

RABIES ENCEPHALITIS IN AN AFRICAN PATIENT WITH AIDS

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Rabies and AIDS are endemic in many subsaharian African countries; however, the association of both conditions has been seldom reported.

A 46 y.o. man, bitten by a dog in Mali, received incomplete antirabies vaccination. Three months later he presented with fever and diarrhoea and was found HIV-seropositive, CD4 were 70. His status worsened rapidly with confusion, hydrophobia, and hypersialorrhoea. Despite serotherapy and vaccination he died suddenly 12 days after admission.

Immunofluorescence on cerebral tissue prints confirmed rabies encephalitis. Neuropathology showed mild encephalitis with occasional Babes nodules and rare perivascular mononuclear cuffs. Intraneuronal Negri inclusion bodies were remarkably diffuse and abundant. They were clearly demonstrated by immunocytochemistry and electron microscopy. There was neither associated HIV encephalitis nor opportunistic infection.

The occurrence of a rabies encephalitis in AIDS likely represents a random association but is probably not exceptional. In this case, although the incubation duration and clinical presentation were comparable to those in classical rabies, it seems likely that immunosuppression may account for the weak inflammatory reaction and unusually abundant viral multiplication. This observation supports the view that post-exposure prophylaxis, including vaccination and administration of human rabies-hyperimmune globuline, must be administered properly and in a timely fashion in all individuals, including immunocompromised patients, bitten by suspected animals.

ARE THERE TWO DIFFERENT FORMS OF HIV-1-RELATED ENCEPHALOPATHY?

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From 11/1987 to 6/1995 640 HIV-1-positive patients were screened for clinical signs and symptoms of HIV-1-related encephalopathy. 39 individuals revealed "cortical" and 50 "subcortical" dementia. Both groups were comparable in respect to age, duration of HIV-1 positivity, T-helper cell count, risk group distribution and CDC-stages. Besides clinical examination, motor tests (tremor peak frequency = TPF, most rapid alternating index finger movements = MRAM, most rapid index finger extensions = MRC), cranial computer tomography (CCT), magnetic resonance tomography (MRI) and EEG-recordings were applied to these patients. They were re-examined every three months. Patients with "cortical" type of dementia initially had normal motor tests, slowing of a-rhythm in EEG-recordings and cortical atrophy in imaging procedures, whereas patients with "subcortical" dementia had pathological motor results (especially prolonged MRCs: 169.8 +/- 52.2 ms right hand and 184.1 +/- 58.1 ms left hand, normal range: 120.0 - 140.0 ms), normal EEG-recordings and normal imaging results or hyperintense subcortical lesions revealed by MRI. During follow-up (12 - 15 months) patients of the "cortical" type deteriorated in motor tests (ANOVA: MRC ri: $p = 0.0032$, le: $p = 0.0054$), the other examinations - including physical status - did not change significantly; patients of "subcortical" type in contrast deteriorated significantly after initial improvement (antiretroviral treatment was intensified in both groups) and died 9 - 12 months at average after manifestation of the first symptoms of HIV-1-related encephalopathy. There is some evidence for the existence of two different types of HIV-1-related encephalopathy. These results must be followed-up in further studies.

DEFINING AND STAGING HIV-1-ASSOCIATED DEMENTIA: BASELINE RESULTS FROM THE DANA CONSORTIUM ON THERAPY FOR HIV DEMENTIA.

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Since 1993, 256 HIV+ subjects with cognitive symptoms ($CD4+ < 300$), or with a profile indicating risk for cognitive decline ($CD4+ < 200$), have been enrolled in a natural history cohort to examine HIV-related dementia. Subjects receive extensive neurologic, serologic, cognitive, and functional evaluations at 6-month intervals. A major goal of the study is to determine the proportion of subjects with minor motor-cognitive disorder who go on to develop dementia in a 3-year follow-up period.

Essential to this effort is an operationalization of NINCDS criteria for HIV-1 dementia, as required for clinical characterization of the cohort and specification of study endpoints. Extensive functional and neuropsychological assessments show that 21% met criteria for dementia (impairments in ADL), and 24% met criteria for the minor motor-cognitive complex (impairment in work and social activity). Demented subjects were largely "mild" in severity, in keeping with high mortality among more severely demented subjects. Demented subjects had significantly poorer motor function ($p < .001$), greater depression ($p < .001$), and lower hemoglobin ($p < .01$), but did not differ from non-demented subjects in $CD4+$ or beta-2 microglobulin. Apart from functional and cognitive impairment, subjects with motor-cognitive disorder did not differ from cognitively normal subjects. Analyses show that self-reported function is clinically informative even at mild stages of dementia.

AIDS-DEMENTIA COMPLEX (ADC) IN A COHORT OF 1205 AIDS PATIENTS: CORRELATION TO CLINICAL VARIABLES AND TO AUTOPSY FINDINGS

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Aim: to establish the frequency of ADC in the different years of AIDS diagnosis, to relate it to clinical variables and to autopsy findings

Methods: data-base containing informations on clinical, immunological and therapy data in a cohort of AIDS patients (pts) diagnosed from 1984 to 1994. The diagnosis of ADC was made according to CDC and Neurology Task Force. Autopsy was made in patients died during hospitalization; findings were recorded as HIV-related lesions: HIV Encephalitis-HIV-E-, HIV-Leukoencephalopathy -HIV-L, and both-HIV-E+HIV-L.

Results: ADC was diagnosed as AIDS-index disease (ID) in 102 pts (8.4%), with a decreasing frequency (18/185 in 1984-1987, 47/404 in 1988-1990, 37/616 in 1991-1994; $p < 0.01$) and in pts with progressively more severe immunodepression (median $CD4+ 42$ vs 63 vs $20/\mu L$; $p = 0.05$) according to the year of diagnosis. In 116/1103 pts (10.5%) ADC was diagnosed after AIDS, also in these cases with a decreasing frequency in the last years (51/167 in 1984-1987, 44/357 in 1988-1990, 21/579 in 1991-1994; $p < 0.001$). Pts initiating zidovudine (ZDV) before AIDS had a not significant lower risk to suffer from ADC as ID (28/396 vs 74/809; OR: 0.75, 95% CI: 0.48-1.18); these pts developed ADC with lower median $CD4+$ counts (18 vs $31/\mu L$) than pts without ZDV. Survival analysis according to the ID and to prior ZDV therapy were performed. Autopsy was made in 80/218 pts with ADC (91% of those died at the Hospital). HIV-E was found in 31 (39%), HIV-L in 19 (24%), HIV-E+L in 21 (26%), non-HIV related lesions were the only finding in 9 pts (11%). A correlation between clinical and autopsy findings was performed.

Conclusion: ADC is becoming a less frequent disease, occurring in later stages of HIV infection. HIV-related lesions were found in 89% of patients with ADC.

ATTENTION DEFICIT AND SPECT FRONTAL LOBE UPTAKE DEFECT IN A COHORT OF HIV POSITIVE PATIENTS.

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Objective: To evaluate the correlation between attention abnormalities and SPECT frontal lobe uptake defects in a cohort of HIV positive patients.

Methods: The study included 99 neuropsychological evaluations and SPECT examinations of HIV positive pts. without clinical sign of dementia. The neuropsychological tests considered in this analysis included: Trial making A and B, Digit Span (sub-test WAIS), Controlled oral association test, Selective matrices.

All pts. underwent to 99 mtc-HM-PAO SPECT. Both qualitative and semiquantitative analysis of spect findings was performed on 14 cortical regions. The sensibility, specificity, positive and negative predictive values of SPECT frontal lobe uptake defects were estimated respect to neuropsychological tests exploring attention considered as gold standard.

Results: The prevalence of attention impairment was 67.7% , as single defect 29.3. The prevalence of SPECT uptake defects in the frontal lobe was 57.6%, as single abnormality 26.2%, associated to defects in other lobes 31.4%. The SPECT sensibility, specificity, positive and negative predictive values were 62.7%, 53.1%, 73.7% and 40.5% respectively.

Conclusion: The sensibility of SPECT frontal uptake defects in pts. with attention impairment was not very high and more less was the specificity, SPECT abnormalities in the frontal lobe may predict attention impairment but a normal exam cannot exclude it.

LONG TERM SURVIVAL IN BIOPSY-PROVEN AIDS-ASSOCIATED PML

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Six HIV-infected persons with biopsy-proven AIDS-associated progressive multifocal leukoencephalopathy (PML) had survivals greater than one year. Two have been previously described (Neurology 1988;38:1060-6). Five were gay men and the sixth, a bisexual woman. The age range at disease onset was 31 to 51 years (mean 39). PML was the presenting manifestation of HIV infection in 5/6. In 3, the CD4 count at the time of diagnosis was >300 cells/cu mm (359-588; mean 446), whereas, in the other 3, CD4 counts were <50 (2-43; mean 18). Radiographic imaging revealed faint contrast enhancement of the PML lesions in 3/6. The disease was exclusively supratentorial in 5. Histopathological examination in one patient showed a significant inflammatory component.

In 5, survival varied between 18 and 92 months (mean 39; median 29). One patient (CD4 >500) is currently alive with a mild hemiparesis more than 20 months after diagnosis. Four patients had complete recovery of their clinical deficits which correlated with resolution of radiographic abnormalities in 3/4. In the other 2, significant clinical improvement was noted in the absence of substantial improvement in radiographic abnormalities. Two/5 died of recurrent PML after an initial improvement; 3/5 died of other AIDS-related complications without recurrent neurological disease. Autopsy performed 37 months after diagnosis in one patient failed to reveal persisting evidence of PML. Treatment protocols included: zidovudine <1 gm/d (2/6); zidovudine >1 gm/d (2/6); zidovudine <1 gm/d with 2 courses of IV ARA-C 2 gm/d (1/6); and no treatment (1/6).

This population of long-term survivors with AIDS-associated PML represents approximately 8% of all biopsy-proven patients from a larger series. Potential predictors for long term survivorship include: PML as the heralding manifestation of AIDS; high (>200 cells/cu mm) CD4 counts; contrast enhancement on radiographic imaging; and inflammatory infiltrate on biopsy. Long term survivorship and neurological recovery did not correlate with any specific therapeutic strategy.

HIV-1 ASSOCIATED CNS DISEASE SYNDROMES IN INFANTS AND CHILDREN: A PROPOSAL FOR RESEARCH CASE DEFINITIONS.

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Objective: To develop "operational" definitions for classifying pediatric HIV-1 associated CNS syndromes.

Background: In the early years of the AIDS epidemic, HIV-1 associated CNS involvement was recognized as a major complication in infants and children. Initially a progressive encephalopathy [PE] was described as was more stable neurologic impairment. [Ann Neurol 1985;17:488 & 18:560]. "AIDS encephalopathy" was added to the CDC's list of pediatric AIDS-defining illnesses. As infants and children were followed longitudinally several patterns of neurologic deterioration were recognized: [Ann Neurol 1985;18:560;AJDC 1988;142:29] In 1991, a consensus report on nomenclature recommended that the term "HIV- associated PE of childhood" replace the various terms found in the literature [Neurology 1991;41:778] While the well described signs of end stage CNS disease were enumerated, different patterns and rate of CNS disease progression were not addressed. Moreover continued clinical observations in both clinical & research settings suggest that the spectrum & diversity of pediatric HIV-1 CNS disease manifestations is wider than previously appreciated. Further characterization of subtypes [case definitions], are now required to provide a common terminology for clinicians & researchers; a classification and staging scheme for pediatric HIV-1 associated CNS disease syndromes; and a framework to monitor efficacy of treatment protocols. A paradigm is proposed based on clinical studies of 97 children followed at a single pediatric AIDS center. Classification includes: age of onset of clinically apparent disease, domains of function most affected [cognitive or motor, or both], and rate & pattern of disease progression [rapid or slow].

Patients: Ninety-seven vertically HIV-1 infected children [61♂ & 36♀] followed longitudinally at a single center.

Methods: Serial neurologic, neuropsychologic & neuroimaging evaluations.

Results:

Infancy: By age 2 years: Fifteen children, [15.5%] of the cohort had severe cognitive & motor deficits [mental deficiency, spastic quadriplegia]. Fifteen children, [15.5%] had marked motor delays. Of these 15 children, 7 had cognitive impairment. Between 3 and 5 years of age, 4 had progressive neurologic deterioration (motor & cognitive); 4 had average or borderline cognition but had marked motor impairment requiring orthotics.

Early Childhood: Between ages 2-5 years: 3 children [3%] developed a diplegia/spastic paraparesis type syndrome. Of these 3, 2 had low average cognition and 1 scored in the deficient range. Five children [5%] had "minor" motor findings; 4/5 had borderline cognition. **Childhood:** 5 years and older: Three [3%] children developed cognitive and motor deficits.

Conclusions: This paradigm may help in the development of a classification & staging system for pediatric HIV-1 associated CNS disease syndromes and to provide a framework for monitoring efficacy of treatment protocols.

BLOOD BRAIN BARRIER BREAKDOWN IN AIDS DEMENTIA: AN MRI STUDY

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Background: A breakdown of the blood brain barrier (BBB) is likely to play an important role in the pathogenesis of AIDS dementia. However, the time course and location of the BBB disruption remains unknown.

Object: To test the hypothesis that BBB breakdown in AIDS dementia can be detected by post-contrast enhanced MRI.

Methods: Pre- and 3 minute post-contrast axial T1 weighted MRI scans were obtained in subjects with AIDS dementia and in non-HIV infected controls. The post-contrast fractional signal enhancement (FE) was determined in six non-overlapping regions of interest (ROI) in the lenticular nuclei and in adjacent white matter of both hemispheres. Statistical significance was established using the 2-sided Mann-Whitney U rank sum test.

Results: In controls, the mean FE was $2.6 \pm 1.5\%$ [mean \pm SD, n=5;60 ROIs total] for subcortical gray matter and $1.3 \pm 1.7\%$ for adjacent white matter. In subjects with AIDS dementia, mean gray matter FE was $6.2 \pm 1.3\%$ [mean \pm SD, n=4; 48 ROIs total] and $2.1 \pm 1.0\%$ for white matter. The subjects with AIDS dementia showed a significantly greater gray matter enhancement ($p < 0.001$), while there was no difference in white matter enhancement.

Conclusion: Contrast enhanced MRI provides a routinely available method to assess BBB breakdown. Preliminary studies in AIDS dementia show a greater than normal FE in the basal ganglia suggesting a regional compromise of the BBB in this disorder.

OXANDROLONE IN AIDS WASTING/MYOPATHY

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Objective: To determine whether the anabolic steroid, oxandrolone, is effective in treating AIDS wasting/myopathy.

Background: Muscle weakness and associated wasting are common manifestations of HIV infection. Anabolic steroids have been associated with increased muscle mass.

Design/Methods: In a double-blind study, 67 HIV-seropositive men with $\geq 10\%$ loss of body weight; evidence of generalized or proximal muscle weakness; and constant antiretroviral therapy were randomized to receive placebo, oxandrolone 5 mg/day or oxandrolone 15 mg/day for 16 weeks. Repeat assessments included body weight, scales of well-being, neuromuscular evaluations, and dynamometry.

Results: 50/67 subjects completed the study. A significant gain in body weight was observed with oxandrolone 15 mg/day and maintained throughout the duration of the study. Weight remained stable in the oxandrolone 5 mg/day group and fell in the placebo group. No definite improvement in body strength was noted with oxandrolone.

Conclusion: Treatment of AIDS wasting/myopathy with oxandrolone at 15 mg/day is associated with a significant and sustained weight gain.

CEREBROSPINAL FLUID NEUROTRANSMITTERS AND CENTRAL NERVOUS SYSTEM INVOLVEMENT IN HIV INFECTION

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Aims: Aim of this work was to search a possible relationship between cerebrospinal fluid (CSF) levels of aminergic metabolites and presence of HIV-induced central nervous system damage in HIV-infected patients.

Methods: CSF was collected from 16 HIV-infected patients with central or peripheral nervous system involvement and from 22 age-matched HIV-negative patients with various neurologic diseases, without signs of dementia, extrapyramidal illness or depression. CSF levels of the dopaminergic metabolites DOPAC and homovanillic acid (HVA) and of the serotonergic metabolite 5-HIAA were measured by reverse-phase HPLC. **Results:** HIV-infected patients showed significantly lower levels of HVA (19.9 ± 20.1 vs. 50.1 ± 20.4 ng/ml, $P < 0.001$) compared to controls, while no significant differences were found for levels of DOPAC and 5-HIAA. HIV-infected patients with findings consistent with HIV encephalopathy showed a significant reduction of 5-HIAA levels (8.56 ± 6.68 contro 26.88 ± 16.22 ng/ml; $P = 0.015$) compared to patients without HIV encephalopathy. **Discussion:** The data so far obtained confirm that HIV infected patients display a selective impairment of dopaminergic systems and in addition show that patients with HIV encephalopathy and cognitive impairment have defects of other neurotransmitter system (i.e. serotonergic). Further work is necessary to state whether these changes could have a causative role for the neurologic manifestations of the disease.

NEUROPSYCHIATRIC FOLLOW-UP IN HIV+ CHILDREN

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We want to show the natural evolution of neurological impairment in a group of 15 children out of 42, all HIV+ for vertical transmission, followed in the Child Department University of Turin. These patients have been examined just from first month of life with a follow-up study which included: clinical evaluation, neurophysiological tests (EEG and E.P.), neuroradiological investigation (CT scan), neuropsychological evaluation (when possible). 11 children died at an age between 19 months and 10 years; the 4 who are still alive are aged between 8 months and 8 years.

We want to discuss:

- the sample's distribution as to neurological signs' age of onset;
- the beginning of neurological symptomatology in relation to: age of onset, clinical signs in other organs, immunological situation;
- the neurological picture's evolution, as regards both clinical aspect and instrumental evolution;
- the prognostic meaning of encephalopathy.

In relation to this data, we point out the main issues of our work, that evolutive feature (characteristic) of encephalopathy, even with respect to therapy, the diagnostic difficulties and meaning of neurophysiological investigations for diagnostic and prognostic purposes.

EVOKED POTENTIALS IN SEROPOSITIVE PATIENTS IN CHILDHOOD

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Evoked Potentials studies in adult seropositive patients have given interesting results, even before encephalopathy onset, mainly for BAEP's absolute and interpeak latency values, whereas in childhood there are few such analysis.

32 seropositive patients with a total of 102 examinations (17 BAER and 85 flash and pattern VEPs), and a control group map of 17 healthy age and sex matched children, have been studied. The age was between 7 months and 9 years (mean age 3 yrs 8 mths). Patients were divided as follows: P1 = 2 (6 exams); P2 without encephalopathy = 22 (80 exams); P2 with encephalopathy = 8 (17 exams). Latency variations were considered as pathologic when their value was above 2 S.D. The results of all exams in P1 group were normal: in P2 non encephalopathic patients: 17/80 (21.3%) exams were pathologic; encephalopathy was seen in 6/22 patients after an average of 4.5 months. Encephalopathic subjects showed pathologic results in 17/17 of exams.

Results of P100 latencies (pattern VEP study) in P2 patients show a difference statistically significant with the group of normal subjects. Statistically significant results are also obtained in BAEP study for both ears subdividing the symptomatic children on the basis of age and clinical conditions: younger children have progressively higher interpeak latency values and encephalopathic P2 patients show the same tendency if confronted with patients without neurologic signs. These results confirm the predictivity of such exam.

In conclusion we can affirm that E.P. is a sensitive, useful and intrusive research method, which represents, also in children, a possible early diagnostic tool.

EXERCISE HISTORY AND COGNITIVE FUNCTION IN HIV INFECTION

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Physical exercise has been shown to have a beneficial effect on immune function, and to buffer the adverse effects of stressful events on CD4 cell decline. Rate of CD4 decline has also been shown to predict cognitive dysfunction in HIV infection. This study examined the effect of exercise history on cognitive function in 155 gay men with asymptomatic HIV infection. Subjects were stratified on history of regular exercise prior to diagnosis of HIV infection.

39 had no history, and 66 reported an exercise history. Those with a history of exercise had a lower summary impairment rating ($p < 0.05$) on a comprehensive neuropsychological examination. The two groups were comparable on age, Full Scale IQ, CD4 level, Beck Depression Scale, and weekly ethanol consumption.

Subjects with no history performed more poorly on measures of dexterity and rapid information processing. These differences were not identified in relation to current exercise practice. These preliminary data raise the possibility that regular exercise may have a long term protective benefit in attenuating the effects of HIV infection. Although the mechanism is not clear, this has potential implications for the development of interventional strategies.

CEREBROSPINAL FLUID (CSF) HIV-1 RNA LEVELS CORRELATE WITH AIDS DEMENTIA COMPLEX (ADC)

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Objectives: To determine the relationship between CSF HIV-1 RNA and i) the severity of ADC and ii) central nervous system (CNS) infections.

Methods: 26 patients were assessed neurologically and neuropsychologically. Other causes of cognitive impairment were excluded by CT brain scan and CSF analyses. The patients were staged according to the severity of the ADC: 7 stage 0, 8 stage 1, 6 stage 2 and 5 stage 3. In addition there were 10 patients with stage 0 ADC with CNS infections were included: 7 with cryptococcal meningitis, 3 with progressive multifocal leukoencephalopathy (PML). HIV-1 RNA was extracted from CSF and plasma and quantified by RT-PCR amplifying a 142 base pair fragment of the gag gene (Roche).

Results: CSF HIV-1 RNA load was $36,824 \pm 14,845$ copies/ml for stage ≥ 1 while in the plasma it was $567,116 \pm 181,296$ copies/ml. There was a significant correlation between the severity of ADC and HIV-1 RNA in the CSF but not in the plasma; CSF HIV-1 RNA burden was significantly less than in the plasma. CSF HIV-1 RNA in cryptococcal meningitis was $94,771 \pm 38,838$ copies/ml which declined to $7,004 \pm 3,470$ copies/ml with treatment and in PML it was 208 ± 152 copies/ml.

Conclusions: CSF HIV-1 RNA levels correlate with ADC severity but may also be increased by CNS infections such as cryptococcal meningitis. The relationship to ADC supports the role of HIV-1 in the pathogenesis of ADC but the relatively small viral load in the CSF suggests the importance of other mechanisms.

ELEVATED CEREBROSPINAL FLUID (CSF) CONCENTRATIONS OF BETA-2 MICROGLOBULIN (B2M) AND NEOPTERIN (NEOP.) AND CD4 CELL COUNT PREDICT DEVELOPMENT OF AIDS DEMENTIA COMPLEX (ADC)

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Objectives: To identify a marker that would predict the development of ADC.

Methods: Neurologically asymptomatic HIV infected patients with a CD4 cell count < 200 were asked to participate in a three year prospective study. At entry patients were assessed neurologically and neuropsychologically and had blood taken for haemoglobin, CD4 cell count, B2M and Neop. and CSF for assay of B2M and Neop., the results of which were blinded from the assessors. The patients were then evaluated every four months neurologically and neuropsychologically.

Results: Thirty five patients had sufficient followup data: 17 progressed to ADC stage ≥ 1 . Only elevated concentrations of CSF B2M and Neop. and CD4 cell counts $< 50/\mu l$ were significantly associated with the development of ADC. By multivariate analysis, concentrations of CSF B2M remained significant with levels above 5mg/l carrying approximately 17 times the risk of ADC compared to concentrations < 2.5 mg/l.

Conclusions: Elevated levels of CSF B2M and Neop. and a CD4 cell count $< 50/\mu l$ signify an increased risk of ADC. Such patients should be targeted for appropriate early antiretroviral therapy.

PSYCHOPATHOLOGY IN HIV-INFECTION

A comparison between Injecting Drug Users and Homosexuals

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Objectives : to study depression, anxiety, emotional deficit and anhedonia in two groups of HIV-positive subjects : a group of injecting drug users and a group of homosexual men.

Methods : 70 HIV-Positive homosexuals and 20 HIV-Positive injecting drug users have been included. They were all in asymptomatic stages of the infection (CDC criteria). All subjects were seen in a semi structured interview. DSM III-R criteria for major depressive, dysthymic and generalized anxiety, MADRS, Retardation Rating Scale (ERD), Depressive Mood Scale (EHD) and Abrams and Taylor Scale for Emotional Blunting were assessed in order to evaluate depressive and anxious symptomatology and emotional perturbations. A questionnaire of Sensation Seeking was filled by all subjects.

Results : showed that the group of injecting drug users knew their seropositivity since a longer period of time (65.5 ± 38 months vs 41.5 ± 25 months, $p = .001$). The injecting drug users presented significantly ($p < .01$) more depressive symptoms, were more retarded and had higher scores of emotional deficit but they were less anxious than homosexual men. The scores of sensation seeking were similar in both groups of subjects.

Conclusions : The present study shows that psychopathological perturbations observed in a group of injecting drug users were different from those observed in homosexuals. Few studies on psychopathology have been published with injecting drug users. In this population it is always difficult to determine if the observed perturbations are consecutive to the drug use or to the HIV-infection. However it should help to improve a taking care as well as a counseling specific for injecting drug users.

DESCRIPTORS OF HIV-ASSOCIATED SENSORY NEUROPATHY
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Background: Specific temporal patterns and symptom descriptors of HIV-associated sensory neuropathy (SN) have not been systematically studied.

Objective: To determine temporal patterns of symptoms of HIV-associated SN.

Methods: A standardized pain questionnaire was administered to 30 HIV+ patients with symptomatic SN or antiretroviral-induced toxic neuropathies. SN was identified by history; confirmed by neurological exam, quantitative sensory testing or skin biopsy.

Results: The study group was 93% male, 70% white; median age 40 years. 26.7% had CDC Stage A infection, 23.3% CDC Stage B and 50% AIDS. 44% were taking pain modifying agents. The following foot symptoms were graded as moderate or severe: aching (36%), burning (32%), tingling (32%), coldness (23%), shooting (23%), and sharpness (14%). 43% reported continuous pain, 29% intermittent pain, and 28% transient pain. 41% had maximum pain during the evening; 11% had maximum pain in the morning. 22% had no temporal pattern. Pain interfered with sleep in 59%.

Conclusions: The most common and intense foot symptoms of SN are aching, burning, and tingling. Although there is variability in the temporal patterns of pain, nocturnal symptoms were very frequent and confirms that therapies must be aimed at symptomatic nocturnal control.

COMBINED USE OF CSF EBV-DNA AND ²⁰¹ Tl-SPECT IN THE MANAGEMENT OF CNS CONTRAST-ENHANCING LESIONS IN AIDS PATIENTS

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Differential diagnosis between toxoplasma encephalitis and primary CNS lymphoma (PCNSL) is difficult because of the low specificity of clinical and neuroradiological findings. Aetiological diagnosis of PCNSL currently relies on stereotactic brain biopsy. Recently, detection of EBV-DNA in CSF has been associated with the presence of PCNSL. Moreover ²⁰¹ Tl Single - Photon Emission Computed Tomography (²⁰¹ Tl SPECT) seems to be a useful, non invasive method to differentiate lymphoma from toxoplasma encephalitis.

We evaluated the combined use of EBV-DNA detection in CSF and ²⁰¹ Tl SPECT in the management of CNS contrast-enhancing lesions in AIDS patients.

19 AIDS patients with CNS contrast-enhancing lesions were prospectively evaluated. All patients started with antitoxo-therapy and underwent ²⁰¹ Tl imaging with CERASPECT. The images were considered positive in case of uptake ratio > 3. EBV DNA detection in CSF and Toxoplasma serology were performed in 16 cases. Diagnosis of toxoplasma encephalitis was made according to CDC guidelines. Histological diagnosis of PCNSL was obtained by brain stereotactic biopsy.

The data obtained are shown in the table.

Diagnosis	N° of cases	TOXO Ab	EBV-DNA	²⁰¹ Tl SPECT	EBV-DNA AND ²⁰¹ Tl SPECT
Toxoplasmosis	10	2/9	2/9	0/10	0/9
Lymphoma	9	5/7	6/7	7/9	7/7

Our preliminary results suggest that the combined use of CSF PCR for EBV-DNA and ²⁰¹ Tl SPECT seems able to correctly identify PCNSL from toxoplasma encephalitis.

NEURODEVELOPMENTAL OUTCOME BY 30 MONTHS IN CHILDREN WITH VERTICALLY TRANSMITTED HIV INFECTION: THE WOMEN AND INFANTS TRANSMISSION (WITS) STUDY

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Objective To identify the risk for encephalopathy associated with HIV status in children 4-30 months of age in the WITS sample.

Sample 595 children (114 INF, 481 SR) born to pregnant women with HIV infection who enrolled in the WITS study during pregnancy.

Method Children were seen for neurodevelopmental assessment at 4, 9, 12, 15, 18, 24 and 30 months of age. BSID Mental Development Index (MDI) and Psychomotor Developmental Index (PDI) were obtained at each assessment. A multivariable Cox proportional hazards model compared the relative risk of HIV status, prematurity (< 37 weeks), drug exposure, maternal education and primary language over time for occurrence of three indices of encephalopathy: 1) MDI or PDI ≤ - 68, 2) confirmed drops of - 1 SD in MDI or PDI, and 3) confirmed drops of - 2 SD in MDI or PDI.

Results HIV status alone was significantly associated with a confirmed - 2 SD drop in MDI or PDI. HIV status and prematurity were associated with the probability of a confirmed drop in PDI of ≤ 1 SD or an MDI or PDI of 68. Mother's use of hard drugs during pregnancy, maternal education, and primary language did not appear to be significantly associated with added risk for encephalopathy.

RELIABILITY OF POLYMERASE CHAIN REACTION (PCR) ON CEREBROSPINAL FLUID (CSF) FOR DIAGNOSIS OF AIDS-ASSOCIATED OPPORTUNISTIC DISEASES OF THE CENTRAL NERVOUS SYSTEM (CNS).

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Opportunistic diseases of the CNS account for the great majority of neurological complications in AIDS patients, but diagnosis is often obtained only post mortem. The diagnostic reliability of CSF PCR for detection of microbial DNA was assessed on CSF samples drawn 1-180 days before death from 219 AIDS patients with neurological disorders, by comparing PCR results to CNS histopathology at autopsy (202) or brain biopsy (17). By histopathology, HIV-related lesions were found in 22% of patients (49), cytomegalovirus (CMV) infection in 21% (45), toxoplasmosis in 19% (42), progressive multifocal leukoencephalopathy (PML) in 18% (39), primary lymphoma in 16% (36), cryptococcosis in 5% (12), tuberculous meningoencephalitis (TB-ME) in 4% (8), herpes simplex virus (HSV-1/2) infection in 3% (6). Sensitivity, specificity, positive and negative predictive values (PPV, NPV) of CSF PCR assays for diagnosis of the respective opportunistic CNS diseases, are given below.

CSF-PCR (CNS disease)	Sensitivity	Specificity	PPV	NPV
CMV (CMV encephalitis/myelitis)	82% (37/45)	98% (171/174)	92%	95%
JC virus (PML)	72% (28/39)	99% (179/180)	93%	95%
Epstein-Barr virus (primary lymphoma)	97% (35/36)	98% (180/183)	90%	99%
M.tuberculosis (TB-ME)	100% (8/8)	100% (35/35)	100%	100%
HSV-1/2 (HSV encephalitis)	100% (6/6)	99.5% (212/213)	86%	100%

Owing to the high diagnostic reliability, CSF PCR for microbial DNA should be included as a major tool in the set of tests for diagnosis of neurological complications in AIDS patients.

CEREBRAL TOMOGRAPHIC STUDY IN 85 HIV POSITIVE CHILDREN: ASSOCIATION BETWEEN NEUROLOGICAL SIGNS AND TOMOGRAPHIC FINDINGS. Czornyj L*

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We undertook a tomographic study in 85 HIV+ children during a three year period starting in June 1990. Mean age was 2 years (range 4 months to 8 years). We intended to correlate the neurological signs on physical examination (NS) with tomographic findings in order to detect a predictive value of the association of these parameters. A cerebral computed tomography (CCT) was performed whenever NS were found and in 15 additional children with AIDS but without NS who were regarded as a control group, who had normal CCT. In 70 symptomatic children, 55 had abnormal CCT (78.6%) ($p < 0.001$). Twenty eight of these children were younger than 1 year and 14 were younger than 6 months. In all cases, NS suggested progressive or static encephalopathy (PE, SE). Tomographic findings included: Cortical and/or Central Atrophy (CCA) in 30 patients, CCA and calcification of basal ganglia (CBG) in 5 patients, hypodensity of white matter in 6 patients, stroke in 1 patient, congenital hydrocephalus and calcifications in 4 patients, lesions caused by intentional injury in 2 patients, subdural collection in 1 patient, and opportunistic infections in 8 patients. Fifteen children older than 1 year with neurological signs of SE had normal CCT. Fifteen children (23.7%) with abnormal CCT died within three years of follow-up, whereas no patient with normal CCT died in the same period. Chi square analysis revealed a statistically significant difference between the symptomatic group (abnormal CCT 78.6%) and the asymptomatic group (abnormal CCT 0%). NS preceded tomographic findings in all cases. CCA (35%) was earlier and more frequent tomographic feature. Whenever present, CBG was associated with CCA. Tomographic followup showed that CBG appeared after CCA in all cases, suggesting a sequential progression. CCT was not able to detect opportunistic infection earlier, but was useful in the followup of more advanced cases. On the contrary, MRI allowed the early diagnosis of OI. We conclude that abnormal CCT are usually an indicator of poor prognosis and are associated with encephalopathy or other neurological complication during the course of HIV infection in children.

JC VIRUS DNA AND mRNA IN THE PERIPHERAL BLOOD LEUKOCYTES OF HIV-INFECTED PATIENTS.

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Among unresolved issues concerning JC Virus (JCV), the opportunistic agent which causes Progressive Multifocal Leuko-encephalopathy, stands the putative role of peripheral blood leukocytes (PBLs) as JCV conveyors across the blood-brain barrier. We started a prospective study to better assess the importance of PBLs in JCV infection.

We first detected JCV DNA in PBLs with a combined Polymerase Chain Reaction (PCR) and liquid hybridization procedure, amplifying the early T gene. Among 157 HIV-infected persons, 39 (24.8%) were found JCV DNA-positive, whatever their CD4 count. In contrast, only 10 (15.3%) of 65 HIV-negative immunocompromised persons were JCV-positive.

To determine whether the amplified viral DNA belonged to latent or reactivated JCV, a reverse transcription-nested PCR was developed. It detects mRNAs for JCV late capsid protein VP1, characteristic of active viral multiplication, in JCV-positive cerebrospinal fluid, urine and blood. However, no JCV mRNA-positive sample was identified yet in the PBLs of JCV DNA-positive patients (39 in 1994 and 31 in 1995).

These preliminary results suggest that, although JCV DNA is precociously present in the blood of more HIV-positive than HIV-negative persons, JCV reactivation may take place elsewhere than in PBLs.

HIV-ASSOCIATED PERIPHERAL NEUROPATHY: ELECTROPHYSIOLOGICAL AND PATHOLOGICAL STUDY.

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We studied 47 patients with HIV infection, AIDS Related Complex or AIDS, 39 without symptoms or signs of peripheral neuropathy and 8 with clinically evident peripheral neuropathy. Latency, amplitude, and conduction velocity of median motor and sensory, ulnar sensory, common peroneal, sural, lateral and medial plantar nerves were measured, with a standardized method. A mild slowing was found in 13 out of 39 asymptomatic patients (33%), both in sensory and motor conduction, with an amplitude reduction more marked in lower limbs. In particular sensory action potential (SAP) of medial and lateral plantar nerves were absent in 5 patients, with a decrease of amplitude and slowing of conduction velocity of sural nerves. Moreover the presence of peripheral neuropathy was confirmed by electrophysiological evaluation in 8 symptomatic patients, and by pathological study in 3 of them. Sural nerve biopsy showed axonal degeneration without inflammation or demyelination. There was a 40.5% mean reduction in myelinated fiber density and the loss principally affected the large fibers. The electrophysiological evaluation may suggest that SAPs absence or changes in plantar nerves could be considered as a marker of a subclinical neuropathy. The pathological changes in the symptomatic patient showed an axonal degeneration similar to that seen in other chronic disorders.

HIV ENCEPHALITIS AND APOLIPOPROTEIN E. A POPULATION-BASED AUTOPSY STUDY FROM OSLO.

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Background: Apolipoprotein E (ApoE) 4 genotype is associated with the occurrence of Alzheimer's dementia and probably Creutzfeldt-Jacob's disease. As the gene product of ApoE is produced by macrophages in the brain, the purpose of this study was to study the effect of ApoE genotypes on the occurrence of HIV encephalitis.

Methods: The patient population comprised all adult AIDS patients in Oslo who were treated at Ullevål Hospital and died during 1983-1994 (n=171). This represents 86% of all adult AIDS patients from Oslo who died during the same period. Full autopsy was performed on 132 (75%). There were no significant difference between autopsy and non-autopsy cases with regards to sex, age risk groups, survival length or zidovudine (ZDV) treatment.

PCR to determine ApoE genotypes, was performed on formalin paraffin embedded tissue from the 132 patients. Multinucleated giant cells (MGCs) (hallmark of HIV encephalitis) were found in 31 patients. The study was powered to find an increase in risk associated with ApoE heterozygosity of 50% or more.

Results:

ApoE genefrequencies	22	23	24	33	34	44	nd
No MGC	1	12	2	58	23	2	3
MGC	0	4	0	17	8	2	0

ApoE genotypes were not associated with any statistically significant change in risk of HIV encephalitis, even after correction for length of survival with AIDS and ZDV treatment (regression analysis).

Conclusion: ApoE genotypes do not seem to have a large influence the occurrence of HIV encephalitis.

QUANTIFICATION OF JC-VIRUS DNA IN CSF DURING TREATMENT OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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Purpose: Analysis of JC virus load in the cerebrospinal fluid (CSF) under treatment of progressive multifocal leukoencephalopathy (PML).

Patients and methods: Two HIV-infected patients with biopsy proven PML underwent a therapeutic trial with a combination of cytosine arabinoside (Ara-C) intravenously and intrathecally (i.th.), Interferon-alpha (IFN- α) subcutaneously and i.th., and polyvalent immunoglobulins (Ig) i.th.. Virus load was measured by PCR analysis with JCV specific primers spanning the non-coding control region of the virus genome. Products were characterized by electrophoretic separation and virus specific hybridization. Semiquantitation was achieved by titration of CSF prior to PCR followed by densitometric evaluation in comparison to a control reaction with JCV plasmid DNA.

Results: Treatment was terminated after 25 and 13 i.th. applications, and the patients died eight and four weeks later, respectively. Only in the first patient seemed the progression to be halted clinically and radiologically for 8 weeks. In both patients early under treatment CSF did not contain detectable amounts of JCV-DNA. However DNA was amplified in later specimens in varying quantities seemingly independent from clinical progression.

Conclusions: We were unable to detect a reduction of JC-Virus load in the CSF that was attributable to the treatment of our PML-patients. This is in agreement with the lack of clinical and radiological improvement. In view of in vitro results that show Ara-C to suppress JCV replication in oligodendrocytes (E. Major, Curr Opin Neurol 1995;8:184) our clinical and virological data do not support a beneficial action of a drug combination including Ara-C in PML-patients.

VALUE OF THE POLYMERASE CHAIN REACTION IN THE DIAGNOSIS OF HIV-ASSOCIATED TOXOPLASMIC ENCEPHALITIS

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Purpose: We evaluated the potential of the polymerase chain reaction (PCR) for the diagnosis of HIV-associated toxoplasmic encephalitis (TE).

Patients and methods: In a prospective study we investigated the cerebrospinal fluid (CSF) of 24 patients with 26 episodes of TE, two patients with primary acute toxoplasma infection and 38 controls with latent toxoplasma infection. TE was diagnosed either histopathologically or by the constellation of typical radiological features, presence of specific toxoplasma antibodies, improvement on specific therapy and exclusion of lymphoma by follow up. CSF was examined by PCR using primer sequences from the B1-gene of the organism and by mouse inoculation.

Results: Detection of *Toxoplasma gondii* by both methods was possible in only three of the TE patients (11,5%). The remaining TE patients and the controls were negative with either method. In contrast, *T. gondii* was detected by PCR and mouse inoculation in both patients with primary acute toxoplasma infection.

Conclusions: Direct detection of *T. gondii* in CSF by PCR or culture methods is of low diagnostic sensitivity in HIV-associated TE, whereas a positive result may confirm the diagnosis. In contrast, organisms may be easily found in CSF in primary acute toxoplasmosis, probably owing to generalization of organisms in this stage of the infection, as opposed to the localized reactivation of toxoplasma cysts that usually occurs with immunodeficiency.

CLINICAL DIAGNOSIS AND RISK FACTORS FOR HIV-ASSOCIATED
MINOR COGNITIVE-MOTOR DISORDER
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RATIONALE. Clinical criteria for HIV-associated minor cognitive-motor disorder (MCMD) have been proposed, but not evaluated. Risk factors, prognosis and treatments are undefined.

METHODS. We studied a cohort of HIV-infected volunteers without frank dementia. MCMD was diagnosed according to published criteria (AAN, 1991) requiring objective evidence of cognitive impairment on neuropsychological (NP) testing; mild, but symptomatic functional decline from a previous baseline; and the absence of etiologic explanations other than HIV.

RESULTS. Of 494 included subjects, 65% were NP normal (NL) and 35% showed global NP impairment. Among impaired subjects, 36% met criteria for MCMD; the remainder were subsyndromally impaired (NPI). Disease stage was the principal risk factor for MCMD: among seropositives free of opportunistic disease, 4% met MCMD criteria, compared to 28% of those with minor opportunistic diseases, and 32% of those with AIDS-defining illnesses. After adjusting for the effect of disease stage, the risk for MCMD increased in association with abnormally high concentrations of serum globulins, and cerebrospinal fluid beta-2-microglobulin (B2MG), but did not differ according to age, education, gender, CD4 lymphocyte count, body mass, or B2MG in serum. Median survival times in the MCMD, NPI and NL groups were 2.2, 3.8 and 5.1 years, respectively.

CONCLUSIONS. Both systemic and CNS-specific immune dysregulation may contribute to MCMD. Because MCMD is common and is associated with longer survival than HIV-associated dementia, patients with MCMD may be better suited for interventional trials.

Supported by NIMH Center Grant MH45294.

CHANGES OF MIGRAINE FEATURES DURING HIV INFECTION

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In several reports headache features of HIV patients have been described but there are no controlled studies on changes of headache features by HIV infection. We examined patients with migraine prior to HIV infection in order to evaluate changes of migraine symptoms, time patterns etc. after infection.

84 patients with different stages of HIV infection were enrolled. Headache diagnosis was made according to the criteria of the International Headache Society. In all patients with migraine with or without aura prior to infection a standardized interview was performed and clinical relevant data were recorded.

38 (45%) of all patients complained relevant headache prior to infection. Headache diagnoses were: migraine (15), tension-type headache (17), sinus thrombosis (1), 5 could not be classified. In the 15 migraine patients (CDC: I=2; II=7; III=6) mean number of migraine attacks per month decreased from 1.6 \pm 0.9 prior to infection to 0.8 \pm 0.5 after infection ($p < 0.002$), mean migraine intensity (10 point rating scale) decreased from 7.1 \pm 1.8 to 5.8 \pm 2.1 ($p < 0.03$). Patients with antiretroviral therapy showed a tendency for better improvement than patients without. There was no significant correlation between duration of HIV infection or CDC classification and changes of migraine features.

Our data suggest that frequency and intensity of migraine are decreased during HIV infection. Possible mechanisms are a prophylactic effect of antiretroviral drug therapy, an impact of HIV infection on neurogenic inflammation of cerebral vessels during a migraine attack or the reduction of sympathetic level, which is normally elevated in migraine, by HIV infection.

LOW LEVELS OF LTB₄ IN CEREBROSPINAL FLUID OF HIV-POSITIVE PATIENTS WITH CEREBRAL CRYPTOCOCCOSIS

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In this study we evaluated the release of leukotriene B₄ (LTB₄) in the cerebrospinal fluid (CSF) of 12 patients with Acquired Immunodeficiency Syndrome (AIDS), complicated by Cryptococcus Meningitis and in CSF of 12 control subjects HIV-negative, with inflammatory and degenerative pathologies of Central Nervous System (CNS). We studied 10 males and 2 females. LTB₄ determination was performed by competitive RIA. The diagnosis of cryptococcosis was made by colouring CSF with indian ink, or by cultural tests, or by the identification of cryptococcus capsular antigen by immunoenzymatic test. The levels of LTB₄ resulted very low in all the AIDS patients. These data are the expression of a reduced inflammatory response and agrees with the limited clinical symptoms of Cryptococcus meningoencephalitis in these patients. The involvement of the immunocompetent cells of CNS in HIV infection can modify the inflammatory reaction against the infectious agent. The low LTB₄ levels could depend either by an altered capacity of the producing cells or by a reduced response of the target cells to the chemotactic stimuli of LTB₄, both factors which lead to a smaller inflammatory reaction in the pathogenesis of the tissue injury, following the infection by cryptococcus Neoformans.

MULTIMODAL EVOKED POTENTIALS AND P300 WAVE IN SEROPOSITIVE ASYMPTOMATIC SUBJECTS

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Central nervous system (CNS) involvement in the early stages of HIV infection is frequently described in subjects without neurological symptoms or signs too. It is known the usefulness of Evoked Potentials (EPs) in detecting sub-clinical alterations in many neurological diseases. In order to verify the presence of early CNS dysfunction and to evaluate their significance in the evolution of the disease, we performed a longitudinal neurophysiological study, including multimodal EPs and event related P300 wave, on a group of 30 neurologically asymptomatic HIV+ subjects without AIDS. Our subjects (19 men - 11 women, mean age 31.5 yrs) were submitted to EPs study, neurological and general examination, immunological evaluation every six months; neuroimaging were performed every year. VEP and BAEP results were normal at baseline and follow-up study. Mean P300 amplitude values were significantly reduced in patients with respect to the controls at every follow-up ($p < .050$); P300 latency were normal at baseline in all subjects, but we found a trend towards an increase in latency at subsequent follow-ups that reached a significance at 6- and 12- month follow-up ($p < .050$ vs baseline). Median nerve SSEPs showed a prolonged N9-N13 intertime ($p < .050$) and a reduction in N20 amplitude ($p < .010$) at follow-ups vs baseline. Tibial nerve SSEPs showed an increase in P35 latency ($p < .050$ vs controls and vs baseline) and a trend towards a prolongation in CCT that was significant at 6- and 12- month follow-up ($p < .050$ vs baseline). The analysis of single subject results showed a progressive increase in SSEP alterations, from 25% at baseline to 57% at 24- month follow-up. Statistical analysis between neurophysiological and immunological data showed a correlation between some SSEP parameters, beta2-microglobulin and CD4 cells count ($p < .050$). No correlation was found between MRI results (56% atrophy) and neurophysiological alterations.

NEUROPSYCHOLOGICAL PERFORMANCE AND SPECT FINDINGS IN A COHORT OF HIV POSITIVE PATIENTS.

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Objective: To determine the useful of SPECT exam in diagnosing cognitive deficit in a cohort of HIV positive patients.

Methods: The study included 99 neuropsychological evaluations and SPECT examinations of HIV positive pts. without clinical sign of dementia. Cognitive functions explored were attention, reasoning, memory, visuoconstructive ability. All pts. underwent to 99 mTc-HM-PAO SPECT. Both qualitative and semiquantitative analysis of SPECT findings were performed on 14 cortical regions.

The sensibility, specificity, positive and negative predictive value of SPECT exam were estimated respect to neuropsychological evaluation considered as gold standard.

Results: The prevalence of cognitive deficit was 71.7% and 67.7% concerned attention. Impairment of attention as single deficit was 29.3%, attention plus memory 29.3%, attention plus memory and reasoning 18.2%.

The prevalence of SPECT uptake defects was 82.8%, the sensibility of SPECT exam respect to neuropsychological evaluation was 90.1% while the specificity was 37.7%. The positive and negative predictive value of SPECT was 78.0% and 58.1% respectively.

Conclusion: SPECT exams showed a strong sensibility to identify an high percentage of pts. with neurocognitive deficits (90.1%) but a low specificity as uptake defects were detected in pts. without neuropsychological impairment (37.7%). SPECT defect were a positive predictive indicator of cognitive deficit (78.0%) while less significantly was a normal exam (58.1%).

Emotional problems linked with introduction to school of AIDS children.

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In our quality as child neuropsychiatrists we have achieved a work experience with HIV-positive children, whom we have been seeing on a daily basis for some years now, in cooperation with infective disease paediatricians. The cases arriving to Turin Child University Departments are representative of the Piemonte area: there are currently 192 cases, of whom 31 P0, 8 P1, 39 P2, 114 not infected. Among the P2, 15 have presented encephalopathy, which in most cases appeared within the first 2 years of life and had a very quick and progressive deterioration, ended with the patients' death within a few months. As far as the remaining P2 who precociously developed the disease are concerned, 50% of them survives up to the age of 6-8 years old in relatively good general physical conditions. At this time, one of our main objectives has become the identification of ways to improve the quality of life of our young patients. With regards to this, the possibility to have these children attend school, from nursery school through to secondary school, is extremely important and so is the impact that the introduction has on the children, on their families and on the school workers. We wish to discuss the emotional problems that the communication of the disease has on the child and his family, as well as on the school context as a whole (workers, schoolmates and families). The problem of safeguarding the child affected with a chronic disease within the school, the need to inform the operators without frightening them, respecting at the same time the right to privacy, are issues that child neuropsychiatrists deal with all the time, but in the case of a HIV-positive child they are further amplified by the very nature of the disease. A disease which is so far incurable and infective, pervaded by a sense of guilt and shame and, therefore, unmentionable.

EMOTIONAL AND MOTOR DYSFUNCTION - TWO SYMPTOMS OF ONE HIV-1-ASSOCIATED COGNITIVE / MOTOR COMPLEX ?

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The HIV-1-associated cognitive / motor complex (HIV-1-CMC) is clinically characterized by cognitive, motor and emotional dysfunction. Motor dysfunction can be evaluated electrophysiologically, emotional dysfunction may manifest as depression which equally can be quantified.

We wanted to find out about the correlation between emotional and motor dysfunction in HIV-1-CMC and analyzed $n = 2366$ data sets ($n = 650$ HIV-1-seropositive patients, $n = 61$ female, mean age 38.61 ± 9.7 yrs, all risk groups and CDC stages). All patients were examined electrophysiologically to evaluate tremor peak frequency (TPF), most rapid alternating movements (MRAM), reaction time (RT) and contraction time (CT). All patients were rated with the HAMILTON depression rating scale with regard to the scores "guilt", "idea of suicide", "impairment of work" and "depression".

With regard to "depression", more depressed patients showed a significantly lower CD 4 cell count. RT was virtually identical in non-depressed and depressed patients, whereas CT (left hand) was significantly prolonged in the depressed and MRAM (both hands) were significantly lower in the depressed.

Thus, depression does not have an effect on motor performance per se (identical reaction times) but correlates with lower CD 4 cell counts and defined motor tests.

REDUCED INTRATHECAL IMMUNOACTIVATION BY ZIDOVUDINE BUT NOT BY DIDANOSINE IN PATIENTS WITH HIV-1 INFECTION

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Cerebrospinal fluid (CSF) concentrations of neopterin was studied in 12 patients with HIV-1 infection 3-12 months after initiation of antiretroviral therapy. Ten treatment periods on zidovudine and 7 on didanosine were analysed. The CSF concentrations of neopterin decreased by 63% (from 29.6 to 12.9 nmol/L, $p < 0.01$) on zidovudine but increased by 15% (from 22.6 to 25.9 nmol/L, NS) on didanosine treatment. The results suggest that zidovudine is superior to didanosine in reducing intrathecal immunoactivation during HIV-1 infection.

A MODIFIED VERSION OF BLESSED DEMENTIA SCALE (MBDS) : A USEFUL TOOL FOR DETECTING HIV COGNITIVE ALTERATIONS

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AIM : to verify the suitability of the MBDS in HIV+ subjects to detect cognitive impairment. DESIGN: Multicenter study. From 1.1 to 1.9.95 HIV+ pre-AIDS patients, with CD4 cells count $> 500/\mu\text{L}$, $201-500/\mu\text{L}$ and $\leq 200/\mu\text{L}$ were consecutive enrolled, satisfying the following criteria: no previous or active neurological and psychiatric diseases, no active drug abuse (at least 6 months), no acute intercurrent diseases. These subjects underwent anamnesis (A), neuropsychological (NPS) tests (Progressive Matrices, Trail Making A/B, Digit Span, Digit Symbol, Story Recall, Corsi, Verbal Fluency, Finger Tapping, Block Design) and neurological examination (NE). The following diagnosis were considered: ADC and Minor Cognitive Motor deficit (MCM) (when A, NPS and NE were altered according to the Criteria of the American Academy of Neurology), NPS deficit (when only NPS was pathologic), Normal (when A, NPS and NE were normal), Other (remaining cases). The patients furthermore underwent part B of the MBDS. Analysis of variance was applied.

RESULTS: 503 patients (age 33 ± 5.7 yrs, 307 M 196 F, education 10.5 ± 3.4 yrs): 53% previous Drug Abusers, 16% Homosexual, 31% Heterosexual. 7 subjects were ADC, 11 MCM, 24 NPS, 184 Normal and 277 Other. The results (mean \pm sd) of MBDS were the following:

	ADC	MCM	NPS	OTHER	NORMAL	p<
Inform.	10.7 \pm 1.9	11.6 \pm 0.7	11.8 \pm 0.4	11.8 \pm 0.4	11.9 \pm 0.4	.001
Memory	11.0 \pm 2.6	12.5 \pm 2.2	13.4 \pm 2.3	14.6 \pm 1.7	15.2 \pm 1.5	.001
Concentr.	3.9 \pm 1.9	4.9 \pm 1.2	4.8 \pm 1.2	5.4 \pm 0.9	5.5 \pm 0.9	.001
Total	25.7 \pm 4.2	29.0 \pm 3.9	29.9 \pm 3.0	31.8 \pm 2.3	32.5 \pm 1.9	.001

CONCLUSIONS: MBDS shows a good correlation with clinical diagnosis. This test may represent an useful tool for the screening of cognitive impairment in HIV+ patients. A further evaluation of sensitivity and specificity is necessary.

EFFICACY AND GOOD TOLERABILITY OF PAROXETINE FOR THE TREATMENT OF DEPRESSED HIV INFECTED PATIENTS.

BARBARA GRASSI, ORSOLA GAMBINI AND SILVIO SCARONE

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DEPARTMENT OF NEUROPSYCHIATRIC SCIENCES
UNIVERSITY OF MILAN SCHOOL OF MEDICINE
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INTRODUCTION: Epidemiological studies point out that depression is a frequent complication of HIV infection. Further, there are evidences that depression can be associated to a decline of the immune function. An effective and well tolerated antidepressant agent is therefore needed for improving not only patients quality of life but also immune function. The aim of this study was to assess the efficacy and tolerability of paroxetine, a new antidepressant drug, in this kind of patients.

SUBJECTS AND METHODS: 10 depressed HIV infected subjects (7 males, 3 females; mean age 36.2 ± 11.39) were given paroxetine at a daily dosage of 20 mg; they were evaluated by means of the Hamilton Depression Rating Scale (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS) at the time of the enrollment (T0) and two weeks (T15), four weeks (T30) and six weeks (T45) later. Adverse effects were also recorded.

STATISTICAL ANALISES: HAM-D and MADRS mean scores for each time were analyzed by means of ANOVA for repeated measures.

RESULTS: 9 patients completed the study; 1 dropped out due to intolerable side effects (insomnia and agitation). HAM-D and MADRS mean scores significantly improved after treatment (HAM-D $p=0.0001$; MADRS $p=0.0001$). Two patients experienced mild side effects (constipation and sexual dysfunction).

CONCLUSIONS: Paroxetine seems to be an effective and well tolerated drug for the treatment of depressed HIV infected subjects.

PREDICTORS OF SEVERE DEPRESSION AND SUICIDAL IDEATION IN HIV INFECTED PATIENTS.

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Objective: To examine the demographics, psychiatric diagnoses and predictors of suicidality and severe depression in HIV infected patients attending a newly established HIV psychiatry service in downtown Toronto.

Methods: Seventy one consecutive HIV infected patients referred by their primary care physician for psychiatric assessment, completed a demographics questionnaire, CAGE survey and Beck Depression Inventory (BDI) prior to undergoing a semi-structured psychiatric interview. Multiaxial diagnoses (DSM-IV, CDC HIV staging, ADC staging and GAF) were determined. Severe depression was categorized as BDI > 27, and suicidality was examined by endorsements on BDI item nine.

Results: The sample was 98% male, 89% white, with a mean age of 37 (± 8) years and a mean education of 14 (± 4) years. Ninety five percent identified as men who have sex with men. Thirty four percent were working, 33% were married/part of a couple, and 48% perceived themselves as having poor or no support. Sixty seven percent had a past psychiatric history and 61% had a positive family history. Nineteen percent endorsed three or more items on the CAGE questionnaire for alcoholism and 27% were concerned about the level of their drug use. Fifty four percent of the sample knew > 10 people who were HIV infected. Forty six percent had asymptomatic HIV disease, 22% had symptomatic non AIDS defining conditions and 32% had AIDS. Mean BDI was 23 ± 9 , mean GAF was 53 ± 16 .

Significant predictors (chi square analyses) of severe depression (36% of sample) included perception of poor social support ($p \leq .001$), not working ($p \leq .01$), living alone ($p \leq .01$), past psychiatric history ($p \leq .03$), knowing < ten HIV positive people ($p \leq .04$), concern over drug use ($p \leq .04$). Significant predictors of suicide were BDI > 27 ($p \leq .001$) and past psychiatric history ($p \leq .03$).

Conclusion: Severe depression and past psychiatric history were significant predictors of suicidal ideation and intent in this sample of HIV infected individuals. Indicators of isolation were predictive of severe depression.

PSYCHOMOTOR SLOWING IN HIV-ASSOCIATED DEMENTIA (HAD): CENTRAL NERVOUS SYSTEM (CNS) DYSFUNCTION OR FATIGUE?

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Background: Psychomotor slowing is characteristic of early HIV-associated cognitive/motor dysfunction (HACMD) (AAN, 1991); therefore, detection of slowing is important in diagnosis/staging of HACMD. One test to evaluate psychomotor slowing is the Grooved Pegboard (GP) (Lezak, 1994). However, it is unclear whether measured slowing on the GP reflects the bradyphrenia of subcortical disease or systemic fatigue.

Objective: To determine if the GP is a valid measure of CNS-related psychomotor slowing by examining GP performance for effects of fatigue.

Methods: 39 HIV seropositives with minor/moderate HACMD, 19 HIV seropositives without evidence of HACMD, and 23 HIV-seronegative controls were tested. In addition to timing to completion, the five rows were timed individually, yielding total and row times. ANOVAs were performed, covarying for serostatus and HACMD.

Results: Means seconds to completion differed significantly between controls ($\bar{x} = 59.2$) and HACMD participants ($\bar{x} = 85.3$) and between non-HACMD participants ($\bar{x} = 63.2$) and HACMD participants ($\bar{x} = 85.3$) ($p < 0.01$). Differences in row times among all three groups were not statistically significant.

Conclusion: Although time to completion was significantly longer in the HACMD group, time to completion of each individual row did not significantly increase, suggesting that CNS dysfunction rather than systemic fatigue may be the critical factor in psychomotor slowing in HACMD.

NEUROPSYCHOLOGICAL PROFILE AND PROGNOSTIC SIGNIFICANCE OF MINOR COGNITIVE/MOTOR DISORDER. R.K. HEATON, T.D. MARCOTTE, R.J. ELLIS, R. DEUTSCH, I. ABRAMSON, I. GRANT, AND THE HNRC GROUP. University of California, San Diego, CA, USA.

A diagnosis of Minor Cognitive/Motor Disorder (MCMD) indicates that a patient has HIV-related neuropsychological (NP) impairment that causes at least mild interference with daily functioning. Of 494 HIV+ subjects who completed comprehensive NP and neurological evaluations and were diagnosed by a multidisciplinary team, 319 were identified as NP normal, 112 were NP impaired but without everyday functioning difficulties (NPI), and 63 met MCMD criteria. The highest rates of MCMD were in CDC Stages B (28%) and C (32%). Compared to the NPI category, the diagnosis of MCMD was associated with more severe NP impairment that affected more ability domains. Significantly increased impairment rates were specifically found in the perceptual-motor, learning, and motor domains. Over a median follow-up period of 2.4 years, the original MCMD and NPI groups showed increased mortality rates when compared to the NP-normals (RR = 2.3 for MCMD and 1.8 for NPI, after adjustments for CD4 cell counts and disease stage). Moreover, MCMD subjects who survived were significantly more likely to show NP worsening on follow-up. We conclude that NP impairment, and particularly the syndrome of MCMD, has adverse prognostic significance. Supported by NIMH Center grant MH45294.

PUNCH SKIN BIOPSY IN SMALL-FIBER SENSORY NEUROPATHY NR HOLLAND, A STOCKS, P HAUER, JW GRIFFIN, JC MCARTHUR Johns Hopkins University, Baltimore, MD, USA

Background: Despite symptoms of spontaneous pain and autonomic disturbance in patients with predominantly small-fiber polyneuropathy, there are often relatively few abnormalities on neurologic examination and routine electrodiagnostic studies. Punch skin biopsy may be useful in the evaluation of such patients.

Objective: We have attempted to correlate clinical estimates of small-fiber dysfunction with the number of intraepidermal nerve fibers (IENF) in sensory neuropathy patients, using punch skin biopsy.

Methods: 3 mm punch skin biopsies from the distal leg have been performed on 62 healthy volunteers (age 19 - 75) with no symptoms or signs of neuropathy. Similar biopsies were performed in 12 patients diagnosed with sensory neuropathy, including both HIV-associated and non-HIV sensory neuropathies, based on clinical features, nerve conduction studies, and/or quantitative sensory testing. The IENF were immunostained using anti-PGP9.5, and then quantified by two observers (inter-rater reliability 96%).

Results: The mean number of IENF in the normal controls was 13.7 (DS 7.48) fibers per mm of epidermal length, whilst in the neuropathy patients, it was 3.43 (SD 3.01) ($p < 0.0001$). The number of IENF correlated with clinical estimates of small-fiber neuropathy severity ($R = 0.60$).

Conclusions: With the establishment of a normative range for number of IENF, punch skin biopsy can be used to confirm the presence of small-fiber sensory neuropathy. The correlation between clinical estimates of severity of neuropathy and skin biopsy suggests that IENF will be a useful tool for quantification in these patients.

THE EMERGENCE OF UNUSUAL CNS OPPORTUNISTIC INFECTIONS

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In addition to the classic opportunistic infections recognized shortly after the beginning of the HIV epidemic, other less common, but potentially treatable, CNS infections have been described more recently. Opportunism may be characterized by the predilection of organisms to cause a higher incidence of neurological disease than in other settings (for example, tuberculosis), unique neurological manifestations (for example, CMV), or both. Depending upon the organism, these newer pathogens may present as meningitis, encephalitis, or space-occupying lesions. Thus, they may mimic more common opportunistic processes such as toxoplasmosis or cryptococcal meningitis.

Two important factors in the rising incidence of these other opportunistic infections will be discussed. CNS histoplasmosis and coccidioidomycosis in the United States are examples of the interplay between endemic, geographically limited infections and the HIV epidemic. The same is true for CNS Chagas disease in South America. In contrast, CNS manifestations of CMV and *Aspergillus* infection occur in individuals who have survived for long periods with profound, end stage immunodeficiency caused by HIV. These are examples of how opportunistic infection prophylaxis and antiretroviral therapy have changed the natural history of HIV disease.

Thermal-sensory threshold: a sensitive and reproducible test of peripheral neuropathy

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Aim: To assess the normal range and establish reproducibility of thermal sensory threshold for heat detection and its correlation with different stages of HIV disease.

Methods: Preliminary measurements of threshold for heat sensation (HS) on the dorsum of the feet using Medoc Thermo-detector were performed on 20 presumed HIV negative staff controls and 67 HIV positive patients, 18 of whom in CDC Stage IV. HIV patients were further divided into 3 groups according to CD4 counts: group 1: $>200/\text{mm}^3$; group 2: $50\text{--}200/\text{mm}^3$; group 3: $<50/\text{mm}^3$. 19 patients had repeated measurements 3–6 months apart to assess short term changes. The results are expressed in degree $^{\circ}\text{C}$.

Results: Mean HS for control group was 1.8, SD 1.8, median 1.1, range 0.1–6.9. Values below 5.4 (mean + 2SD) were considered normal. Coefficient of variation between two tests on the same day was 20.5 (N=29). There were no significant short term change in HS. 44% of Stage IV patients and 20% of Stage II/III patients had abnormal HS ($p<0.05$); HIV positive patients at all stages were more likely to have abnormal HS than controls (5%) ($p<0.005$). Group 1: N=35; median HS=2.6, range 0.4–9.9; group 2: N=15; median=1.4, range 0.1–5.4; group 3: N=17, median=5.0, range 0.7–24.1. Group 3 had significantly higher HS values compared to groups 1 & 2 ($p=0.029$ and 0.006 respectively). There were no difference between groups 1 & 2. Data on threshold for cold sensation (CS) will also be presented.

Conclusion: Threshold for temperature sensation is a sensitive and reproducible test of peripheral neuropathy. Its correlation with clinical examination will be presented.

Abnormalities in tryptophan metabolism in HIV infection.

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Introduction: Abnormalities in amino-acid metabolism have been reported in HIV infection. Abnormal tryptophan metabolism has been correlated with dementia and polyneuropathy. There is evidence of activation of alternative pathway of tryptophan metabolism with increased production of neurotoxic metabolites.

Aim: To determine whether tryptophan metabolism is abnormal in HIV infection; whether these abnormalities correlate with HIV disease progression and predict onset of AIDS or neurological abnormalities.

Methods: Stored sera from a retrospective cohort of 110 HIV infected men, in whom data on clinical end-points were available, were analysed for tryptophan (T), and kynurenine (K), product of the rate-limiting enzyme indoleamine 2,3-dioxygenase (IDO) of the alternative tryptophan pathway. Patients were divided into: Group 1: AIDS without neurological complications; Group 2: AIDS with peripheral neuropathy and/or dementia; Group 3: AIDS related death within 6 months. Group 4: Asymptomatic patients. T and K were measured from 72 HIV negative gay men as control (Group 5). Levels were correlated with disease progression, neurological manifestations and CD4 count.

Results: Preliminary data shows that T is significantly depressed in Group 1 ($45.5\pm 9.0\mu\text{mol/L}$), Group 2 ($46.4\pm 10.9\mu\text{mol/L}$) and Group 3 ($43.55\pm 11.61\mu\text{mol/L}$) compared to Group 4 ($62.0\pm 13.9\mu\text{mol/L}$) and 5 ($56.3\pm 9.2\mu\text{mol/L}$) ($p<0.001$); K is significantly elevated in Group 1 ($3.3\pm 0.59\mu\text{mol/L}$), Group 2 ($3.6\pm 0.7\mu\text{mol/L}$) and Group 3 ($3.4\pm 0.9\mu\text{mol/L}$) compared to Group 4 ($2.1\pm 0.8\mu\text{mol/L}$) and 5 ($2.0\pm 0.5\mu\text{mol/L}$) ($p<0.01$). K is significantly elevated within 6 months prior to an AIDS defining illness ($3.7\pm 0.6\mu\text{mol/L}$) compared with afterwards ($3.03\pm 0.7\mu\text{mol/L}$) ($p<0.05$). Data correlating with CD4 count will also be presented.

Conclusion: Patients with advanced HIV disease have profound metabolic abnormalities. The stimulation of potentially neurotoxic pathways can contribute to the pathogenesis of neurological abnormalities.

CLINICAL AND NEUROPHYSIOLOGICAL PARAMETERS INDICATE PROGRESSION OF POLYNEUROPATHY ACCORDING TO STAGES OF HIV-INFECTION

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INTRODUCTION: In HIV-infected patients different forms of polyneuropathy may occur. Distal-symmetric polyneuropathy (DSP) is the most common form and may be correlated to the progression of HIV-infection itself.

Patients and Methods: Clinical, neurophysiological and immunological investigations were performed in 486 patients during different stages of HIV-infection (CDC-Classification; I:n=100, II:n=184, III:n=202). Neurophysiological examinations were carried out using surface electrodes on the peroneal and sural nerve including paired stimuli. In the sural nerve conduction velocity, amplitude, latency prolongation after paired stimulation were estimated, in the peroneal nerve conduction velocity, distal latency and F-wave.

Results: T4-helper cells were statistically significant different ($\text{mv}1\pm\text{sd}$) ($p<0.001$) (I: $696\pm 183/\mu\text{l}$, II: $345\pm 85/\mu\text{l}$, III: $70\pm 55/\mu\text{l}$). E. g. paresthesia was found in 28 % of the patients during stage I and in 58 % of the patients during stage III. Hypesthesia, diminution of vibration and reflexes increased also from stages I to III. All neurophysiological results of stage III were statistically significant different from stages I and II ($p<0.01$).

Discussion: During HIV-infection DSP is rapidly progressive and correlated to immunologic deterioration. Up to now pathogenesis of DSP is conjectural and remains unclear. Besides HI-Virus itself, nutritional deficiencies, induction by CM-Virus, TNF- α productive macrophages may play an important part in the development of HIV-induced DSP.

A BRAIN MRI "FORNIX WHITE LINE" (FWL) MAY PREDICT SHORT TERM MEMORY LOSS IN AIDS PATIENTS. LEENA KETONEN, M.D., Ph.D., DAVID PAAR, M.D., ERIC AVERY, M.D., RICHARD B. POLLARD, M.D., SHARON WILLS, Ph.D., ANDREA DAYE, R.N., RUSSELL GARDNER, JR., M.D. The University of Texas Medical Branch at Galveston, Galveston, Texas, U.S.A.

PURPOSE FWL is our term for a hyperintense signal in the posterior fornix on proton density MRI. The fornix is a part of the hippocampal-fornix-diencephalic memory system. One of us (LK) reported in a retrospective review that FWL correlates with cognitive deficit measured by clinical documentation in AIDS patients. Here, we asked whether FWL truly correlates with short-term memory deficit measured with a standardized test.

METHODS Five patients enrolled in the AIDS Clinical Trial Group Study 193A (combination chemotherapy for patients with ≤ 50 CD4 cells/ μ l) had serial Rey Auditory Verbal Memory Tests per protocol (mean of 6 tests/patient administered over 14.6 months) and 9 MRI scans for clinical reasons. Reys and MRIs were evaluated blindly.

RESULTS

Case	FWL	Serial Rey Scores	Other MRI Findings
1	present	decline	no atrophy
2	present	decline	no atrophy
3	present	equivocal decline	no atrophy
4	absent	stable	resolving toxoplasmosis periventricular high signal atrophy
5	absent	stable	no atrophy

CONCLUSION These preliminary results suggest that FWL marks memory loss. If FWL's etiology can be determined, then associated memory loss may be preventable or treatable. We are currently investigating whether cytomegalovirus infection plays a role in FWL and associated memory loss and is, therefore, a treatable factor.

COGNITIVE AND MOTOR EFFECTS OF PEDIATRIC HIV INFECTION AND PRENATAL SUBSTANCE EXPOSURE

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Little is known about how factors other than chronic disease influence the developmental outcomes of infants born to women with HIV. Children with HIV often have neurological complications and/or developmental delays. However, these children are at risk from other factors that may also influence child development, in particular, prenatal substance exposure. It is important to understand how prenatal substance exposure influences cognitive and motor development in this population. Subjects were 54 children who were prenatally exposed to HIV. These subjects were divided into groups based on viral status (HIV- or HIV+) and prenatal drug and/or alcohol exposure status (PSE- or PSE+). The Bayley Scales of Infant Development were used to examine the developmental outcome of children in the four groups. Standard scores for each group on the Mental and Motor Scales were fit to curves using growth-curve modeling. Results of outcome measures indicate that children with prenatal substance exposure show early deficits in cognitive and motor performance, regardless of viral status. Early results indicate that these deficits decrease over time and that differing types and/or amounts of substance exposure show different rates of improvement. The effects of viral status are seen later, with the performance of HIV+ children in both PSE groups declining over time in both mental and motor skills.

ANTIOXIDANT TREATMENT IN HIV DEMENTIA

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Cognitive impairment is a common and disabling complication of advance HIV infection. Antiretroviral agents are the only therapy currently used for treatment of HIV dementia, but treatment response is frequently unsatisfactory, short-lived or poorly tolerated. We hypothesized that OPC-14,117, a lipophilic compound which acts to scavenge superoxide anion radicals may interfere with the toxic interactions between HIV infected cells and neurons. We performed a double-blind, placebo-controlled clinical trial to assess the safety and tolerability of OPC-14,117 240 mg per day. Thirty patients (25 men/5 women; 17 white, 11 black, 2 other) with an average age of 41.7 ± 10.3 (mean \pm SD) and a CD4+ lymphocyte count of 245 ± 182 were enrolled in the 12 week trial. All patients had cognitive impairment defined as impaired performance on neuropsychological tests (2 tests 1 SD, or 1 test 2 SD, below mean). The primary outcome measure was the portion of patients able to complete the study on their assigned experimental medication. Five patients prematurely withdrew because of adverse experiences (2 diarrhea, 1 parotitis, 1 rash and 1 decreasing renal function) and 6 patients voluntarily withdrew from study participation. Overall, OPC-14,117 was as well tolerated as placebo, and there were non-statistically significant trends toward improvement in cognitive test scores. These results suggest that a larger clinical trial primarily designed to assess the impact of OPC-14,117 on cognitive performance is warranted.

An 11-minute computerised screening test for HIV in the Central Nervous System

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Objectives

It has been found previously that those HIV seropositive individuals who develop cognitive deficits as a direct result of HIV activity in the Central Nervous System show slowing of motor and information processing reaction times (RTs). In addition they show attentional deficits even in mild cases of brain impairment. However the exact nature of these attentional deficits is as yet insufficiently understood. The aims of this study therefore were:

- To use our existing understanding to develop a short and sensitive screening battery for the central cognitive deficit in HIV related brain impairment, for early detection and for monitoring of drug efficacy.
- To contribute to the theoretical understanding of the nature of the attentional deficit which can progress to AIDS Dementia

Method

Three computer administered tasks, (two 3 minute tasks and one 8 minute task) were used. (Broadbent's Focused Attention and Categorical Search Tasks and the St Mary's Dual Attention Task). These were administered to 80 males, 40 well HIV seropositive and 40 HIV seronegatives. The HIV seropositive group were matched on age and NART (test of premorbid intelligence) and divided into normal or low scorers on a more traditional battery of tests (Benton Word Fluency, Rey Auditory Verbal Learning, Trail-Making Test, Digit Symbol, Grooved Pegboard, Finger Tapping, Twos and Sevens). Further data is being collected.

Results

In comparison to controls, HIV seropositives had slowed RTs as predicted, both for motor and information processing. However the Categorical Search and the St Mary's Dual Attention Task taken together predicted 86% of the low scorers

Conclusion

Performance on an eleven minute computerised battery requiring complex responses to attentional tasks predicts n% of those scoring low on a much fuller neuropsychological battery. In addition n% of those scoring high on the traditional tests were identified as significantly poorer than controls. The methodological implications for the use of these tests in clinical versus research settings will be discussed.

HIV-RELATED NEUROLOGICAL DISEASES SHOULD NOT BE THE POOR STEPCHILD OF HIV RESEARCH. KORSIA, S. and SPIRE, B. and the National Volunteer Group on HIV Research, AIDES Fédération Nationale, Paris, France.

Despite the more frequent occurrence of HIV-related neurological affections, this field of research still suffers from a lack of interest from major AIDS research organizations. It seems as if most HIV-related neurological diseases were a milestone beyond which proper diagnosis is superfluous and aggressive therapy illusory. We propose a few research priorities based on our volunteers' experience in their daily activities with persons with AIDS.

Today, persons living with HIV would greatly benefit from improved diagnosis tools for neurological affections. Brain biopsy is often considered as too invasive, and patients die of poorly-diagnosed CNS diseases.

HIV encephalopathy is still a major fear and we need to identify antivirals which will more effectively penetrate the CNS. Furthermore, if combination therapy with nucleoside analogs and protease inhibitors confirms itself as being able to drastically reduce viral production outside the CNS, the brain is going to become the main reservoir of viral replication and the place where resistant strains develop.

Peripheral neuropathy, especially its drug-induced irreversible form, is a widespread and extremely disabling condition. Better knowledge of its mechanisms and pathways would undoubtedly help design better treatments. In addition, we find unacceptable the lack of research on the epidemiology, pathogenesis and treatment of PML.

Neurology does not have to be the poor stepchild of HIV-related research. It is up to us, scientists, physicians, volunteers and persons with HIV to apply proper pressure on proper wheels to make sure that these diseases are addressed as effectively and rapidly as PCP or MAC have been in the past.

LOCALIZED BRAIN PROTON MAGNETIC RESONANCE SPECTROSCOPY IN PROGRESSIVE ENCEPHALOPATHIES OF CHILDREN WITH CONGENITAL HIV-1 INFECTION.

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The most common clinical manifestation of CNS involvement in HIV-1 infected children is a progressive encephalopathy with predominant motor clinical signs. To define the metabolic lesions occurring in these progressive encephalopathies, we have examined 23 children (26 examinations) with a congenital (maternal-fetal transmission) HIV-1 infection, using short echo-time proton MRS of the brain (Siemens Magnetom SP 63, STEAM sequence, TE = 20 ms). Brain MR spectra have been acquired from a volume of interest located in the centrum ovale (corona radiata). Six of these young patients displayed a clinical progressive encephalopathy. The main results of this study are: 1) Only 2 patients had a strictly normal metabolic profile of the brain and 24 spectra displayed significant modifications of the MR spectrum (including in children without neurological signs); 2) No correlation was found between MRI (showing mainly atrophy and no specific WM hyperintensities) and MRS; 3) HIV progressive encephalopathies were characterized by a decrease of the NAA signal (neuronal marker), an increase of the inositol signal (glial marker), and surprisingly, by a decrease of the choline signal. The brain metabolic consequences of the congenital HIV-infection appear to be different from those characterizing the acquired HIV-infection in adults.

ACKNOWLEDGEMENTS: This work is supported by CNRS (URA 1186), APM (Assistance Publique à Marseille), the Programme Hospitalier de Recherche Clinique (Ministère de la Santé) and SIDACTION.

NOREPINEPHRINE RESPONSE TO COLD PRESSOR CHALLENGE IS RELATED TO INFORMATION PROCESSING IN HIV-1 INFECTION

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It is now well recognized that a pattern of specific mild cognitive impairments occur in early HIV-1 infection. Although the pathogenesis of this impairment remains unclear, our investigations suggest that a defective autonomic reactivity may be playing an important role.

We have reported that the norepinephrine (NE) and ACTH responses to a cold pressor challenge carried out by immersing one hand in ice-water mixture for 2 minutes, were blunted in asymptomatic HIV+ subjects (Kumar et al, 1991;1994).

In this report, we investigated the norepinephrine response to the cold pressor challenge in 59 HIV+ subjects as a function of their memory, reaction time, information processing time, language and visual spatial activity. Our data show that there was a significant interaction with the time course of the norepinephrine response with reaction time composite ($F=2.79$, $p=0.05$). Examination of the time course shows NE levels at base line to be significantly lower ($F=5.19$, $p=.03$) and immediately post-cold pressor had a tendency to be lower ($F=3.83$, $p=0.056$) in subjects who showed a slower reaction time. A similar time interaction was found with the information processing speed composite ($F=5.19$, $p=0.03$). Out of 59 HIV+ subjects, 6 subjects died. When we compared the NE response in these two groups, repeated measures analysis of variance showed that the response in the group of subjects who died was significantly blunted at all time points ($p=0.05$) compared with survivors.

TREATMENT OF NEUROLOGICAL COMPLICATIONS ASSOCIATED WITH VZV, MONITORING BY PCR ON CEREBROSPINAL FLUID.

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Involvement of the central nervous system (CNS) by the varicella-zoster virus (VZV) is frequent in patients with AIDS. Polymerase chain reaction (PCR) assay of cerebrospinal fluid (CSF) has been shown to be a rapid and specific diagnostic tool.

Objective: to evaluate the efficiency of antiviral therapy and the value of CSF PCR in the treatment's follow-up.

Methods: we retrospectively studied the HIV patients in whom VZV DNA was found in the CSF in 1993 and 1994. The outcome after antiviral therapy was monitoring by clinical neurological assessment and by repeated PCR on CSF.

Results: 6 cases were observed. A characteristic skin eruption was seen before or after the onset of neurological complications in all cases. All patients were treated within a few days.

Patient	CD4	Brainstem signs	CSF		Treatment	PCR result in serial CSF		Neurological outcome	General outcome
			WBC	Protein		date	result		
1	30	Hemiparesis Cerebral infarction	1	1,35	Foscarnet	N.D.	-	Static	death 2 months later (septicemia)
2	20	Encephalitis	2	1,1	Foscarnet	week 3 week 5	- -	recovery	death 1 year later (CNS lymphoma)
3	270	Meningo-encephalitis VI	1230	3,44	Acyclovir	day 7 day 17 month 3	+ - -	recovery	asymptomatic after 1 year
4	335	Meningo-encephalitis VII	1320	7,87	Acyclovir	day 10 day 30	- -	recovery	asymptomatic after 16 months
5	5	Encephalitis Myelitis VII - VIII	250	8,4	Acyclovir	day 16 month 12	- -	recovery	alive after 32 months
6	16	Myelitis Paraplegia	380	4,1	Acyclovir	day 13 month 6 month 12	+ - -	recovery	alive after 28 months

Conclusions: 1/ A wide variety of neurological syndromes may be associated with VZV infection. 2/ Early treatment seems to be associated with recovery, except when irreversible vascular complications occur. 3/ PCR is helpful for the follow-up and will help the understanding of the pathogenesis of VZV CNS involvement in patients with AIDS.

RARE SECONDARY NEUROLOGICAL COMPLICATIONS IN HIV-INFECTION

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Well-known secondary neurological manifestations in HIV-infection concern toxoplasmosis, PML, and lymphoma. We describe three rare secondary neurological complications which represent interesting differential diagnoses:

I. Pseudotumor cerebri in HIV-infection with headache as the only presenting sign

We describe an HIV-infected patient with headache as the only presenting sign of a pseudotumor cerebri. CSF findings of elevated protein and immunoglobulins in our patient suggest an underlying chronic HIV-related meningitis, representing a putative pathogenetic factor. We conclude that in every case with new onset headache in HIV-infected patients, CSF pressure should be measured.

II. Hyperintense pyramidal tracts on T1-weighted MRI in HIV-infection

Brain-MRI of an HIV-infected patient showed increased focal symmetric signals in the pyramidal tracts on native T1-weighted images without corresponding signals on T2-weighted images; strongly resembling lesions, described in chronic hepatic failure. As liver function was normal, we suggest that these signal changes represent a novel cerebral lesion of advanced HIV-infection. Like in hepatic failure, the pathogenesis of these hyperintensities remains to be established.

III. Lymphomatoid Granulomatosis with CNS involvement in an HIV-infected patient

Lymphomatoid granulomatosis (LG) is an uncommon multisystem disease. LG is associated with immunosuppression, however, there are only few reports on LG in AIDS. We describe the case of an HIV-infected patient, who was admitted to hospital for tumefaction of the salivary glands and for multiple neurological symptoms. CSF analysis, brain-MRI, chest-CT, ultrasonic sonography of the neck, and histological examination of the glandula parotis were consistent with LG. A brain biopsy will now be performed to unequivocally prove the diagnosis.

We conclude that in HIV-infection, also these rare secondary neurological complications should be considered as differential diagnoses.

Reaction Time Performance of Male and Female HIV-Seropositive Substance Abusers: A Preliminary Report

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Objective: To evaluate the performance of HIV-seropositive drug abusers on computerized reaction time (RT) tasks for evidence of gender differences in performance on these measures of subclinical HIV-related mental slowing.

Methods: In this preliminary study, we tested 26 HIV-seropositive women and 103 seropositive men with a history of current or previous substance abuse. The groups were matched for age and mean CD4 count. They performed computerized measures of simple and choice RT and a more cognitively complex measure, an RT version of the Stroop task. We have previously shown that these tasks are sensitive to subclinical mental slowing in HIV-1 infection.

Results: We found no evidence of gender differences on any of these three tasks, with no significant differences in simple RTs ($p < .35$), choice RTs ($F < 1$) or Stroop performance ($F < 1$) between males and females ($F < 1$ for each comparison). Seropositive women were significantly less educated than seropositive men ($p < .001$) but results were unchanged when education was covaried from analysis of RTs.

Conclusions: Previous investigations using conventional neuropsychological tasks have speculated that HIV-seropositive women show evidence of earlier and more severe neurobehavioral deficits than seropositive men. The current results do not support these conclusions and provide no evidence that HIV-related cognitive deficits are more marked in seropositive women.

ENCEPHALOPATHY IN CHILDREN INFECTED THROUGH CHILD-TO-MOTHER TRANSMISSION

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M. TARDIEU for the French Pediatric HIV Infection Study Group.

The objective of this study is to describe the epidemiologic features and survival of children with HIV encephalopathy among infected children born to HIV1 seropositive mothers and to examine possible predictors of the development of encephalopathy. The analysis involves all infants ($n = 53$), with a diagnosis of HIV encephalopathy, recruited in the pediatric centers participating to the French Pediatric Study and 28 Children with HIV encephalopathy consulting before the age of 5 years in the neurological department of Bicêtre Hospital. The association between the mother's and child's characteristics at birth and the age at diagnosis of encephalopathy will be studied. A comparison between children who develop encephalopathy before or after one year of age in terms of zidovudine treatment, evolution of CD4 cell counts and survival will also be presented.

A COMPARISON OF MR IMAGING AND CSF ANALYSIS WITH NEUROPATHOLOGICAL FINDINGS IN THE DIAGNOSIS OF HIV AND CMV ASSOCIATED CNS DISEASE IN AIDS.

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It is frequently difficult to discriminate between HIV and CMV associated CNS disease using clinical criteria and MR imaging abnormalities. We retrospectively compared results of CSF analysis and MR imaging with neuropathological findings in 35 HIV infected individuals (33 men), median CD4 count = $15 \times 10^6/L$, who underwent necropsy between 4 and 70 (median = 20) days after neurological assessment. Of the 35 patients, 23 had diffuse white matter signal abnormalities (DWA) on MR imaging. At necropsy 10 of these patients had HIV leukoencephalopathy (HIVE) and multi nucleate giant cell encephalitis (MGCE) 6 had CMV encephalitis (CMVE) but no HIVE/MGCE, 2 had CMVE and HIVE/MGCE, 4 had non-HIV associated abnormalities and 1 had vasculitis secondary to lymphoma. Necropsy in 5 other patients without DWA showed CMVE in 3 and MGCE (but not HIVE) in 2. CMV DNA was detected in CSF of 5/11 with CMVE and in 2 with CMV polyradiculopathy but no CMVE. DWA on MR imaging had a sensitivity of 92% for diagnosis of HIVE but a specificity and positive predictive value of only 52%. The low sensitivity and specificity of CMV DNA detection in CSF limits its diagnostic usefulness in patients with encephalopathy.

PARKINSONISM WITH HIV INFECTION. S. MIRSATTARI¹, C. POWER^{1,2}, A. NATH^{1,2}. Departments of Internal Medicine (Section of Neurology)¹ and Medical Microbiology², University of Manitoba, Winnipeg, Manitoba, Canada

The clinical association between HIV infection and parkinsonism has been suspected but not established. This study describes the clinical parameters, possible etiological factors and response to treatment of parkinsonism in patients with HIV infection. Of 75 consecutive HIV-positive patients seen at the Neuro-AIDS clinic, 7 (9%) had parkinsonism (age range 25-44 years). All patients had a CD4 count of $<50 \text{ cells/mm}^3$. All patients had bradykinesia, 4/7 had cogwheel rigidity, 4/7 had postural instability without loss of proprioception or a myelopathy and 0/7 had a resting tremor. Illustrative video recordings will be presented. Associated neurological findings included dementia (2/7), psychosis (3/7), essential tremor (2/7), peripheral neuropathy (3/7) and myelopathy (1/7). Parkinsonism was caused by neuroleptics (4/7), cerebral toxoplasmosis (1/7) and no obvious cause other than HIV infection (2/7). Discontinuation of the neuroleptics produced complete recovery in 1 patient and partial or no response in others. Treatment of toxoplasmosis also resolved the parkinsonism. Treatment with high dose AZT and benztropine in a patient with parkinsonism with HIV infection alone resulted in no response. We conclude that, i) patients with AIDS may be at risk of developing an akinetic parkinsonism, ii) neuroleptics should be used cautiously in these patients and, iii) parkinsonism may be another primary HIV-induced syndrome.

LEVODOPA (L-DOPA) THERAPY IMPROVES MOTOR FUNCTION IN HUMAN IMMUNODEFICIENCY VIRUS TYPE-1 (HIV-1)-INFECTED CHILDREN WITH EXTRAPYRAMIDAL SYNDROMES

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Objective: To improve motor function in children with HIV-1 infection who manifest significant rigidity and extrapyramidal dysfunction, utilizing L-DOPA therapy.

Patients: Five children aged 4-13 years with extrapyramidal dysfunction as characterized by: poor ambulation or a shuffling gait; dysarthria/drooling; hypomimetic/inexpressive faces; rigidity/stiffness; and/or postural instability. Four of the five patients manifested an HIV-1-associated progressive encephalopathy. Three patients were perinatally infected; two patients were infected from contaminated blood products.

Therapy: L-DOPA at an average dose of 50mg orally every four hours, three times daily.

Results: Improvement in all areas of extrapyramidal dysfunction of all five children. These benefits were sustained in 4/5 patients. One patient improved further with dosages increased to 100mg, but this amount was poorly tolerated.

Conclusion: L-DOPA is an useful adjunctive therapy in HIV-infected children with rigidity that severely limits motor function. The average effective dose is 50mg of L-DOPA equivalent every hours for a total of three doses daily. Larger doses may cause further improvements, but may not be tolerated well by the patients.

CENTRAL NERVOUS SYSTEM CRYPTOCOCCOSIS: A MAGNETIC RESONANCE IMAGING STUDY

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Introduction: Cryptococcus neoformans, a ubiquitous saprophytic fungus is particularly pathogenic in immunocompromised patients; 5% of AIDS patients develop cryptococcal meningitis. In this study we review the spectrum of MRI findings in AIDS patients with CNS cryptococcosis.

Methods: T2 and T1-weighted cranial MR scans performed at 1.5T on all AIDS patients with microbiologically confirmed cryptococcal meningitis between August 1991 and October 1995, were independently, retrospectively, reviewed by two radiologists.

Results: 27 patients, mean age = 37.8 years and median CD4 count of $50 \times 10^6/L$ were studied.

MR scans were normal in 4 patients.

11(41%) patients had either atrophy and/or HIV related white matter changes only.

10 (37%) patients had dilated perivascular Virchow Robin spaces in the brainstem, basal ganglia or cerebral hemispheres and all 10 patients had coexistent non-enhancing cryptococcomas; these were present in the basal ganglia in 8 patients. One patient developed an arachnoid cyst during the course of the illness.

Meningeal or abnormal dural enhancement was not detected in any patient.

Conclusion: The spectrum of MR findings in CNS cryptococcosis reflects the pathological mechanism of invasion by the fungus; a normal or nonspecific MR scan does not exclude the diagnosis, but dilatation of Virchow Robin spaces is one of the earliest manifestations of the disease process.

MEASUREMENT OF R' IN HIV POSITIVE PATIENTS USING PRIME FOR ESTIMATION OF BRAIN IRON DEPOSITION

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Introduction:

Haemosiderin laden macrophages have been observed at autopsy in the brain white matter of AIDS patients; brain iron deposition also preferentially occurs in the globus pallidus and substantia nigra. In this study we used a multiple spin-echo with interleaved gradient echo MR technique for measuring T2', thought to be a more specific measure of brain iron deposition than T2 and T2*.

Methods:

6 low risk control and 24 HIV+ patients were studied at 1.5T using the PRIME (Partially Refocused Interleaved Multi-Echo) sequence. The relaxation rates of T2, T2* and T2' (i.e. R2, R2* and R') were calculated by sampling frontal and parietal white matter, the caudate nucleus and globus pallidus.

Results:

- HIV+ patients with white matter hyperintensity had a significantly increased R2' in the globus pallidus ($p < 0.05$, Student's *t* test) than HIV+ patients with normal white matter.
- A CD4 count of $< 200 \times 10^6/l$ was associated with a significantly increased R2' and R2* in parietal white matter ($p < 0.01$, $p < 0.05$ respectively) and increased R2' in the globus pallidus ($p < 0.05$).

Conclusion:

Significant increases in the R2' values of the globus pallidus and parietal white matter have been demonstrated in different subgroups of the HIV+ patients; whether these represent small increases in brain iron deposition requires further evaluation.

PROJECTING RISKS AND MORBIDITY FROM HIV-ASSOCIATED SENSORY NEUROPATHY (SN) IN THE MULTI-CENTER AIDS COHORT STUDY (MACS).

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Background: While SN is common in advanced HIV infection, specific risk projections and effects of increasing survival times on incidence have not been systematically characterized.

Objective: To project risks and morbidity from HIV-associated SN.

Methods: We studied 1323 HIV+ participants in an active surveillance program for HIV-associated and toxic SN. Cumulative risk, and morbidity time with SN, were determined using a four-stage disease-death process modelled non-parametrically. Life-table analysis assessed risk of SN after reaching a CD4+ cell count of $100/mm^3$.

Results: Twenty-four-month cumulative risk of SN after CD4=500 cells/ mm^3 was 3%; after CD4=200, 11%; after CD4=100, 14%; after CD4=50, 17%. Ten-year cumulative risk of SN after CD4=500 was 20%. Rate of SN for those surviving 0-12 months after CD4=100 was 5.3%, and 9.1% for those surviving >24 months. For every 100 HIV+ subjects without history of SN, 320 days of SN morbidity time can be expected in the first 24 months after CD4=500, and 3870 days in the first 24 months after CD4=50.

Conclusion: Cumulative lifetime risk of SN in HIV infection is approximately 20%. In profoundly immunosuppressed individuals, risk and expected morbidity time attributable to SN increase as CD4 count declines and as survival time increases.

AN ASSOCIATION BETWEEN MYCOBACTERIUM AVIUM COMPLEX (MAC) INFECTION AND HIV DISTAL SYMMETRICAL POLYNEUROPATHY (DSPN)

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Objectives: We sought to prospectively examine the relationship between MAC and DSPN.

Methods: 150 consecutive patients admitted to St. Vincent's Hospital, Sydney were assessed neurologically. MAC blood cultures (3) were performed in the investigation of unexplained fever, anaemia, weight loss or diarrhoea. The results were analysed with respect to the probability of an association between MAC and DSPN using a "chi square test for trend".

Results: There were 145 males and 5 females: median age 37 yrs (23-62), median CD4 count was 27(0-740). The number of patients with DSPN was: none 78, possible 20, probable 14, definite 22, excluded 16. MAC blood cultures were performed on 80 patients of which 39 were positive and 41 negative.

DSPN	normal	possible	probable	definite	excluded
MAC (+ve)	9	7	9	12	4
MAC (-ve)	21	5	1	5	7

Applying a "chi square test for trend" gave a *p* value of 0.0013, adjusting for CD4 count gave a *p* value of 0.003.

Discussion: Recent studies of DSPN have demonstrated universal axonal degeneration in advanced HIV infection with macrophage infiltration which is both dense and hyperactive. Neuronal damage is hypothesised to be mediated by toxins elaborated principally by macrophages. Both HIV and Mycobacterium are macrophage infections. It has been postulated that they may provoke each other's multiplication as well as intensify the cytokine response including the elaboration of neuronal toxins. Our study has shown that those with MAC infection are more likely to have clinically significant DSPN. Of future interest will be the influence of MAC prophylaxis on the incidence of neuropathy.

ACUTE HIV INFECTION AND MENINGOENCEPHALITIS WITH SINUS THROMBOSIS

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Central nervous system complications are an important part of HIV infection and AIDS. We report a case of a young female patient - CAC, 18 years old, white, student, who six weeks after a sexual contact developed fever and a headache. Some days later a confusional state was noted, with rapid progression to coma. On physical examination a right hemiparesis with a babinski toe sign were present. CT Scan was normal, CSF was abnormal with 39 leukocytes- (94% lymphocytes, 4% polymorphonuclear, 2% monocytes); protein level was 80 mg/dl and glucose level was 45 mg/dl.

The patient was treated with intravenous administration acyclovir and ceftriaxone. No infectious agent was isolated from CSF, and PCR for herpes simplex was negative in CSF. CD4 count was 416/mm. The only abnormality on blood tests was an hemoglobin of 7.6 g/dl. Serologic studies were negative for all infections, except for HIV - ELISA and Western Blot in blood, and ELISA in CSF. MRI showed lesion in left temporal lobe, and a transverse sinus thrombosis. EEG showed a diffuse slow wave pattern. CSF was repeated in the second day with the same abnormalities. The patient had a complete recovery in three weeks, and also the laboratorial and imageologic studies. No residual abnormalities was noted in neurological and neuropsychological evaluation. The authors will discuss the clinical presentation, diagnostic and evolution at the time of the presentation.

VIRAL COINFECTIONS IN HIV-1 ASSOCIATED NEUROPATHIES.

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Different groups of neuropathies (NP) are associated with HIV infection. The most prevalent of these, the predominantly sensory neuropathy (PSN) of AIDS, rivals AIDS dementia in incidence and subclinical forms are present in near all pts at the late stage of the disease. Even if pathogenesis of NPs in AIDS is still unclear, some authors suggested that viral agents other than HIV-1 should play a role in it. Cytomegalovirus (CMV) has been associated with a spectrum of peripheral nerve syndromes in pts with AIDS. Lumbosacral polyradiculopathy (LPR), mononeuritis multiplex (MM), and PSN were associated to CMV infection in AIDS pts. Otherwise, CMV, like many other infectious agents, has been related to Guillain Barré Syndrome (GBS) in pts without HIV-1 infection. Other viruses of the Herpes group, like Herpes Zoster (VZV) and Herpes Simplex (HSV), and other viruses (HAV, HBV) could be associated to NPs. Also HTLV-II is thought to be involved in NP pathogenesis. Therefore some viral coinfections could be related to NP in HIV infected pts. In this study has been evaluated the incidence of viral coinfections in HIV infected pts with diagnosed NP and the possible correlations with different clinical aspects has been investigated. 247 pts with HIV infection were admitted to the study. In 179 pts a NP was diagnosed following the CDC criteria. 68 pts composed the control group. Age, sex, epidemiology and clinical stage of HIV infection were not significantly different in the two groups. Pts were investigated for the occurrence of CMV, VZV, HSV, HAV, HBV and HCV infections, by means of the presence of IgG antibodies (for previous infection) and IgM antibodies, seric antigens, blood cultures and PCR techniques (for active infection). Active CMV infection was present in the 46% (21 pts) of NP pts seropositive for CMV (46 pts) and in the 20% (5 pts) of control pts seropositive for CMV (25 pts). In 14 of the patients with active CMV infection was diagnosed a PSN, while in 6 pts was detected a idiopathic demyelinating neuropathy (IDP). One pt showed a brachial MM and one a LPR. The presence of previous coinfection of HSV, HAV, HBV and HCV was high in NP and control groups and no correlation was found between NP and each of these viruses. 39 HIV-1 positive and CMV negative pts with NP (8 IDP, 31 PSN) and controls were screened for anti HTLV I/II Ab. The prevalence of Anti-HTLV-II was significantly higher in the pts than in controls (29% vs 8.3%; $p=0.002$). All of the seropositive NP pts showed HTLV-II DNA in their peripheral blood mononucleate cells at PCR.

In conclusion results support the hypothesis that CMV and HTLV-II represent etiological factors in the pathogenesis of a considerable proportion of NPs in patients with HIV-1 infection.

NEUROCOGNITIVE FUNCTION IN CHILDREN WITH VERTICALLY TRANSMITTED HIV-1 INFECTION.

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Forty-five children (27 boys, 18 girls) with vertically acquired HIV-1 infection were followed at a single pediatric AIDS center. They ranged in age from 4-16 years. (38% in the 4-5 year range, 34% in the 6-8 year range, 23% in the 9-12 year range and 4% in the 13-16 year range). All children received antiretroviral therapy, although regimens varied according to protocol. Neurocognitive assessment included standardized measures of intellect, achievement, visuoconstructive skill, and motor dexterity/speed.

Half (49%) of the children had composite IQ scores within the average range; 22% had IQ scores within the low average range, 13% were within the borderline range, and 13% were deficient. Data from other tasks were essentially commensurate with this distribution, suggesting that our sample of children is functioning at a generally lower level than those in the normative samples of these tests, and at a lower level than those seen in the Tardieu et al. (1995) study. There were, however, two important findings regarding specific skills. First, this small cohort showed a significantly greater frequency of VIQ<PIQ discrepancy than expected from normative data; second, their graphomotor visuo-constructive skill was weak relative to general intellect on a more frequent basis than that seen in the normative data. These results support earlier findings in the literature.

Of the 42 children for whom concurrent immunologic data were available, 19% had no evidence of CD4+ cell suppression as defined by the CDC (MMWR, 1994); 38% were moderately suppressed, and 43% were severely suppressed. Due to the relatively small sample size, categories were collapsed to analyse the relationship between neurocognitive and immunologic status. No significant relationships were seen between neurocognitive status and concurrent CD4+ level. Even in the few cases where long-term serial examination of CD4+ cells and cognitive function was possible the two factors appeared to be unrelated. However, we were limited in our investigation by both small sample size and lack of serial data from birth onward.

The relationship of neurocognitive status to socioeconomic status, foster home or biological home placement, prenatal drug exposure, and birth/postnatal complications was also explored. None of these factors were shown to be significantly related to neurocognitive status at time of examination.

In summary, these findings are partially consistent with earlier data. These children did show both a VIQ < PIQ discrepancy, and particular weakness in graphomotor visuoconstructive skill, on a more frequent basis than would be expected. In contrast to earlier findings, however, our small cohort is generally lower functioning than the norm. In addition, no direct relationship was seen between level of CD4+ cells and neurocognitive status, nor between neurocognitive status and psychosocial or birth history variables. Although these findings are intriguing, the sample size is small and it will be important to obtain concurrent serial data from birth through school age to substantiate them.

EXPRESSION OF JCV-SPECIFIC CDNA IN PERIPHERAL BLOOD LYMPHOCYTES OF PATIENTS WITH PML, HIV-INFECTION, MULTIPLE SCLEROSIS AND IN HEALTHY CONTROLSA. PIETZUCH¹, M. BODEMER¹, S. FRYE^{1,2}, P. CINQUE³, C. TREBST^{1,2}, W. LÜKE², TH. WEBER⁴

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By reverse transcription polymerase chain reaction (RT-PCR) peripheral blood lymphocytes (PBLs) of 25 patients with progressive multifocal leukoencephalopathy (PML) and three control groups were investigated for JC virus (JCV) specific cDNA.

JCV-specific cDNA was detected in PBLs of 13 of 25 PML patients (52%), in 12 of 20 HIV-positive patients (60%), in 9 of 20 MS patients and in 13 of 22 healthy controls (59%). In 41 patients PBLs could be separated into B- and non-B-cells using monoclonal antibody (CD19) coated magnetic beads. JCV-specific cDNA was found in B and non-B-lymphocytes in 23 of 41 patients (56%). In 11 cases JCV-specific cDNA was detected in both B and non-B-cells of the same patient, in 5 cases in B-cells only and in 7 cases in non-B-cells only.

These results demonstrate the presence of viral transcripts of early JCV genes in circulating PBLs irrespective of their medical condition. These findings indicate that JCV is latent in PBLs of immunocompetent patients and healthy individuals. These findings show that both, B- and non-B-cells can serve as vectors for the hematogenous dissemination of JCV to the central nervous system.

THE EDINBURGH COHORT OF HIV POSITIVE DRUG USERS - A COMPARISON OF NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL PERFORMANCE OF NON-DEMENTED HIV POSITIVE AND HIV NEGATIVE DRUG USERS AND 50 CONTROLS

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Three hundred and sixty four patients (272 CDC Stage I/II and 92 CDC Stage IV) and 95 HIV-seronegative IVDU controls were tested using a 2-tone auditory evoked potential (AEP) task and a core battery of neuropsychological tests. These tests assessed memory using Auditory Verbal Learning Test (AVLT), information processing speed using Trail Making Test Parts A and B, WAIS-R Digit Symbol Substitution Test and AEPs and mood using the Hospital Anxiety and Depression Rating Scale. In addition, a group of fifty controls of similar socio-economic background and IQ were tested from a local army regiment. Memory function (AVLT) in asymptomatic IVDUs and seronegative IVDUs did not differ from that of the controls, but measures of information processing speed were worse for all IVDUs and depressive complaints were common. There were no differences between HIV negative and asymptomatic IVDUs. Symptomatic patients showed some evidence of cognitive decline in memory function and information processing speed, but no change in mood compared with asymptomatic IVDUs.

These data establish basic normative values for non-demented drug users at all stages of HIV infection.

HIV DEMENTIA IN THE EDINBURGH COHORT OF IV-DRUG USERS
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Since 1987, 296 patients have been tested on the a basic neuropsychology battery and 379 have had auditory event related potential (AEP) testing. Forty five patients who had become clinically demented were selected along with 45 individually age- and sex-matched non-demented controls from this cohort. A 'month of onset' was estimated for each of the patients and also applied to the individually matched controls.

P300 and N200 latencies of the AEP test lengthened sharply in demented patients tested immediately before the onset date. By contrast, none of the neuropsychological measures showed evidence of a similar decline in advance of the onset of dementia. Dementia was characterised by slowed N200 and P300, slowing in the Trail-Making test part B, reduced scaled scores in the WAIS-R Digit Symbol Substitution Test, the WAIS-R Digit Span Test and the WAIS-R Block Design Test and decline in memory function in the AVLT memory test and the WMS-R Logical Memory Subtest. The control group did not show similar decline over time.

The rapid decline of neuropsychological function in HIV dementia is preceded by slowing of cognitive AEPs. This has potential as a surrogate marker of brain involvement both clinically and in trials of treatment.

IMPAIRED METHIONINE METABOLISM IN AIDS MYELOPATHY AND DEMENTIA: A THEORETICAL MODEL AND A CLINICAL STUDY.

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There is growing evidence of impaired trans-methylation in the nervous system in AIDS. The enzyme methyl-transferase is crucial in the production of methionine, the direct precursor of S-adenosyl-methionine, which is the major methyl group donor in the nervous system. Vacuolar myelopathy pathologically indistinguishable from AIDS associated myelopathy can be produced by blocking the enzyme methyl-transferase and decreasing the production of methionine. The suppression of this enzyme can also lead to decreased production of cystathionine and glutathione, leaving the nervous system more vulnerable to oxidative stress. Animal studies demonstrate that treatment with methionine can prevent the vacuolar myelopathy associated with the functional block of methionine synthetase. We report 10 patients with AIDS-related myelopathy treated for six months with oral methionine, 6g/day. Eight patients had various degrees of clinical improvement, with those with milder forms responding better to the treatment. In most of these patients, the clinical improvement was confirmed by somatosensory evoked potentials. Three patients also showed memory improvement after treatment. One patient did not respond to the treatment and another withdrew because of gastrointestinal side effects. Impaired methionine metabolism may play a role in the pathogenesis of AIDS associated myelopathy and dementia and methionine treatment may improve these disorders.

MONOKINE NEUROTOXINS IN PATIENTS WITH AIDS DEMENTIA

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Objective: To determine whether products of peripheral blood mononuclear cells (PBMCs) from demented patients with AIDS differ from nondemented patients.

Methods: PBMCs were studied after determining that patients with AIDS dementia lacked adherent-isolated macrophages. We prospectively studied 16 patients with AIDS dementia (8 "pure" dementia as an AIDS defining illness), 13 healthy HIV-seropositive patients and 8 seronegative controls. Supernatants from PBMCs were assayed for TNF alpha, IL-6 and alone for neurotoxicity on primary brain aggregates in vitro.

Results: Levels of IL-6 were significantly lower from patients with dementia as compared to the "pure" dementia patients. There was a trend towards lower TNF alpha in demented patients. Supernatants from PBMCs of demented patients were significantly more neurotoxic in vitro than nondemented PBMC supernatants. **Conclusions:** Lowered TNF alpha and IL-6 levels may reflect a kind of macrophage "anergia", a state relatively unresponsive to persistent HIV infection. The difference in neurotoxicity in vitro between PBMCs from demented and nondemented patients was significant. This neurotoxicity was independent of cytokine elevation. We concluded that macrophage function in patients with AIDS dementia was altered; HIV strain variation was probably responsible for macrophage dysfunction and neurotoxin production.

CSF patterns in 1147 HIV + patients. A 11 years period analysis.

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CNS involvement is recognized in at least 40% of HIV infected persons. In order to evaluate the neurologic disorders associated to AIDS, we analyzed CSF patterns of 1147 ensured AIDS patients seen over 11 years. CSF patterns were entirely normal in 5%. Elisa for HIV antibodies was performed in 1032 cases and was positive in 93.9%.

Total proteins were increased in 64% and γ globulin in 70% with an oligoclonal distribution in 18%. We observed that adenosine deaminase was increased in 53% and lactic dehydrogenase in 34%.

Associated pathologies were found in 49.6% in single (41%) or multiple presentation (8.6%).

Among the opportunistic infection, toxoplasmosis was the most frequent (47.6%), followed by cryptococcosis (25.5%), syphilis (16.7%), CMV (7.6%) and herpes viruses infection (4.2%). Lymphoma was observed in 1.9% of cases.

This study assessed the great importance of CSF analysis in AIDS patients particularly for early diagnosis of associated pathologies.

AN INCREASE IN CSF HIV-1 P24 ANTIGEN PARALLELS THE CLINICAL MANIFESTATION OF HIV-1-ASSOCIATED ENCEPHALOPATHY.

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The pathogenesis of Human Immunodeficiency Virus Type 1 (HIV-1) associated encephalopathy is largely unknown. To assess the temporal correlation between the manifestation of the encephalopathy and virus replication in the brain we have measured the levels of HIV-1 p24-antigen in CSF and serum samples obtained from $n = 48$ patients during a time span from 34 months before to 32 months after the development of HIV-1 associated encephalopathy. p24 was detectable exclusively in samples obtained between 8 months before and 8 months after the clinical manifestation of encephalopathy (15 positives out of 38 samples). All specimens obtained 34 to 8 months before onset were free of p24. Significantly, four samples taken between 10 and 32 months after onset showed no detectable p24 in spite of continuing deterioration in psychopathological findings. A second group of $n = 23$ HIV-1 infected individuals with extracerebral manifestation of AIDS did not develop HIV-1-associated encephalopathy during the observation period. In only two of these, low levels of p24 were detectable 2 and 4 weeks prior to death. In both groups of patients, p24 levels in the CSF and serum did not correlate, indicating local virus replication in the brain. The present observation indicates that HIV-1 replication in the brain is temporally correlated with the manifestation of HIV-1-associated encephalopathy and suggests that a transient increase of HIV-1 replication in the brain may be directly involved in the pathogenesis of the encephalopathy, but not for its maintenance or continuing aggravation. The findings further support the need for learning the mechanisms involved in the triggering of HIV-1 replication in the CNS.

PSYCHOMOTOR SLOWING IN HIV INFECTION PREDICTS INCREASED RISK OF DEMENTIA, AIDS, AND DEATH

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Objective. To evaluate whether decline in psychomotor performance, an early sign of HIV-associated cognitive/motor complex, predicts overt dementia, AIDS, or death in HIV-infected homosexual men. **Methods.** Semiannual neuropsychological evaluations were performed on 291 HIV+ homosexual men participating in the Baltimore site of the Multicenter AIDS Cohort Study over a 9 year period. Proportional hazards models assessed the predictive value of psychomotor slowing (i.e. 2.0 SD decline in an individual's performance on Symbol Digit or Trailmaking Parts A or B sustained for 2 consecutive visits). **Results.** After adjusting for number of attended visits, CD4 count, and hemoglobin, HIV+ men with psychomotor decline (compared to HIV+ men without decline) had an increased risk of subsequent dementia (risk ratio (RR)=5.0, $p=.008$), AIDS (RR=2.4, $p=.02$), and death (RR=2.0, $p=.04$). **Conclusion.** Sustained decline in psychomotor performance predicted dementia, AIDS, and death. This brief neuropsychology screen may be useful for early detection of HIV+ individuals with a poorer prognosis who may benefit from more aggressive treatment to prevent HIV dementia.

CEREBROSPINAL FLUID AND BLOOD LEVELS OF A RETINOL TRANSPORT PROTEIN, TRANSTHYRETIN, AND RETINOL IN HIV-1 INFECTION

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Background: Retinol levels are decreased in patients with symptomatic HIV-1 infection and are associated with low blood CD4+ lymphocyte numbers, an increased frequency of AIDS, and an increased risk of mother-to-child transmission of HIV-1. Transthyretin (TTR) is a 55 kd molecule that is important for transport of retinol in plasma. Plasma TTR is produced by the liver. TTR is also synthesized by the choroid plexus and secreted into cerebrospinal fluid (CSF). In these studies, we analyzed measurements of TTR and retinol in blood (serum and plasma) and CSF from HIV-1 seropositive and seronegative subjects.

Methods: Using an indirect enzyme-linked immunosorbent assay, we measured levels of TTR in CSF and blood samples. Retinol was measured using reverse-phase HPLC.

Results: Median CSF TTR levels were 9.8 mg/l (range 0-33.2 mg/l) for seropositive (SP; $n=34$) and 20.8 mg/l (range 0-71.5 mg/l) for seronegative (SN; $n=53$) individuals ($p=0.0002$; Kruskal-Wallis). Median TTR levels in blood were 188.2 mg/l (range 49.8-728.8 mg/l) and 469.5 mg/l (range 152.1-4,293.2) for SP ($n=34$) and SN ($n=43$) subjects, respectively ($p < 1 \times 10^{-7}$). Among SN individuals with CSF and blood TTR and retinol measurements, there was an inverse correlation noted between CSF TTR and CSF retinol levels ($n=14$; corr. coeff.=-0.671; $p=0.016$; Spearman's rank). Among SP subjects with such measurements, there was a borderline correlation between TTR levels in CSF and blood ($n=24$; corr. coeff.=-0.38; $p=0.07$).

Conclusions: TTR levels were lower in blood and CSF from HIV-1 SP subjects as compared to SN individuals. Among SN subjects, production of CSF TTR may be potentially tightly regulated by the concentration of retinol present in CSF. Such regulatory control may be impaired in the setting of HIV-1 infection. Alternatively, increased levels of TTR among SN with low CSF retinol measurements may be related to abnormalities of the blood-brain barrier in these individuals. However, CSF and blood TTR levels correlated only among SP subjects. These and other issues will require further study.

INVOLUNTARY MOVEMENTS IN PATIENTS WITH HIV INFECTION. SAID G. MASNOU P, CHEMOULLI P, PLANTE V, GOULON-GOEAU C, VITTECOQ S, DURIN S, LEBRAS P, COUROUBLE Y, LEIBOWITZ J, SAIMOT AG (PARIS, FRANCE)

A variety of involuntary, hyperkinetic, movements occurs in AIDS, due to the involvement of basal ganglia by the HIV and/or by opportunistic infections. In this paper we report on our findings in a series of 10 HIV infected patients, most of them at a late stage of HIV infection, who had been referred for involuntary movements. Different patterns of involuntary hyperkinetic movements were observed. They included acute chorea in one patient; hemiballismus in three, associated in some with myoclonic twitching; complex tic-like movements associated with severe mental deterioration in relation with diffuse, reversible under treatment, toxoplasmic encephalitis in one; tremoro-choreo-athetosis movements increased by voluntary movement, which suggested rubro-subthalamic lesions, were associated with facial dyskinesia in three patients. Focal myoclonus was observed in one. In most patients the occurrence of involuntary movements revealed opportunistic infections. In 3 of them, involuntary movements revealed cerebral toxoplasmosis; in 4 patients, they were related to lesions of progressive multifocal leukoencephalitis, and to a cerebral malignant lymphoma in one. In two patients, no opportunistic infection could be detected neither at the time of the onset of involuntary movements which improved with symptomatic treatment with thiopropazine, nor during the following weeks. In such cases, the responsibility of the HIV is likely. The involuntary movements observed in this setting are different, more complex, than those seen routinely in neurology, after stroke for example. Some complex movements are reminiscent of those described during the Von Economo's epidemic encephalitis (1918-1930). Release by activated macrophages of substances acting as neurotransmitters near some groups of neurons may be the common mechanism to the involuntary movements occurring in inflammatory-infectious disorders. From a therapeutic point of view, the involuntary movement could be controlled by treatment with neuroleptics in nearly all cases.

LOCALIZED BRAIN PROTON MRS IDENTIFIES DIFFERENT METABOLIC PATTERNS IN HIV-RELATED ENCEPHALOPATHIES.

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Modifications in the concentration of brain metabolites, detected by proton localized Magnetic Resonance Spectroscopy (MRS), have been described in patients with AIDS-related dementia complex (ADC) in relation with the presence of a diffuse encephalopathy. We have examined i) 9 healthy volunteers ii) 16 seropositive neuroasymptomatic patients, and iii) 47 ADC patients using proton MRS of the brain (Siemens Magnetom SP 63, PRESS sequence, TE = 135 ms). We have delineated 3 different patterns for HIV-related metabolic encephalopathies. The "undifferentiated encephalopathy" pattern (NAA/Cho ratio only below the range of control values) has been observed in 7 patients. The "NAA encephalopathy" pattern (NAA/Cr-PCr ratio below the range of control values) has been observed in 27 patients. "Cho encephalopathy" (Cho/Cr-PCr ratio under to the range of control values) has been observed in 14 patients. A number of neuroasymptomatic patients (9/16) displayed no MR signs of encephalopathy. In ADC patients, the most frequent metabolic encephalopathy was the "NAA encephalopathy", related to the occurrence of atrophy. "Cho encephalopathies" are not correlated to any MRI findings. The relative number of ADC patients increases from "undifferentiated encephalopathy" group (30%) to the group displaying a "Cho encephalopathy" (62%), and then to the "NAA encephalopathy" group (87%).

ACKNOWLEDGEMENTS: This work is supported by CNRS (URA 1186), APM (Assistance Publique à Marseille), the Programme Hospitalier de Recherche Clinique (Ministère de la Santé) and SIDACTION.

NEUROCISTICERCOSIS AND AIDS ACTIVITY - IS THERE A POSSIBLE RELATIONSHIP?

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Neurocisticercosis is a high prevalence infestation in our environment and it is responsible for 5% of the epilepsy cases in Brazil. In spite of the increasing number of HIV infected patients, no cases of co-infection have yet been reported. Very few cases have been presented internationally and there are no references of active form of neurocisticercosis in symptomatic HIV patients.

This case report aims to present an HIV infected patient with no AIDS symptoms but active parenchymal neurocisticercosis. This patient was treated for neurocisticercosis in 1994, when diagnosis of HIV infection was also made. Patient responded well to treatment and had clinical and radiological evidence of improvement. Five months later the patient developed fever and mental confusion. Admittance examination revealed Zoster in the back and right buttock, confusion and pyramidal syndrome with impairment of the right side. Pneumonia was diagnosed clinically and confirmed with chest X-ray which showed interstitial and exudative patterns. Laboratory tests revealed CD4 = 71 (13.4%) and CD8 = 423 (80.1%) R-0.17. CSF examination showed increased number of cells, mainly lymphocytes and a positive AFB test. Computed tomography demonstrated cerebral atrophy only.

In spite of the treatment patient developed respiratory failure and died. Autopsy disclosed multiple focal areas of brain damage and infarction. However, no evidence of neurocisticercosis was found. The authors approach different aspects of this co-infection and discuss the possibility of cure of neurocisticercosis before the development of AIDS.

IMMUNOCYTOCHEMICAL STUDY OF NERVE BIOPSIES FROM PATIENTS WITH HIV-1 ASSOCIATED PAINFUL SENSORY NEUROPATHY

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The presence of HIV-1 in the PNS may give rise to clinical and histological findings either through direct infection of cells and/or induction of toxic products of inflammatory cells. Alternatively, the virus may (by helper T cell deletion) allow secondary events to occur such as opportunistic infections. We report the findings of a neurobiological and pathological study on sural nerve biopsies from 10 AIDS patients with clinically evident painful peripheral neuropathy. We focused on the expression of HIV-1 specific antigens, i. e. external envelope protein gp-120, transmembrane protein gp-41, gag proteins of the core p-24 by immunocytochemical assays and on the state of immunological activation using immunocytochemical staining for inflammatory cells, Major Histocompatibility Complex (MHC) class I and II molecules, reactive Schwann cells, IL-1, TNF α and β , IL-6 and interferon γ (IFN- γ). Nerve biopsies showed mild to severe demyelination and inflammatory cells infiltrates. In all the cases we studied, we did not identify HIV-1 antigens in light microscopy. We have found an increased expression of HLA-DR in the endoneurium, in the perineurium and on endothelial cells. Inflammatory infiltrates were predominantly composed of macrophages. Specific immunostaining for IL-1, IL-6, TNF α and β was negative. Our data confirm the hypothesis that HIV-associated painful axonal neuropathy is not the consequence of a direct viral invasion and that nerve injury would ultimately result from viral and cellular factors (i.e. other cytokines) released from virus-infected macrophages.

AUTONOMIC DYSFUNCTION IN HIV-1 ASSOCIATED COGNITIVE IMPAIRMENT

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Objective- To evaluate the relationship between HIV-1 associated cognitive impairment, autonomic nervous system and CD4 cell count. **Background-** The prevalence of HIV-1 associated cognitive/motor complex increases with progression to AIDS similarly to symptoms of autonomic dysfunction. The mechanisms of HIV dementia and autonomic impairment are unknown, but there is evidence that indirect mechanisms such as cytokines dysregulation may play an important role. The autonomic nervous system innervates lymphoid organs, thus its dysfunction may further impair the immune system. **Design/Method-** HIV subjects with cognitive complaints were evaluated with a standardized neurological exam, neuropsychological and autonomic battery. **Results-** 12 patients (6M, 6F) aged (range) 30-51 years, CD4 cell count 35-567 were evaluated. Higher autonomic score were associated with an increasing degree of cognitive impairment (Spearman $r_{s} = 0.35$). This correlation was not found with CD4 cell count. Patients with moderate versus mild autonomic deficits had a 15% increase in cognitive impairment. **Conclusion-** Our data suggest that the severity of autonomic dysfunction has a stronger correlation than CD4 cell count with cognitive impairment. This may imply that similar mechanisms underlie both HIV-1 associated cognitive and autonomic impairment. It is also possible that autonomic dysfunction amplifies such mechanisms.

NEUROPSYCHOLOGICAL EVALUATION IN A GROUP OF NEUROLOGICALLY ASYMPTOMATIC HIV INFECTED CHILDREN

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The aim of the study was to evaluate the neuropsychological functioning of HIV infected school-aged children, born from HIV+ mothers in order to detect the presence of subtle neuropsychological impairments in absence of any other sign of neurological involvement.

The study group consisted of twenty children. Their age ranged from 6 to 12 years. Twelve of the subjects were HIV infected while eight were seroreverters. All the infected patients underwent standard neurological evaluation, CT scan and/or MRI.

Patients were grouped according to age; their performance was compared with age-matched groups of 30 normal controls.

Cognitive functions were tested through a neuropsychological battery designed to assess a broad range of cognitive functions which covered perception, attention, psycho-motor ability, constructional praxis, language skills, working memory, verbal learning and long term memory, planning and reasoning.

All subjects performed within normal range with respect to language and constructional abilities. On psychomotor test, attention, working memory and visuo-spatial planning tasks HIV+ patients showed a significantly worse performance when compared with both seroreverters and normal controls.

Our data seem to suggest that neurologically asymptomatic school-aged infected children may exhibit selective impairment when performing tasks characterised by a high level of attention demands.

A longitudinal study of these patients will be relevant in characterising the evolution of the neuropsychological impairments detected, and in evaluating whether the patterns obtained could be considered the first signs of HIV encephalopathy.

CEREBELLAR SYNDROME ASSOCIATED WITH HIV INFECTION

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Although ataxia, tremor and dysarthria may accompany HIV encephalopathy, there are only rare reports of primary cerebellar involvement in AIDS. We describe nine cases of a primary cerebellar syndrome without associated dementia in association with HIV infection. Symptoms included progressive unsteady gait, slurred speech, and limb clumsiness. Patients were dysarthric, with eye movement abnormalities, gait ataxia, impairment of coordination and limb dysmetria, with intact cognition, strength and sensory function. CD4 lymphocyte counts ranged from 10 to 364 cells/mm³.

Neuroimaging studies revealed prominent cerebellar atrophy. Pathologic findings in three cases included focal degeneration of the cerebellar granular cell layer and unusual focal axonal swellings in the brainstem and spinal cord. Although there was no histologic or immunochemical evidence of primary viral infection, polymerase chain reaction analysis of a cerebellar biopsy sample revealed the presence of JC virus DNA. In summary, a cerebellar syndrome unassociated with the clinical features or pathological hallmarks of HIV dementia may be observed in AIDS. In some instances it may be associated with JC viral infection, although the specific etiology of this syndrome remains to be determined in most cases.

BRAIN BIOPSY IN HIV-INFECTION: UTILITY AND ROLE IN MANAGEMENT

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Objective: To determine safety, efficacy, and utility of brain biopsy of HIV-related cerebral mass lesions.

Methods: Meta-analysis of 395 biopsied cases based on literature (14 papers/360 cases) and local case series (35 cases).

Results: Definitive diagnosis was obtained in 90% of cases [125 primary CNS lymphoma (PCNSL), 71 CNS toxoplasmosis (CNS-TOXO) (2 PCNSL+TOXO), 100 progressive multifocal leukoencephalopathy (PML), 60 other specific diagnoses, and 39 non-diagnostic]. Of 194 cases biopsied because empiric anti-toxoplasmosis therapy failed, 125 (64.4%) had PCNSL confirmed resulting in opportunity to alter therapy. Thirty day post-biopsy complication rate was 7.0%, with major hemorrhage the most common. Thirty day mortality rate was low (3.0%). Using local data on biopsied and nonbiopsied (autopsy-confirmed) cases of CNS-TOXO (38 cases) and PCNSL (34 cases), CNS-TOXO patients survived longer than PCNSL patients (308.28 days versus 104.86 days, logrank=17.6426, p<.0001), but within diagnostic groups, biopsy did not appear to extend survival.

Conclusion: Biopsy is safe and effective in establishing diagnoses in selected HIV-seropositive patients. However, the options for treatment of confirmed PCNSL and PML remain poor and biopsy cannot be shown to improve survival in patients with other diagnoses. Improved non-invasive diagnostic techniques or empiric therapy may be more cost-effective than brain biopsy.

PREDICTIVE VALUE OF CEREBRAL MAGNETIC RESONANCE IMAGING IN HIV INFECTION AND AIDS

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Although cerebral atrophy (CA) and diffuse white matter abnormality (DWA) are both associated with HIV infection their exact clinical and pathological correlates are unclear. DWA in particular may reflect HIV infection and non-HIV specific diseases such as CMV encephalitis. In this study we examined the effect of the presence of these changes on the outcomes of (a) neurological abnormality at six month follow-up and (b) mortality at three year follow-up in 90 homosexual/bisexual anti-HIV-1 antibody positive men participating in the Middlesex/MRC neurology cohort study.

Magnetic resonance images were obtained using a dual spin spin echo sequence on a 1.5T Siemens scanner. All images were examined by two radiologists blinded to all data apart from age and rated for the presence or absence of CA-large ventricles, CA-sulcal widening and DWA. Haemoglobin, white cell count, total lymphocyte count, CD4 cell count were measured at the time of imaging. All these variables were entered into logistic regression models to predict the outcomes (a) and (b) described above.

Results: The presence of large ventricles was the only measure significantly associated with the outcome of neurological abnormality. None of the imaging abnormalities was associated with mortality in the three year follow-up.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN AIDS: INITIAL AND FOLLOW-UP CT AND MR IMAGING

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Purpose: To determine the value of follow-up computed tomography (CT) and magnetic resonance (MR) imaging in patients with acquired immunodeficiency syndrome (AIDS) and documented progressive multifocal leukoencephalopathy (PML).

Materials and Methods: A total of 50 CT and 19 MR examinations performed in 21 biopsy or autopsy-proven PML patients were retrospectively reviewed. Seventeen of 21 patients had follow-up examinations (mean time 5.9 weeks). The radiological examinations were correlated with pathological findings at autopsy.

Results: At the initial imaging studies, a total of 73 lesions were found. At follow-up studies, the most striking feature was rapid progression in size and number of lesions (from a mean of 3.2 to a mean of 6.9 lesions/patient). 33% of patients showed evidence of increasing mass effect. Additionally, a central area of variable size, suggesting necrosis, was found in 12/16 patients. Autopsy revealed macroscopic necrotic changes in PML lesions in 11/16 patients.

Conclusion: Follow-up studies of PML in AIDS demonstrate rapid progress of lesions with frequent development of necrosis and mass effect.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY, AN ENCEPHALITIS?

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Progressive multifocal leukoencephalopathy (PML) is usually considered as a subacute to chronic slow viral infection of the central nervous system (CNS) without a significant humoral or cellular immune response to JC virus (JCV).

We report the application of the molecularly cloned and expressed major structural gene of JCV, VP1 in a quantitative analysis by enzyme linked immuno sorbent assay (ELISA) of the systemic and intrathecal humoral immune response in a series of 34 PML patients as compared to four control groups.

A systemic immune response to recombinant VP1 was found in 85% of the control groups (131/155) and in 100% of PML patients (34/34). Thus the absence of detectable serum antibodies to VP1 in a patient make the diagnosis of PML highly unlikely, while a positive test result has a predictive value of only 44%.

An intrathecal synthesis of IgG antibodies to recombinant VP1 in 76% of PML patients (28/34) as compared to only 3% in the control groups (5/155) supports the concept of an active inflammation in PML in the majority of patients.

The sensitivity of the quantitative ELISA using recombinant VP1 is 76% with a specificity of 96.7% for the diagnosis of PML.

FUNCTIONAL MAGNETIC SUSCEPTIBILITY CONTRAST DETERMINATION OF CEREBRAL BLOOD VOLUME IN HIV+ PATIENTS

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Introduction

Studies estimate that 20-30% of AIDS patients develop dementia (AIDS Dementia Complex:ADC). Central nervous system (CNS) changes, however, probably occur prior to distinct neuropsychological symptoms. The link between blood flow and cerebral metabolism is well documented; a disturbance in neuronal metabolism, subsequent to HIV infection, might affect blood flow or volume in early stages. We determined normalized Cerebral Blood Volume (CBV) maps from controls and HIV+ patients at all stages of CDC and ADC progression to determine whether blood volume abnormalities occur early in HIV+ patients.

Methods

Fourteen HIV+ patients, were compared to seven controls. A 1.5 T GE-Signa 4.x system with echo-planar capabilities was used for fast imaging. Patients were injected with 0.2 mmol/Kg Gd-DTPA contrast reagent for CBV determination.

Results and Discussion

A generalised increase in CBV was found in gray matter (more notably deep gray) but not in white matter regions of HIV+ patients when compared to controls. Trends were found between increasing CBV and worsening CDC and ADC stage. Evidence exists that an increased CBV can result from metabolic or hypoxic stress to the CNS; based upon our data it might also occur with viral infection. These CBV maps provide novel data on how the CNS responds to HIV+ infection with respect to blood volume.

REVERSION OF BRAIN METABOLIC ALTERATIONS DETECTED BY PROTON MRS IN PATIENTS WITH AIDS DEMENTIA COMPLEX UNDER ZIDOVUDINE TREATMENT.

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Several laboratories, including our own, have demonstrated that HIV encephalopathy induces modifications of brain metabolism which can be detected by localized proton Magnetic Resonance Spectroscopy (MRS). We have examined the effects of AZT on the brain metabolism of 8 patients with HIV-related encephalopathy using proton MRS of the brain. Neurological, neuropsychological and MRS examinations (Siemens SP63, PRESS Sequence, TE 135 ms) were conducted before and after a three to six month Zidovudine treatment (800 to 1000 mg/day). All patients displayed a significant improvement of their neurological status under treatment. In 7 patients, an increase of the NAA signal (neuronal marker) was observed after treatment. In a longer-term follow-up, we have observed that several patients displayed a diphasic evolution with a metabolic improvement followed, when resistance to Zidovudine develops, by a metabolic degradation.

In conclusion, Zidovudine does reverse the cerebral metabolic alterations detected by MRS. The decrease of the NAA signal reflects a (transitory) neuronal metabolic suffering, and not only neuronal loss. In addition MRS has detected the occurrence of a secondary resistance to the initial antiretroviral treatment, and constitutes a quantitative method to assess the efficiency of new or future neurotropic drugs in ADC.

ACKNOWLEDGEMENTS: This work is supported by CNRS (URA 1186), APM (Assistance Publique à Marseille), the Programme Hospitalier de Recherche Clinique (Ministère de la Santé) and SIDACTION.

BRAIN PROTON MAGNETIC RESONANCE SPECTROSCOPY IN HIV-RELATED ENCEPHALOPATHIES: A SURVEY OF 382 EXAMINATIONS PERFORMED ON 171 PATIENTS

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HIV-related encephalopathies constitute a frequent complication of AIDS, leading to sub-cortical dementia. They can be studied by proton MRS which is the first non invasive method allowing to perform live human neurochemistry. We have examined 171 HIV-positive adults (382 examinations) with various stages of HIV infection, using proton MRS of the brain (Siemens SP63, PRESS Sequence, TE 135 ms; STEAM sequence TE 20 ms). The main results are: 1) HIV encephalopathies induce significant and reproducible modifications of brain metabolism detected by localized proton MRS, 2) these metabolic modifications are a decrease of N-acetyl-aspartate (neuronal marker), an increase of the choline-containing compounds (marker of demyelination) and an increase of inositol (marker of glial metabolic activation); 3) these metabolic modifications are closely correlated to the neuropsychological impairment; 4) MRS is able to detect these metabolic modifications infraclinically and before any lesion is seen by MRI. In neuroasymptomatic patients with normal MRI, MR spectra have been found abnormal in 20% (PRESS spectra) to 30% (STEAM spectra) of patients examined; 5) the metabolic modifications induced by encephalopathies can be partially or totally reversed by antiretroviral treatment, when detected early.

ACKNOWLEDGEMENTS: This work is supported by CNRS (URA 1186), APM (Assistance Publique à Marseille), the Programme Hospitalier de Recherche Clinique (Ministère de la Santé) and SIDACTION.

CERVICAL SPINAL CORD LESION IN A HIV POSITIVE PATIENT

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A 46-year-old homosexual man was examined for recent onset of progressive dysesthesia in both legs. Upon clinical examination a T10 sensory level was detected without pyramidal or urinary sign, suggesting a spinal cord lesion. He had no previous medical history.

Blood testing for human immunodeficiency virus (HIV) was positive (CD4 count = 250/mm³). The spinal fluid showed increased protein level with a mild pleiocytosis.

Magnetic resonance imaging demonstrated an enlarged spinal cord from C3 to T3 with faint gadolinium enhancement on T1-weighted images. A vacuolar myelopathy or a myelitis were suspected. Symptoms worsened although the patient received zidovudine for six weeks followed by foscarnet for two weeks.

Clinical and radiological evolution led to the suspicion of a spinal cord tumor, mainly lymphoma, although enhancement was faint. The patient died three months after the first signs occurred. A cervical glioma was found at autopsy.

This is the third report in literature of spinal cord astrocytoma in a HIV positive patient, suggesting unusually high occurrence of such a rare pathology in those patients. Although this diagnosis is rare enough not to be suspected at first, it should be considered in patients with acquired immunodeficiency developing a myelopathy.

PREDICTION OF NEURO-AIDS IN PERINATALLY ACQUIRED HIV INFECTED INFANTS

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Background. Perinatal transmission is the most frequent route of HIV infection in the pediatric population. Pediatric neuroAIDS is an early manifestation of HIV infection in some children; others show neurologic or developmental impairments later in the course of their illness.

Methods. Twenty-four children with vertically acquired HIV infection were followed prospectively from birth to twenty four months using standardized neurodevelopmental measures. At six months of age, quantitative measures of T lymphocytes were determined in peripheral blood specimens. Control specimens were obtained from a cohort of 44 uninfected children born to women with HIV infection.

Results. HIV infected children had lower mean CD 4 lymphocyte counts (2603 +/- 1510 versus 3364 +/- 1111, p = .038) and higher percentage of CD 8 lymphocytes (23 +/- 7.6 versus 18 +/- 5.3, p = .002) than uninfected children. Neurodevelopmental functioning at six months was correlated with the percentage of CD 8 lymphocytes, while numbers of CD 4 or CD 8 lymphocytes showed a concurrent relationship. Using a standardized regression model, a predictive relationship was found between numbers of CD 4 and CD 8 lymphocytes at 6 months and later neurodevelopment at 12 months. Only the CD 4 cell count at 6 months was predictive of neurodevelopment at 24 months of age. Kaplan-Meier analysis showed significant relationships between CD 4 lymphocyte counts above 1500 at 6 months of age and the Bayley Mental Development Index remaining above 70 to 24 months of age.

Conclusion. The status of the immunologic system at 6 months of age is predictive of subsequent neurodevelopmental impairment in perinatally acquired HIV infection. The ability to predict neurodevelopmental impairment will assist in more targeted therapeutic intervention.

SUCCESSFUL USE OF SNX-111, A NOVEL N-TYPE NEURONAL CALCIUM CHANNEL BLOCKER, IN THE TREATMENT OF SEVERE AIDS NEUROPATHIC PAIN

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Neuropathic pain is a significant source of disability in AIDS patients. We report the use of a novel neuronal calcium channel blocker in 3 AIDS patients with intractable pain.

SNX-111 is the only selective neuron-specific, N-type voltage sensitive calcium channel (VSCC) antagonist to enter clinical drug development. Intrathecal (IT) SNX-111 has successfully treated intractable neuropathic pain in Phase 1 studies in cancer patients.

PATIENT 1: IT SNX-111 was infused at escalating doses from 0.3 ng/kg/h to 100 ng/kg/h in a male AIDS patient with severe (10/10) distal pain refractory to conventional opioid and nonopioid oral and parenteral analgesics. At baseline, pain prevented him from walking. At a dose of 10 ng/kg/h, pain was eliminated, and he was able to ambulate. At doses > 20 ng/kg/h, possible drug-related vestibular toxicity and mental clouding was observed. All side effects resolved with dose reduction, and pain relief was maintained. He was discharged on 10 ng/kg/h. Therapeutic results in additional AIDS patients are presented.

Early results with IT SNX-111 for the treatment of pain in AIDS are encouraging. A controlled clinical trial of SNX-111 in cancer and AIDS patients is underway.

QUANTITATION OF DIFFUSE HIV-RELATED WHITE MATTER HYPERINTENSITY SEEN ON T2-WEIGHTED MAGNETIC RESONANCE IMAGING

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Introduction: One of the radiological correlates of HIV-associated dementia complex (HADC) is increased signal from cerebral white matter on T2-weighted MRI. Radiological changes during the early stages of disease are subtle and a quantitative assessment of this finding would be useful.

Methods: Sixty-three HIV+ve subjects, 47 seronegative low-risk for HIV blood donors and 17 seronegative high-risk for HIV homosexual men underwent T2-weighted MRI at 1.5T. Quantitative analysis was performed by obtaining ratios of pixel intensities between parieto-occipital white and head of caudate grey matter.

Results: Significant differences in white/grey matter ratios were observed between subjects: (i) with and without abnormal white matter on qualitative radiological interpretation ($p < 0.0001$); (ii) with and without atrophy ($p < 0.0001$); (iii) with higher ($> 200 \times 10^6$) compared to lower ($< 200 \times 10^6$) CD4 counts ($p < 0.05$) and (iv) with and without abnormal neurological signs consistent with a diagnosis of HADC ($p < 0.05$).

Discussion: The detection of diffuse white matter abnormality is important in patient management as it provides supporting evidence for a diagnosis of HADC. Recent reports document qualitative changes in severity of white matter hyperintensity with concomitant clinical improvement following antiretroviral therapy, hence this technique may be a useful marker for the neurological response to therapeutic agents.

QUANTITATIVE MR IMAGING AND SPECTROSCOPIC ASSESSMENT OF THE EFFECTS OF ANTI-RETROVIRAL THERAPY

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Introduction: Objective methods are needed with which to monitor progression of HIV-associated dementia and its response to therapy. The results from 3 MR techniques are reported: (i) evaluation of sub-cortical white-grey matter contrast as a quantitative marker of parenchymal abnormality; (ii) determination of CSF to intracranial volume (CSF/ICV) ratio to monitor atrophy and (iii) evaluation of the relative levels of metabolites by proton spectroscopy as a putative marker of neuronal integrity/function.

Methods: Three patients with HIV-associated dementia were studied before and after treatment with AZT. Axial T2-weighted images and proton spectra were acquired at 1.5T. Seventeen seronegative male homosexuals acted as controls.

Results: The CSF/ICV ratio increased in all 3 cases over the study period. The spectra mirrored the clinical neuropsychological findings in all 3 patients while the sub-cortical white/grey matter contrast followed the clinical status in 2/3 patients.

Conclusions: AZT did not appear to halt the development of atrophy. Spectroscopy was the best marker of response to therapy and suggests that alterations in the N-acetyl resonance may not be entirely due to neuronal cell death and possibly reflect reversible neuronal dysfunction.