells was higher in AIDS than in controls (p=0.004 in the cortex; p=0.085 in the white matter; p=0.001 in the basal ganglia), and paralleled astrogliosis (r=0.75, p<0.001 in the cortex; r=0.70, p=0.002 in the white matter; r=0.90, p<0.01 in the basal ganglia). It did not differ significantly between AIDS cases with HIV-α CNS-encephalitis, or with polychistostomy. Demented patients (MMS<24, n=8) had higher densities of TNF-α positive microglia than non demented patients in both cortical and deep gray matter (p<0.02). Cerebral expression of TNF-α is increased during HIV infection, and may play a role, together with induction of astrogliosis, in neuronal dysfunction and dementia.

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**PATHOLOGY OF THE CENTRAL NERVOUS SYSTEM IN 241 AIDS AUTOPSEES**

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Based on a consecutive autopsy series of 341 unselected patients with AIDS from 1984 to 1995, a critical review of the pathology of the central nervous system (CNS) is given.

Marked lesions of the CNS were found in 60%, while mild/ nonspecific changes were seen in 35%.

Toxoplasmosis (23%) was the most frequent CNS infection, followed by cytomegalovirus (17%), and papovavirus (8%). HIV encephalitis and HIV leukoencephalopathy were observed in 11%.

Primary CNS lymphomas were found in 7%, while secondary involvement of the CNS in systemic lymphomas was seen less frequently. In fungal infections (9%) cryptococciosis, candida and aspergillosis were diagnosed in decreasing frequency. Metastatic cerebral lesions due to bacterial pathogens were found in 4%.

Frequently there are multiple infections/tumours with simultaneous involvement of the CNS.

Pathologic findings of Vienna AIDS cases and changing incidences of the different lesions over a period of more than 10 years are presented.

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**BAX IS A MARKER FOR APOPTOTIC MICROGLIA IN PEDIATRIC PATIENTS WITH HIV-1 ENCEPHALITIS**

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We have previously demonstrated TUNEL staining in cytoplasm of HIV-1 p24-positive and negative macrophages and microglia in pediatric patients with HIV-1 encephalitis, possibly representing either phagocytosis of fragmented DNA from apoptotic neurons or apoptosis of the macrophages and microglia themselves. Using immunocytochemistry, we investigated the expression of the pro-apoptotic gene product bax and the anti-apoptosis gene products bcl-2 and bcl-x in formalin-fixed, paraffin-embedded autopsy brain tissue from children with HIV-1 encephalitis (HIVE) and HIV-1 infection without encephalitis (HIV) and from HIV-1 seronegative controls (HIV-). With an antibody to bax, there was staining of the cytoplasm of small cells with ramified processes, resembling microglia, in the HIV+ and HIV patients, with an 8.4-fold elevation of these cells in cerebral cortex and a 7-fold elevation in basal ganglia, in the HIV+ vs. HIV- patients. In the HIV+ vs. the HIV- patients, there was a 5.3-fold elevation in cortex and a 1.5-fold elevation in basal ganglia of microglia expressing bax. There was no clear pattern of expression of either bcl-2 or bcl-x in any of the patient groups. The relative numbers of bax-positive microglia in the HIV+ vs. HIV- patients closely paralleled microglial expression of activated nuclear factor kappa B (NFkB) in these same patients (Doddell et al., Neurophatol. Appl. Neurobiol, in press). Activation of microglia during inflammatory responses in the CNS may lead to apoptosis, perhaps as a defense mechanism to limit pathogenic immune responses within the brain.
CONCOMITANT HERPES-VIRUSES INFECTIONS OF THE CENTRAL NERVOUS SYSTEM (CNS) IN AIDS PATIENTS.

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OBJECTIVE. To study the frequency and morphological features of concomitant infections of the CNS due to cytomegalovirus (CMV) and both herpes simplex virus 1/2 (HSV 1/2) and varicella-zoster virus (VZV) in patients died from AIDS.

METHODS. Eighty-two autopsy cases with histological diagnosis of CMV necrotizing encephalitis were retrospectively examined. CMV and HSV 1/2 antigens were detected by immunohistochemistry in all the cases; VZV antigens were studied in 26 cases until now, the remaining being currently under investigation. A nested polymerase chain reaction (PCR) for HSV1 and 2, and for VZV was performed on DNA extracted from paraffin blocks positive by immunohistochemistry.

RESULTS. A concomitant CMV/HSV infection was demonstrated by immunohistochemistry in 13 cases (16%). A concomitant CMV/VZV infection was found in only 1 of the 26 studied (3.8%). PCR for HSV 1/2 was positive in 5/9 HSV1 cases and in 2/4 HSV2 cases. In the remaining immunopositive cases, PCR for beta-globin were repeatedly negative. PCR for VZV was positive in the only one case examined.

CONCLUSIONS. HSV infection due to type 1 and 2 virus is frequently observed in otherwise typical CMV necrotizing cerebral infection occurring in AIDS patients. In the 26 cases examined, encephalitis due to CMV/VZV co-infection seems to be a sporadic event.

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