agents may play an important yet undefined role in the pathogenesis of this syndrome.

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Clinical and spectroscopic improvement in HIV-associated cognitive impairment

Article abstract—To assess the impact of highly active antiretroviral therapy (HAART) on AIDS-associated cognitive impairment, 22 patients with AIDS with (n = 11) and without (n = 11) cognitive deficit were evaluated clinically and by MRS every 3 months for 9 months. Nineteen patients were on HAART at study entry, 21 after 2 months. Cognitively impaired patients presented with a subcorticofrontal deficit and decreased *N*-acetyl-aspartate in frontal white matter. These clinical and metabolic abnormalities reversed partially on HAART, whereas they remained within normal limits in cognitively unimpaired patients.

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Whether highly active antiretroviral therapy (HAART) treats or prevents AIDS-associated cognitive impairment is a critically important issue in neuro-AIDS. Since HAART was first widely used, a major decline in the incidence of this complication has been reported.[1] Few studies, however, have analyzed the impact of HAART on cerebral dysfunction.[2-4]

Methods. We prospectively studied 22 AIDS patients (20 men and two women) without previous or ongoing neurologic disease, major psychiatric disorder, or current alcohol or drug addiction. All had a CD4 cell count below 200/mm^3 at study entry or at anytime during the preceding year. The study was approved by the ethical committee of our institution and all patients provided informed consent prior to enrollment.

Using *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* (DSM-IV) criteria for AIDS dementia, 11 patients were classified as cognitively unimpaired (CU), and 11 as cognitively impaired (CI). Of the latter, nine had a mild cognitive impairment and two were demented.

Neuropsychological and MRS evaluations were performed at study entry (M0), then every 3 months (M3, M6, and M9) for 9 months. CD4 cell count and plasma HIV-1 RNA level were obtained at M0, then when requested by the treating physician.

The neuropsychological battery, already described,[5,6] comprised the Mini-Mental State Examination (MMSE), Mattis Dementia Rating Scale, Trail Making A and B, Purdue Pegboard, and Grober and Buschke tests. Depression was evaluated with Montgomery and Asberg Depression Rating Scale (MADRS).

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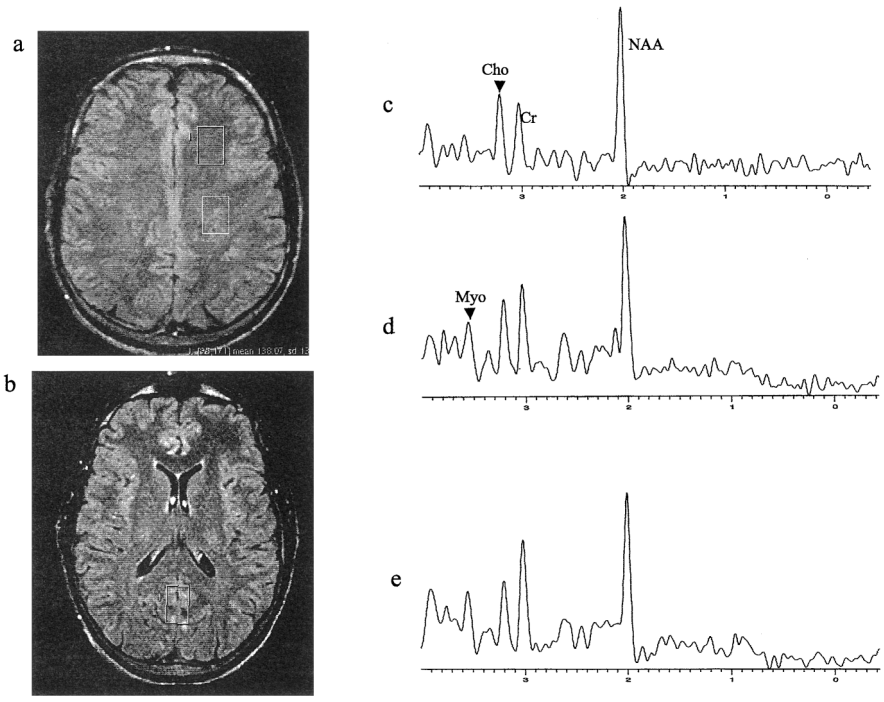

Figure 1. Brain MRI showing on axial fluid-attenuated inversion recovery sequences the two volumes selected in the white matter, one in the centrum semi-ovale and the other in the frontal white matter (a) and the volume selected in the medial parieto-occipital gray matter (b). (c) Spectrum at ET = 136 ms showing the NAA and Cho peaks; (d) spectrum at ET = 18 ms showing the Myo peak; (e) spectrum at ET = 30 ms.

MRI (1.5 T) was performed using axial fluid-attenuated inversion recovery (FLAIR) sequences. MRS spectra were acquired and analyzed as previously described,[7] with three volumes of interest: two in the white matter (centrum semi-ovale and frontal white matter) and one in the medial parieto-occipital gray matter. The following ratios were analyzed: area of NAA/Cr (*N*-acetylaspartate to Creatine), Cho/Cr (Choline to Creatine), and amplitude of Myo/Cr (Myoinositol to Creatine) (figure 1). Mean (±SEM) ratios of a reference control group[7] were 2.11 ± 0.05 (range: 1.86 to 2.48) for NAA/Cr, 1.09 ± 0.03 (range: 0.92 to 1.24) for Cho/Cr, and 0.93 ± 0.08 (range: 0.49 to 0.87) for Myo/Cr.

Statistical analysis was performed with BMDP software. Groups were compared using non-parametric tests (Mann–Whitney *U* test). Correlations were calculated using the Spearman coefficient. Results are presented as mean ± SEM.

Results. Mean age was 36.4 years (range: 26 to 44 years) and the mean educational level was 10.7 years (range: 2 to 20 years). Mean duration of disease was 10 years (range: 4 to 12 years). No statistical difference between groups was found in terms of age, educational level, or HIV infection duration. Nine patients were HIV-infected through homosexual contact, six through heterosexual transmission, and four had a history of drug addiction for several years. For three patients, the cause of HIV transmission was unknown.

At baseline, 19 patients received HAART with at least one protease inhibitor, and duration of HAART before inclusion was one to 15 months. In the CI group, two patients had no antiretroviral treatment, one was on bitherapy with nucleosides. One patient remained untreated; and in the two other cases, HAART was initiated during the first 2 months of the study.

Mean duration of treatment was 10 months (range: 1 to 19) in the CU group and 6 months (range: 0 to 15) in the CI group. Mean CD4 cell count was 241 ± 53 in the CU group, and 117 ± 35 in the CI group. Plasmatic HIV RNA level (log10) was 3.87 ± 1.6 in the CU group, and 4.58 ± 1.2 in the CI group.

Neuropsychological data for the 22 patients (11 CI and 11 CU) at baseline are detailed in table 1. The 11 CI patients had a subcorticofrontal deficit with bradykinesia, verbal slowing, and sensitivity to semantic cues, as compared to CU patients. Mattis subtests and the Grober and Buschke test showed that memory was more affected than other cognitive performances, and was different between groups ($p < 0.01$) (not shown). MADRS score was significantly higher in the CI group, although not exceeding 28, reflecting the absence of severely depressed patients.

Brain atrophy was detected in two CU patients and

Table 1 *Neuropsychological data*

Cognitive group	Mattis	MMSE	Grober Buschke (TRS)	Purdue Pegboard	Trail B	MADRS
Cognitively impaired, n = 11	133.8 (2.0)	26.8 (0.9)	27.1 (1.9)	12.9 (0.7)	132.6 (22.2)	19.4 (1.8)
Cognitively unimpaired, n = 11	140.0 (1)*	29.4 (0.3)*	34.4 (1.4)†	14.7 (0.9)	94.2 (15.4)	10.6 (2.3)†

Values are mean (SEM).
* $p < 0.05$; † $p < 0.01$.

MMSE = Mini-Mental State Examination; TRS = total recall score; MADRS = Montgomery and Asberg Depression Rating Scale.

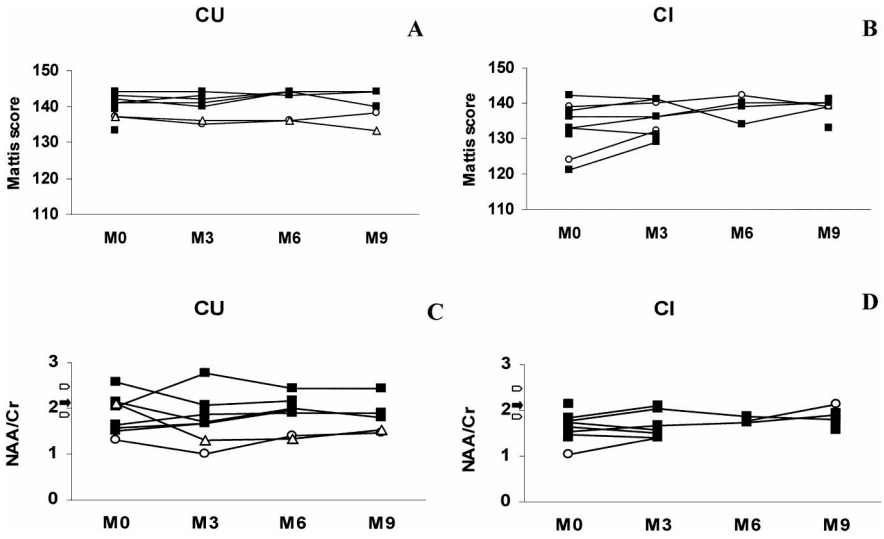

Figure 2. Individual neuropsychological and MRS data: longitudinal study. Mattis score (A, B) and frontal NAA/Cr (C, D) evolution in cognitively unimpaired (CU) (A, C) and impaired (B, D) patients. Normal mean (black arrow) and range (white arrowhead) of NAA/Cr. White circles correspond to the three patients with leukoencephalopathy. White triangles correspond to the single CU patient with cognitive decline. Note that he was also the only CU patient with a decrease of NAA/Cr ratio throughout follow-up.

seven CI patients. Diffuse white matter abnormalities suggestive of HIV leuco-encephalopathy was detected in three cases (one CU and two CI), who were analyzed separately at M0.

Baseline MRS data were collected in 15 (eight CI and seven CU) patients without white matter abnormalities (table 2). In the frontal white matter, mean NAA/Cr levels were within normal range in the CU group, whereas they were below normal range in the CI group. Mean posterior white matter NAA/Cr levels were within normal range in both groups. Cho/Cr levels were elevated for all patients in both areas. Myo/Cr levels were above the normal range in the posterior white matter of CI patients, and normal for all patients in the frontal white matter. Gray matter values were within normal limits (not shown).

Seventeen patients were evaluated neuropsychologically at least twice (figure 2, A and B). Of the eight CU patients, Mattis scores remained stable in seven cases, and declined in one case. Of the nine CI patients, Mattis scores improved in six cases, including the two patients who received HAART after study entry, and remained unchanged in three cases. Despite this neuropsychological improvement, no CI patient had a normalization of his cognitive status. The only untreated CI patient had no cognitive change between M0 and M9 (not shown).

Fifteen patients had a MRS follow-up (figure 2, C and D). Of the seven CU patients, frontal NAA/Cr ratios remained stable in three cases, increased in three cases, and decreased in one case, which was the only CU patient to develop a cognitive deficit. Of the eight CI patients, NAA/Cr increased in six cases, and decreased in the two cases who started HAART after study entry. Improvement of clinical and MRS data were detected at M3 in most cases and continued thereafter.

In addition to this individual analysis, a comparison of neuropsychological and spectroscopic variables between M0 and M9 was performed on the subgroup of patients who completed the study. Fourteen patients completed the neuropsychological evaluation. In the CI group (n = 8), the mean Mattis score improved (134.5 ± 1.9 at M0, and 138.0 ± 1.1 at M9). All other neuropsychological tests improved, significantly for attention and memory evaluation. In the CU group (n = 6), Mattis scores remained unchanged.

Eleven patients completed the MRS study. In the CU group (n = 5), mean frontal NAA/Cr levels remained within normal range (1.95 ± 0.22 at M0, and 1.83 ± 0.17 at M9), whereas they increased from 1.67 ± 0.06 (below the normal range) to 1.86 ± 0.08 (within the normal range) in the CI group (n = 6). Cho/Cr levels remained elevated in the frontal anterior white matter in both groups. Posterior Myo/Cr normalized in CI patients. Gray matter values (n = 5) remained within normal limits (not shown).

At M0, white matter NAA/Cr or Cho/Cr levels did not correlate with total Mattis or Mattis subtests. Myo/Cr levels in white matter did not correlate with the total Mattis score, but correlated inversely with the Mattis memory score ($r = -0.52$ for frontal Myo/Cre, $p < 0.05$) as well as with NAA/Cr level ($r = -0.58$ for frontal ratios, $p < 0.05$; and $r = -0.79$ for posterior ratios, $p < 0.005$). No correlation between cognitive status and disease duration was found.

At M0, mean CD4 cell count correlated with the Mattis

Table 2 *White matter MRS ratios at M0*

Cognitive group	NAA/Cr frontal	NAA/Cr posterior	Cho/Cr frontal	Cho/Cr posterior	Myo/Cr frontal	Myo/Cr posterior
Cognitively impaired, n = 8	1.69 (0.08)	1.97 (0.06)	1.19 (0.09)	1.17 (0.09)	0.81 (0.06)	0.95 (0.09)
Cognitively unimpaired, n = 7	2.02 (0.17)	2.2 (0.09)	1.3 (0.13)	1.3 (0.13)	0.68 (0.04)	0.81 (0.08)

Values are mean (SEM).

NAA = *N*-acetylaspartate; Cr = creatine; Myo = myoinositol.

memory subtest ($r = 0.52$, $p < 0.02$), and weakly with the total Mattis score ($r = 0.46$, $p < 0.05$). HIV RNA level correlated inversely with the memory subtest of the Mattis scale ($r = -0.47$, $p < 0.05$), but not with the total Mattis score.

Discussion. This study confirms reported metabolic abnormalities of HIV encephalopathy,[8-10] with decreased *N*-acetylaspartate and increased choline, and underscores their regional (frontal) or diffuse distribution. The longitudinal evaluation demonstrated that HAART partially reverses both clinical and metabolic abnormalities. Long-term follow-up will be needed to determine if patients with cognitive deficits recover.

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A *prepro-orexin* gene polymorphism is associated with narcolepsy

Article abstract—The orexin (hypocretin) neurotransmitter system was recently shown to be directly involved in the pathogenesis of narcolepsy in two animal models. Furthermore, decreased levels of orexin A in the CSF were shown in narcoleptic patients. To define any genetic contribution of orexin to the etiology of narcolepsy, the authors screened the entire *prepro-orexin* gene for mutations or polymorphisms in 133 patients suffering from narcolepsy. They report an association of a rare polymorphism in the *prepro-orexin* gene with narcolepsy in a cohort of 178 patients.

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Narcolepsy is a debilitating disorder of the sleep/wake regulation characterized by excessive daytime sleepiness, short episodes of involuntary muscle relaxation (cataplexy), sleep paralysis, and hypnagogue and hypnopompic hallucinations. The etiopathogenesis of narcolepsy has remained unclear despite a strong human leukocyte antigen (HLA) association. Although the HLA-DR2 and the linked HLA-DQB1*0602 allele is found in >95% of narcoleptic patients but only in 8 to 35% of normal populations,[1] the pathogenetic role of the HLA system has remained unclear, especially because autoimmune phenomena are not obvious. Recently, abnormalities in the orexin neurotransmitter system have been shown to cause narcolepsy-related symptoms in an *orexin*-knockout mouse model,[2] as well as in narcoleptic breeds of Doberman pinschers and Labrador retrievers.[3] Finally, orexin A was not detected in seven of nine patients with narcolepsy, indicating disturbed orexin transmission (limit of the assay: 40 pg/mL). All nine healthy controls showed orexin A levels ranging from 250 to 285 pg/mL.[4]

Orexin A and orexin B are both encoded by the *prepro-*

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