Journal of NeuroVirology (1999) 5, 500–506

http://www.jneurovirology.com

Measuring HIV-1 RNA and interferon-α in the cerebrospinal fluid of AIDS patients: insights into the pathogenesis of AIDS Dementia Complex

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The aim of this work was to study the role of HIV replication and the role of endogenous secretion of interferon-α in the pathogenesis of AIDS Dementia Complex (ADC). To accurately establish the diagnosis of ADC, 39 consecutive HIV-positive patients who presented with immune and intellectual deficiency underwent an extensive neurological evaluation. This included magnetic resonance imaging, neuropsychological testing and a lumbar puncture. The levels of HIV-1 RNA were measured in the cerebrospinal fluid (CSF) and blood by HIV Monitor (Roche Diagnostics) and those of interferon-α by an in-house biological assay. The diagnosis of ADC was established in 22 cases, which included nine out of the ten patients who had a high CSF viral load (above 4 log HIV-1 RNA copy per ml). Patients receiving highly active antiretroviral therapy had low viral loads in blood and CSF. In all 22 ADC patients, viral load in the CSF correlated with the staging of ADC (r=0.46, P=0.03), the CSF level of interferon-α (r=0.42, P=0.05) and with the bicaudate ratio (r=0.43, P=0.06), a measure of cerebral atrophy in the region of the caudate nucleus. No correlation was observed between CSF and plasma HIV-1 RNA. These results show that HIV may play a role in the neurological impairment of ADC patients possibly in part through the deleterious effect of interferon-α on the central nervous system and that highly active combination therapy should reduce or prevent these complications.

Keywords: neurological/brain; viral load; pathogenesis; antiretroviral therapy; interferon; magnetic resonance imaging

Introduction

The AIDS dementia complex (ADC) is a major neurological disorder, occurring in about 20% of AIDS patients; its clinical features associate cognitive impairment and several behavioural and motor disabilities, leading to severe degradation and death. The diagnosis of ADC in living patients is difficult, since clinical features are not specific for CNS HIV infection and may also be observed in opportunistic diseases or psychiatric disorders (Navia *et al*, 1986; Simpson and Tagliati, 1994). The most frequent radiologic features of ADC are cortical atrophy and diffuse or multifocal white matter abnormalities. Although the frequency of magnetic resonance imaging (MRI) abnormalities is higher in patients with neurological symptoms, they are not specific for ADC and may be present in AIDS patients without neurological symptoms or during opportunistic infections of the central nervous system (CNS) (Simpson and Tagliati, 1994; Bencherif and Rottenberg, 1998). Nevertheless, cerebral atrophy can be quantitated by MRI by measuring ventricle bicaudate (BCR) and bifrontal (BFR) ratios; Dal Pan *et al* (1992) have reported that increased BCR was associated with the presence of ADC in AIDS patients.

As it is not clear whether viral factors or immunological activation play a predominant role in its pathogenesis, we were interested in studying

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Received 22 January 1999; revised 5 April 1999; accepted 23 April 1999

the role of HIV replication in the CNS and the potential role of interferon-α (IFN-α) on the development of ADC. High CSF levels of HIV-1 RNA have been reported in ADC patients (Cinque *et al*, 1998; di Stefano *et al*, 1997; Robertson *et al*, 1998) but also in patients with opportunistic infections such as cryptococcal meningitis (Brew *et al*, 1997; Morris *et al*, 1998). Because of this lack of specificity, the level of CSF HIV-1 RNA was not considered as a useful marker for the diagnosis of ADC. Brew *et al* (1997) have shown however, that HIV-1 RNA correlated with the stage of dementia in ADC patients, providing an argument for the importance of viral replication in the CNS for the pathogeny of neurological damage.

On the other hand, a role for immunological factors in the pathogenesis of ADC has been proposed several years ago by authors who noticed the contrast between the small number of infected cells within the CNS and the intensity of cognitive and motor deficits in ADC patients (Price *et al*, 1988; Epstein and Gendelman, 1993). Increased levels of β_2-microglobulin, TNF-α, neopterin and neurotoxins such as quinolinic acid have been reported in the CSF or the brain of ADC patients (Griffin *et al*, 1991; Heyes *et al*, 1991; McArthur *et al*, 1992) but no clear correlation was found between CSF levels of these factors and the severity of dementia. We have chosen to measure the CSF and serum levels of interferon-α since the expression of this molecule is induced preferentially by viral pathogens including HIV (Rozenberg and Lebon, 1991; Von Sydow *et al*, 1991) and its neurotoxicity has been reported (Rohatiner *et al*, 1983; Gutterman, 1994). We then looked for correlations between CSF HIV-1 RNA and cerebral atrophy or IFN-α levels in patients with ADC.

Table 1 Neurological diagnosis in 17 patients excluded from the ADC group

CMV encephalitis	$n=3$*
Progressive multifocal leucoencephalitis	$n=3$
Toxoplasmosis	$n=4$*
Neuromeningeal cryptococcosis	$n=4$
CNS lymphoma	$n=4$
VZV encephalitis	$n=1$

*In two patients, both CMV and toxoplasmosis were diagnosed.

Results

In 17 out of 39 patients screened for ADC, an alternate diagnosis was established (Table 1): CNS lymphoma in four cases and current opportunistic infection in 13. Three cases of cytomegalovirus (CMV) encephalitis, two cases of progressive multifocal leucoencephalopathy (PML) and one case of varicella-zoster virus (VZV) encephalitis were diagnosed by an in-house polymerase chain reaction;

Table 2 Clinical characteristics and biological results of 22 ADC patients listed in order of decreasing CSF HIV-1 viral load

Age/ Sex	*CSF HIV-1 RNA (log copy/ml)*	*Plasma HIV-1 RNA (log copy/ml)*	*CSF cells (cell/μl)*	*CSF IFN-α (IU/ml)*	*Serum IFN-α (IU/ml)*	*Albumin index*	*Blood CD4⁺ (cells/μl)*	*ADC stage*	*Antiretroviral therapy*
29-M	5.69	5.1	1	<2	2	4.1	8	III	0
39-M	5.35	5.42	0	4	6	10.9	5	III	0
32-M	5.27	4.86	4	2	3	12.3	10	III	mono
41-M	5.17	5.58	0	6	400	7.3	33	III	bi
38-M	5.08	5.41	8	9	6	12.1	291	III	0
32-M	4.95	6.11	1	<2	<2	3.5	216	IV	0
41-M	4.79	5.66	4	2	100	5.4	66	II	0
37-M	4.59	5.24	0	<2	12	6.4	14	IV	bi
41-F	4.26	4.82	8	<2	<2	11.9	172	I	0
40-M	3.96	4.46	4	<2	<2	17.5	140	I	bi
36-M	3.32	5.64	0	<2	<2	2.9	61	II	bi
67-M	3.20	6.02	1	3	75	10.2	42	III	mono
44-F	3.20	5.52	0	<2	6	3.4	12	III	0
49-M	3.20	3.99	0	<2	18	2.9	319	III	HAART
36-F	2.78	6.27	1	3	75	17.4	7	III	0
65-M	2.78	5.52	0	<2	25	9.4	51	IV	0
37-M	2.65	4.90	0	2	35	14.2	4	II	0
30-M	<2.3	5.90	0	<2	35	14.3	13	II	mono
58-M	<2.3	2.60	0	<2	<2	14.2	5	III	bi
32-M	<2.3	<2.3	0	<2	<2	12.3	114	II	HAART
62-M	<2.3	5.09	2	<2	18	4	5	II	0
43-M	<2.3	3.71	0	<2	<2	3.1	71	II	HAART

0: no treatment; nd: not done; mono: nucleosid analogue monotherapy; bi: nucleosid analogue bitherapy; HAART: combination therapy with a protease inhibit.

four cases of neuromeningeal cryptococcosis were diagnosed by culture and antigenaemia, and four cases of toxoplasmosis by biological and radiological features. Two of these patients had a dual infection: CMV encephalitis and cerebral toxoplasmosis. Among the four patients with CNS lymphoma, two had detectable Epstein-Barr virus (EBV) DNA in the CSF.

The diagnosis of ADC was then established in 22 patients (Table 2) and staged as follows: two stage I, eight stage II, nine stage III, three stage IV. They were 19 male, three female, median age 39 years, median CD4=38 per mm^3 of blood. Eleven patients were untreated (50%), three were on highly active antiretroviral therapy (HAART) and eight were on various regimens of nucleosidic analogue therapy. Pleiocytosis was rare: only two patients had more than 4 cells per μl of CSF. The 22 ADC patients and the 17 excluded patients were similar in terms of age, sex, blood CD4 cell count and antiretroviral therapy.

Seventeen out of 22 ADC patients (77%) had detectable HIV-1 RNA in their CSF. Mean values in log copy number per ml was 3.65 ± 1.29 in the CSF and 4.99 ± 1.08 in the plasma. These results were not significantly different from those obtained in the 17 excluded patients (3.14 ± 0.74 and 4.41 ± 1.40); however, nine out of the ten patients (90%) with high CSF viral load (above 4 log per ml) were classified in the ADC group. In two ADC patients, viral load was higher in the CSF than in the plasma. Patients under HAART had low viral load in both compartments. Mean albumin index was similar in the two groups (9.07 ± 4.94 in the ADC group and 8.68 ± 4.52 in the excluded patients).

Among the 22 ADC patients, eight had an increased level of IFN-α in the CSF and 15 in the serum. On neurological imaging, cortical atrophy was present in 14 out of 20 patients. There was no correlation between CSF and plasma HIV-1 RNA (r=0.25, P=0.27) and no correlation between CSF HIV-1 RNA and albumin index or blood CD4 cell count. In contrast, the level of HIV-1 RNA correlated with the CSF level of IFN-α (r=0.42, P=0.05), with the bicaudate ratio (r=0.43, P=0.06 Figure 1a) and with the staging of dementia (r=0.46, P=0.03). The level of IFN in the CSF also correlated with the stage of dementia (r=0.39, P=0.08) but with a low statistical significance. In contrast, HIV-1 RNA in the CSF did not correlate with the bifrontal ratio (Figure 1b) nor with the serum level of IFN-α.

Because of profound intellectual deficiency, too many patients were unable to perform the whole set of neuropsychological tests and this led to hardly interpretable results.

Mortality rate was 14/22 (64%) at the end of the follow-up period.

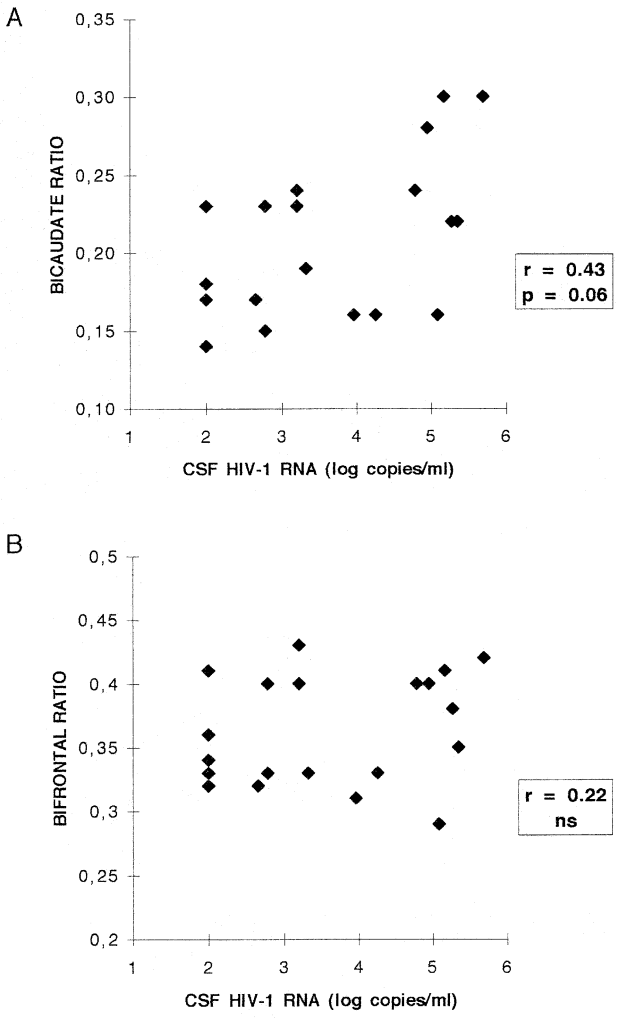

Figure 1 Scatterplot of CSF HIV-1 RNA levels and MRI measures of cerebral atrophy. (**A**) Correlation between CSF HIV-1 RNA and bicaudate ratio. (**B**) Absence of correlation between CSF HIV-1 RNA and bifrontal ratio.

Discussion

In this work, we show that in ADC patients, CSF viral load correlates with the intensity of cerebral atrophy in the region of the caudate nucleus and with the CSF level of IFN-α.

Cerebral atrophy, a major radiological feature of ADC, can be quantitated through MRI by measuring ventricle brain ratio, bifrontal and bicaudate ratios. Dal Pan *et al* (1992) have reported increased bicaudate ratios in patients with HIV dementia compared to HIV-positive patients without neurological symptoms or HIV-negative patients. This was not the case for the bifrontal ratio, which measured cerebral atrophy in the regions of the frontal horns. One study reporting volumetric brain analysis by MRI in 11 AIDS patients has shown the caudate volume but not hippocampal volume

correlated with poor performances on neuropsychological tests (Kieburtz *et al*, 1996). We show here that in 20 ADC patients, HIV-1 RNA in the CSF is correlated with the bicaudate but not bifrontal ratio (Figure 1). These results, in conjunction with those of the former studies, suggest that HIV replication within the central nervous system plays a role in the cerebral atrophy of the caudate nucleus observed in ADC. Moreover, this is in agreement with the results of immunohistochemical studies showing that in ADC patients, p24 antigen-positive cells were located preferentially in the basal ganglia and other deep brain structures (Brew *et al*, 1995).

To assess HIV replication in the CNS, we have measured HIV-1 RNA in the CSF, keeping in mind that the brain and the CSF are two related but distinct compartments; since only the CSF is easily accessible in clinical practice, and since plexus choroidal cells cannot sustain HIV replication (Brew *et al*, 1995), we, as others, have relied on this approach. McArthur *et al* (1997) have reported that viral load in CSF and in cerebral tissue are correlated in ADC patients. These results, however, need to be confirmed. A prospective study addressing this question could be undertaken on autopsy samples.

As other authors, we found no correlation between the permeability of the blood-brain barrier and the level of HIV RNA in the CSF (Brew *et al*, 1997; Ellis *et al*, 1997); this finding does not argue in favour of HIV penetration of the CNS through blood-brain barrier leakage.

The absence of correlation between the CSF and plasma HIV viral load in patients with ADC is in agreement with the model proposed by Ellis *et al* (1997) who suggest that, during the asymptomatic phase of HIV infection, the virus found in the CSF is brought from the blood to the CNS by the intense trafficking of CD4+ infected cells through the blood-brain barrier, but that later on, CSF virus is produced by resident cells, mostly microglial cells. According to this scheme, it is difficult to understand the reduction of viral RNA in the CSF of patients treated with protease inhibitors during the late phase of infection, since these drugs have been reported to cross the blood-brain barrier with a poor efficiency (Flexner, 1998). Recently, however, therapeutic concentrations of indinavir have been reported in the CSF of patients under combination therapy (Flexner, 1998; Brinkman *et al*, 1998) and rapid decay of CSF HIV-1 RNA has been observed in such patients (Stellbrink *et al*, 1997).

Although we agree that HIV-1 RNA in the CSF cannot be used as a diagnostic marker for HIV encephalitis due to poor sensitivity, we report that CSF HIV RNA >4 logs is indicative of HIV dementia. The ten patients who had >4 logs of RNA copies/ml of CSF were more likely to have current ADC than the 29 subjects who had <4 (90% *versus* 45%, $P=0.01$). It is interesting to note that none of our patients presented acute meningitis, a pathology reported to be associated with high CSF viral loads in HIV patients (Morris *et al*, 1998).

Peripheral blood mononuclear cells cocultivated *in vitro* with HIV-infected monocytes were shown to release high levels of IFN-α (Gendelman *et al*, 1992). Moderately-increased levels of IFN-α were reported by Rho *et al* (1995) in the CSF of ADC patients. We found that the level of IFN-α in the CSF correlates both with CSF viral load and with the stage of dementia: this argues in favour of a role for interferon in ADC neuropathogenesis. In humans, the production of IFN-α by leukocytes is induced by viruses or virus-infected cells and is devoted to fighting against infection. Thus, high levels of IFN-α are transiently observed in the CSF during herpesvirus (HSV1 and HSV2, CMV, VZV) meningoencephalitis (Rozenberg and Lebon, 1991). In the absence of systemic opportunistic infection, high serum levels of IFN-α were also reported during primo-infection or end-stage HIV disease (Von Sydow *et al*, 1991), two situations in which HIV replication is intensive. Since we have excluded from the ADC group all the patients with opportunistic infection, we can assume that interferon secretion in ADC patients is related to HIV and not to other viral pathogens. The source of CSF IFN is mainly intracerebral though this is not clear in three patients who had high IFN levels in the serum and an altered blood-brain barrier (Table 2). We propose that interferon neurotoxicity might be due to chronic low secretion rather than to transient but high concentration of IFN in the CSF. Currently, IFN-α is approved for the treatment of 13 malignant or viral disorders (Gutterman, 1994).

Neurobehavioural changes such as depression, cognitive slowing, and impaired executive function have been reported in some patients although IFN-α was systemically administered; most of these symptoms are consistent with mild subcortical dementia (Valentine *et al*, 1998). Interestingly, Akwa *et al* (1998) report that transgenic mice with astrocyte-targeted expression of IFN-α develop a progressive encephalopathy with gliosis and calcifications of the basal ganglia. This animal model provides an example of the adverse effects of chronic intracerebral secretion of IFN-α. Also, the similarity between some features of ADC and those of Aicardi-Goutières syndrome, a progressive familial encephalopathy associated with persistent elevated levels of IFN-α in the CSF (Lebon *et al*, 1988; Goutières *et al*, 1998) could argue in favour of a role of interferon in the pathogenesis of AIDS dementia.

Overall, this study stresses the role of HIV-1 replication in damaging the central nervous system and especially in inducing atrophy of

the caudate nucleus in ADC patients; these effects may be mediated in part through the neurotoxicity of chronic low-level secretion of IFN-α. Highly active antiretroviral therapy, in reducing blood and CSF viral load might prevent the onset of ADC in AIDS patients. Further studies including virological and clinical follow-up on a larger number of patients will help to confirm these findings.

Patients and methods

ADC patients were recruited among 39 consecutive in-patients from the AIDS Unit, Medical Center St Martin du Tertre, France, who presented with intellectual deficiency, previous opportunistic disease and had a lumbar puncture for diagnostic purpose between February 1996 and February 1997. These 32 men and seven women were severely immunosuppressed (median CD4=33 per mm^3, range 4–390). Eighteen patients (46%) were untreated and eight were receiving highly active antiretroviral therapy including a protease inhibitor.

Neurological evaluation included clinical examination, neuropsychological tests for evaluation of cognitive status, MRI, lumbar puncture. Neurological diagnosis was established by a neurologist and an internist after reviewing all clinical, radiological and biological findings excluding HIV-1 RNA results. The diagnosis of ADC was based on the association of specific cognitive or motor impairment, MRI findings and the absence of any evolving CNS opportunistic infection or lymphoma. Patients with ADC were classified according to the Memorial Sloan Kettering staging scheme in grades 1–4 (Sidtis and Price, 1990).

HIV-1 RNA was quantified in plasma and CSF using the commercially available RT–PCR assay Amplicor HIV-1 Monitor (Roche Diagnostics Branchburg, NJ, USA). Within 4 h of collection, CSF samples were centrifuged, aliquoted and stored at −80°C until testing. Routinely, 200 μl of unconcentrated CSF were used for HIV-1 RNA quantitation. The CSF and plasma samples from a single patient were tested in the same run of experiments to avoid interassay variations. A log transformation of the results obtained in copy number per ml of fluid was performed to normalize the distribution. All values below the threshold of detection of 200 copies per ml were assigned a value of 100 copies for log calculations.

All the CSF samples were examined for the presence of bacteria, fungi and parasites by culture and for the presence of CMV and JC virus DNA by an in-house PCR. Depending on clinical presentation, some samples were tested by PCR for herpes simplex virus (HSV), VZV or EBV DNA. Integrity of the blood-brain barrier was evaluated by the albumin index as follows: albumin index=(CSF albumin/serum albumin) ×1000. Values above 7 were considered to reflect an increased permeability of the blood-brain-barrier.

IFN-α was measured in the serum and CSF of all the patients by a biological assay based upon cell protection from vesicular stomatitis virus (VSV) infection (Lebon *et al*, 1988). The sensitivity of this assay is 2 IU/ml of fluid and the results are highly reproducible. Briefly, serial twofold dilutions (50 μl) of samples were mixed with Madin-Darby bovine kidney cells (MDBK), plated in microtiter wells and incubated at 37°C. Twenty-four hours later, the cells were washed and challenged with VSV at a multiplicity of infection of 0.1 and incubated for 18 h. The titer was determined as the highest dilution of sample which protected 50% of the cell population. In order to obtain quantitative results, a calibrated positive control was included in each run of experiments.

Neuropsychological impairment was determined by the same neuropsychologist using mini mental status, HIV dementia scale, Trail making test (part A and B) and Rey figure (copy and memory).

MRI measures were performed by a single operator on a 1.5-tesla instrument (Siemens) using echo imaging to obtain T1 and T2 weighted images. Ventricle bifrontal (BFR) and bicaudate (BCR) ratios were calculated in the axial plane: these parameters estimate cerebral atrophy in the frontal horns and caudate nucleus regions, respectively (Dal Pan *et al*, 1992). Only CT scans were available for two patients.

Survival time was recorded in January 1998, 11 months after the last patient inclusion.

Statistical analysis was performed by calculating Spearman's rank correlation coefficients in order to compare continuous measures.

Acknowledgements

The authors thank Jean Bouyer for help with statistics and Jennifer Richardson for comments on the manuscript. This work was supported in part by a grant from Sidaction, Fondation pour la Recherche Medicale, Paris, France.

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