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EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) CLASS II AND CYTOKINES IN BRAINS OF ASYMPTOMATIC AND SYMPTOMATIC 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-α, IL-1α, interleukin-4, 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 exempt 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 (15/17) 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, combained 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 (7CNS 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 emphasising 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 antioxidant agent. Selenium deficiency, alone or in association with a deficiency in vitamin E, another antioxidant, is known to induce a skeletal muscle disorder manifesting by pain and proximal weakness (J Parent Ent Nutr 1985; 9:58-60; Am J Clin Nutr 1986; 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 DIDANOSINE (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 contain 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 ddI may also prevent from HIV replication within the CNS.

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 preprosomatostatin (SRIF) mRNA positive interneurons was present in layer IV-VI and subcortical white matter (SWM) in HIV-1 infected children with HIV-1 encephalitis. This alteration was confined 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 SRIF mRNA is via alterations in trans-synaptic activity and cytokine (IL-1, TNF-α) release. Altered function of somatostatinergic interneurons likely contributes to HIV-1 encephalopathy.

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 gp41. Estimation 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-quantitive analysis of staining for GFAP and gp41 was also carried out.

Clinical neuropathological examination did not reveal evidence of ischaemia 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 either the levels of mRNA for 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.

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

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Objective. To describe neurogical, nerve biopsy and virological findings in 12 patients with DILS (Itescu et al, Ann Intern Med 1990; 112: 3-10).

Background. A subset of HIV-infected patients develop persistent CD8 hyperlymphocytosis and a syndrome ressembling Sjögren's syndrome, associated with multivisceral 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 multivisceral involvement. The neuropathy was acute or subacute, painful, symmetrical (8/12) or not (4/12), and usually axonal (10/12). Nerve biopsy showed marked angiocentric 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 is 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.

WHAT IS HIDDEN UNDER ADC TERM?

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Dementia cases not related to HIV brain infection are often misdiagnosed as AIDS dementia complex (ADC). Distinguishing criteria between such cases and ADC are needed.
AIM: to identify the clinical distinguishing criteria among the forms of dementia related to different pathological patterns.
METHOD: Out of 680 HIV+ patients neurologically evaluated between 1990 and 1995, 157 were autopsied, including 49 who were previously diagnosed to suffer ADC. The brain tissue and the medical records of the latter patients were examined.
RESULTS:ADC was diagnosed in patients later shown to be affected with the following pathological patterns: - **21 HIV encephalopathy**: 7 leucoencephalopathy (HIVL), 5 encephalitis (HIVE) ,9 HIVL+HIVE; **-13 cytomegalovirus (CMV) encephalopathy**: 7 microglial nodular encephalitis (MGNE), 3 ventriculo-encephalitis (VE), 2 ependimitis,1 focal necrosis;- **5 HIV encephalopathy** with coinfections ; - **4 brain gliosis**; **-2 brain calcifications**; - **4 cases without any detectable brain pathology**.
The table shows the main characteristics of the studied patients:

	preAIDS/ AIDS %	CD4 mean (sd)	onset insidious(i) subacute(s)	Neurol.signs focal/diffuse	Radiology atrophy/WMD*
HIV-L	86/ 14	103.1(50.4)	i/s	++ / +	+ / +
-E	0 /100	9.4(4.6)	insidious	- /+	+ / -
-L+E	67/ 33	91.5(62.6)	i/s	++/+	+ / +
CMV-MGNE	57/43	20.7(26.0)	acute	- / +	+ / -
-VE	100/0	80.6(41.5)	i/s	++/ +	+ / +
GLIOSIS	0/100	19.0(16.4)	insidious	-/+	+ / -
CALCIFIC.	0/100	45.0(26.8)	insidious	-/+	+ / -
SINEMAT.	0/100	35.2(24.1)	i/s	+/++	+/+

* white matter disease
Additional data (CMV viremia , cerebrospinal fluid, neuropsychological evaluation, survival, therapy) have been considered for the comparison among the groups.
CONCLUSIONS : Under ADC term a broad spectrum of brain pathologies is hidden. Distinguishing criteria for some of these cases have been identified . In particular it is possible to distinguish between HIV encephalopathy and CMV one and among their different subgroups : HIVE-HIVL,CMVMGNE-CMVVE.On the contrary the distinction of both brain gliosis and brain calcification from HIVE is difficult. The finding of dementia "sine materia" cases is an intriguing issue, which needs further investigations.

PERIPHERAL NERVE AND MUSCLE PATHOLOGY OF 260 HIV INFECTED PATIENTS.

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260 patients with HIV infection, including 35 females and 225 males at different stages of HIV infection, were referred for peripheral neuropathy or muscle disorder. They had a nerve and/or a muscle biopsy; 6 patients had 2 biopsies. We have studied 262 muscle and 222 nerve specimens. Several pathologies were associated in some patients.
An HIV related neuropathy was observed in 48 % of the patients, including 11% with mononeuritis multiplex (MM), 25% with distal painful neuropathy (DN) and 12% with acute or subacute polyradiculoneuritis. Endoneurial inflammatory infiltrates were found in 54 % of the nerve specimens, axonal degeneration in 62 % and segmental demyelination in 11 %. In 24 patients with MM or radiculitis, CMV pathology was detected in the nerve specimens. 3 other patients with endoneurial microabcesses were highly likely to have CMV infection. 26 additional patients referred for spinal cord disorder and radiculitis had a probable proximal CMV infection without abnormalities in the distal nerve and some of these patients improved with ganciclovir. 5 patients had a toxic neuropathy, 2 a neoplastic neuropathy, one a lepromatous neuropathy and one an alcoholic neuropathy. HIV polymyositis was detected in 36 patients and AZT myopathy in 18. A myopathy with rod fibres was observed in 5 patients. We observed 2 pyomyositis and 2 muscle toxoplamosis. Muscle siderosis was detected in 80 patients. Different patterns of vasculitis were observed in 70 patients (27 %): acute necrotizing arteritis in 10 patients and old lesion of necrotizing arteritis in 2, granulomatous angiitis in 7, in association with CMV neuropathy in 15, giant cell arteritis in 1, and microvasculitis in 35. Depending on the results of the neuromuscular biopsy, specific therapy such as steroids or ganciclovir could be recommended.

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 [Everall et al. *J Neuropathol 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 tumour. 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 cases. Apoptosis was not observed in seronegative asymptomatic controls. Neuronal apoptosis was more severe in atrophic brains, 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 [Tardieu 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 TNFα (200 n/ml for 18h). Primary embryonic CNS cultures may represent an useful tool to investigate the mechanisms involved in HIV-induced neuronal damage.

CEREBRAL GLIAL TUMORS IN AIDS

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The incidence of primary brain tumors is higher in AIDS patients, than in the population without HIV infection. Most of the intracerebral space occupying solitary lesions proved to be lymphomas and only in rare conditions we find gliomas associated with the HIV infection.

We examined neuropathologically 95 AIDS cases in Hungary. Two of them had brain stem astrocytomas. Both were homosexual men, 40 and 37 in age. The first patient suffered of ophtalmoplegia and the CT scan demonstrated a space occupying lesion in the hypothalamus and upper brain stem, which was suggested to be a lymphoma. In the other case no focal clinical signs were observed.

In the first case the brain tumor infiltrated the left hypothalamic region and the peduncular tegmental area. In the other the neoplasm was limited in the nuclear region of the VIII nerve. Both those tumors were fibrillary astrocytomas with GFAP positivity. In one case the tumor was accompanied by a mild encephalitis, while the other was complicated with leukoencephalopathy and vascular alterations were revealed.

The unusual discovery of these tumors may postulate that the astrocytomas occuring in AIDS patients are not only coincidental findings. / Moulignier, Mikol, *et al.* / It is suggested, that while HIV destroys the immuno defense, it could favour the induction of brain neoplasms by oncoviruses. / Gasnault, *et al.* /

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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, sexe 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 hypthesis 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 (1), indicating that other factors for BCL-2 activation could be important in these cases.

(1: Camilleri-Broët and al., Blood 1995)

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; $p<0.005$ 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; $r= 0.60$, $p<0.01$ in the basal ganglia). It did not differ significantly between AIDS cases with HIV- or CMV- encephalitis, or with poliodystrophy. 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.

PATHOLOGY OF THE CENTRAL NERVOUS SYSTEM IN 341 AIDS AUTOPSIES

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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 present in 7%, while secondary involvement of the CNS in systemic lymphomas was seen less frequently. In fungal infections (9%) cryptococcosis, candida and aspergillus were diagnosed in decreasing frequency. Metastatic pyemic 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.

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-apoptosis 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 HIVE 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 HIVE vs. the 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 HIVE vs. HIV vs. HIV- patients closely paralleled microglial expression of activated nuclear factor kappa B (NFκB) in these same patients (Dollard et al, Neuropathol. 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. Eigthy-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 immunochemistry.

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 occuring in AIDS patients. In the 26 cases examined, encephalitis due to CMV/VZV coinfection seems to be a sporadic event.

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