

Volume 12, issue 1, March 2001 | Articles originaux

Transforming growth factor beta-1 and interferon-alpha in the aids dementia complex: possible relationship with cerebral viral load?

Abstract

Mechanisms involved in the pathogenesis of the AIDS-dementia complex are still unclear. The dichotomy between a small number of HIV-infected cells in the brain and their marked dysfunction could be related to a cellular amplification and/or activation of cerebral viral load by several cytokines. This link between cytokines and viral load could play a role in the generation of the clinical

dementia syndrome. We have studied cerebral levels of transforming growth factor-beta1 and interferon-alpha, both in the mild and severe AIDS-dementia complex and also compared these cytokines with HIV RNA load in patients with different degrees of dementia. Our data indicate that production of different cytokines characterized the expression of clinical dementia. In the mild AIDS-dementia complex, there was a significant inverse correlation between interferon-alpha and transforming factor-beta1 ($r = -0.743$; $p < 0.001$), and HIV-RNA was present in inverse proportion to transforming growth beta1 ($r = -0.751$; $p < 0.001$). In patients with severe AIDS-dementia, transforming factor-beta1 was undetectable, while interferon-alpha level were higher than in mild AIDS dementia and correlated positively to cerebral HIV-RNA. No significant difference was evident between these cytokines in the serum of ADC patients and in the control samples. Our study suggests that a relationship is possible between productive HIV infection in the cerebral nervous system and a heterogenous and different expression of the immune response via a complex interaction of cytokines with a differential modulation of the dementia phenotype.

Full text

INTRODUCTION

A quarter to a third of HIV-infected subjects is affected by neurological manifestations that are a direct consequence of HIV-infection of the brain [1]. The cell type that is predominantly infected in the CNS is represented by mononuclear phagocytes such as brain macrophages, microglia and multinucleated giant cells and also astrocytes. The major question of the pathogenesis is related to the dichotomy between a small number of HIV-infected cells in the brain and the marked dysfunction of uninfected neurons. This suggests that a cellular amplification and/or activation is necessary for the production of viral and cellular toxins that lead to tissue injury and substained viral infection. Recent advances [2-4] in the understanding of the pathogenic mechanisms underlying the AIDS-dementia complex raise the possibility that several noxious substances - many of which are released by activated HIV-infected macrophages, microglia and astrocytes - may play a role in the generation of the clinical dementia syndrome. These substances may also include proinflammatory cytokines that participate in the neuronal injury. Most important among the cytokines produced by activated macrophages are tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta) [5-7], but a

significant role has been also assigned to many other cytokines [8-10]. Transforming growth factor-beta1 (TGF-beta1), which belongs to a large family of growth regulatory peptides, is produced by a wide variety of cells including platelets, lymphocytes, and macrophages, and may play a role in the regulation of many immunological processes [11-13]. TGF-beta1 is a multifunctional tissue regulator involved in a number of physiological and pathological functions, and its expression and secretion may be controlled by a variety of cytokines.

In particular, TGF-beta-1 can deactivate macrophages, and may play a critical role in the regulation of their cytokine production [14, 15]. Among the cytokines regulating the macrophages, the action of interferon-alpha (IFN-alpha) on TGF-beta secretion can be remarkable: Dhanani *et al.* [16] showed that IFN-alpha and TGF-beta had opposite activities on IFN-gamma (IFN-gamma). In fact IFN-alpha decreased TGF-beta expression in murine macrophages and stimulated IFN-gamma production, while TGF-beta had an inhibitory effect on IFN-gamma [16, 17]. At present, little information is available on the effect of HIV infection on cytokine synthesis *in vivo* within the brain. In this context, we have performed the present study to determine a possible link between TGF-beta1 and IFN-alpha and HIV load and the induction of the clinical expression of ADC.

PATIENTS AND METHODS

We studied 18 patients (6 females and 12 males, with a mean age of 31.0 years, range 24-46 yrs) with clinically defined ADC according to the criteria of Brew and Price [18] including either brain computed tomography scan or magnetic resonance imaging (MRI). Nine patients (4 females and 5 males, mean duration of the disease 4.0 years) were classified at the time cerebrospinal fluid (CSF) and blood samples were obtained, as 0.5 stage (mild stage). The other nine patients (2 females and 7 males, mean duration of the disease 5.5 years) were classified as 2 stage (severe stage). At the time of sampling, the median $CD4^+$ cell count of patients with mild ADC was $230 \pm 195 \times 10^6$, while the patients with severe ADC had $107 \pm 98 \times 10^6$.

The $CD8^+$ cell count was $527 \pm 239 \times 10^6$ and $679 \pm 415 \times 10^6$ in mild and severe ADC, respectively. The majority of patients (n = 13, 72%) had acquired HIV infection through injected-drug use, (n = 1, 1.5%) through homosexual contact and in (n = 4 patients, 22%) the mode of HIV transmission was unknown. Written informed consent was given by all patients included in the study. At the time of

the lumbar puncture, all ADC patients were treated with highly active, antiretroviral therapy (HAART) consisting of a combination of zidovudine, lamivudine and one protease inhibitor such as indinavir or ritonavir. We also studied 15 HIV negative subjects (six females and nine males) sex and age matched, with one of the following other neurological diseases (OND): degenerative disk problem, headache or ataxia. None of the patients had fever, upper respiratory or opportunistic cerebral infection during the study. Serum and CSF samples were obtained simultaneously from all patients. CSF was obtained by lumbar puncture and samples were collected in silicon-coated glass tubes. Xantochromic specimens and those with one red blood cell per field were excluded. In the CSF of all the patients and controls, cell count by phase contrast microscopy, glucose, protein, albumin and IgG by nephelometry, and microbiological analyses were performed; the IgG index according to the criteria of Link and Tibbling [19] was also calculated. We evaluated HIV RNA load by Monitor Amplicor Roche according to a standard procedure. The detection limit of this method was 500 copies/ml. Serum and CSF IFN-alpha and TGF-beta1 levels were detected by two ELISA assay kits (Medgenix, Fleurus, Belgium and Bender Medisystems, Wien, respectively). To determine IFN-alpha, precoated goat anti-rabbit antibodies were used to capture a specific cytokine complex in each sample, and consisted of cytokine antibody, standard or unknown, and biotinylated cytokine conjugate (competitive ligand), and a sample of the standard; this is a competitive reaction in which the samples of standards compete for antibody binding sites with the biotinylated cytokine. Therefore, as the concentration of cytokine in the samples increased, the amount of biotinylated cytokine captured by the antibody decreased. With the addition of streptavidin-conjugated alkaline phosphatase, substrate solution and amplifier solution, the amount of biotinylated cytokine was detected, resulting in an inverse relationship between OD and concentration: the higher OD is related to the lower concentration of cytokines in the sample. The sensitivity of IFN-alpha with this method was of 1 pg/ml. To measure TGF-beta1, another ELISA method was used. Briefly, TGF-beta1 was evaluated as follows: an anti-TGF-beta coating antibody was absorbed onto microwells. TGF-beta present in the sample or standard binds to antibodies absorbed onto the microwells. After a second incubation, a monoclonal anti-TGF-beta antibody was added, binding to TGF-beta captured by the first antibody. After a third incubation, unbound monoclonal anti-TGF-beta was removed during a wash step. An anti-mouse IgG-biotin conjugate was added, binding to the monoclonal anti-TGF antibody. After another incubation, the unbound anti-mouse IgG-biotin was removed: streptavidin-HPR was added, binding to the biotinylated anti-mouse IgG. After a

fourth incubation and a wash step a substrate solution reactive with HRP was added to the wells. A coloured product was formed in proportion to the amount of TGF-beta present in the sample. The reaction was terminated by the addition of aerol and absorbance was measured at 450 nm. A standard curve was prepared from six
TGF-beta standard dilutions and TGF-beta sample concentration was determined. With this method, the limit of detection was determined to be: 1.9 pg/ml. Statistical analysis was performed with the Wilcoxon rank sum test. The Spearman rank correlation coefficient was also used. The results are expressed as the mean ± SD.

RESULTS

No ADC patients had abnormal CSF glucose; mononuclear pleocytosis (number cells > 5×10^6/l) was present in ten ADC patients (range 10-15 x 10^6/l), five in stage 0.5 and five in stage 2.0. CSF/serum albumin ratio was increased in eight ADC patients in stage 2 and in two patients in stage 0.5. An elevated IgG index (> 0.7) was found in five ADC patients with advanced stage (2.0) of dementia. No correlation was present in either the mild or the advanced stage of ADC as regards cell count, albumin ratio and IgG index. All the controls had normal CSF findings (data not shown). None of the patients showed any opportunistic cerebral infections. CSF HIV-RNA was higher in the advanced ADC than in the mild ADC and the difference was statistically significant ($p < 0.001$). Moreover, HIV-RNA was detectable in all patients with advanced dementia, and was present in eight of nine patients with mild dementia. IFN-alpha was detected in the CSF of ADC patients, both in mild and in severe stage, but not in the controls, and IFN-alpha levels in ADC patients in the initial stage were significantly different from ADC patients with severe stage disease ($p < 0.001$) (Figure 1). Moreover, a significant inverse correlation was observed between IFN-alpha and TGF-beta1 in the CSF of patients with mild ADC ($r = - 0.940$; $p < 0.001$) while HIV RNA was in inverse proportion to TGF-beta1 ($r = - 0.838$; $p < 0.01$). Furthemore, the patients with severe ADC showed undetectable levels of TGF-beta1 but not in mild ADC. In patients with mild ADC both TGF-beta1 and IFN-alpha were detectable, but TGF-beta1 levels were higher than those of IFN-alpha. Moreover, IFN-alpha levels correlated positively ($r = 0.740$; $p < 0.001$) with HIV-RNA load. No statistically significant correlation was observed between CSF and serum TGF-beta and IFN-alpha levels in either mild or severe ADC (data

shown in Table 1). Finally the serum levels of IFN-alpha and TGF-beta1, both in mild and severe ADC, were not significantly different from the OND patients.

DISCUSSION

In this study, we have observed three interesting findings: a distinct cytokine secretion pattern in the different clinical expressions of the ADC, a significant and specific association between CSF HIV load and degree of ADC, and a relationship between TGF-beta1 and IFN-alpha influencing both the levels of HIV RNA and the degree of ADC. Taken together, these data suggest that different mechanisms may occur during the immune response in ADC: in the advanced stages, higher levels of IFN-alpha and HIV RNA are produced, while in the mild stages there is a preferential production of TGF-beta1 and a lower CSF HIV load. Moreover, both cytokines seem to be independent of serum levels and this suggests that IFN-alpha and TGF-beta1 can also be produced in the central nervous system tissue. In particular, TGF-beta1 seems to inhibit IFN-alpha production and possibly exerts a role in the regulation of the amplification of viral load. The balance between these cytokines *in vivo* and in the microenvironment in which they are produced, may be important in the regulation of the processes of cerebral inflammation. A recent pathogenetic model of ADC supports the hypothesis that interactions between neuroresident cells such as macrophages/microglia and astrocytes may play an important role in determining the production of substances with both harmful and beneficial effects in the brain [20]. In this context, the significant and specific association between CSF HIV RNA concentrations, the degree of encephalitis and cytokine expression could represent valuable tools for studying the natural course of HIV-related dementia and underline the role of the brain as a viral reservoir. Quantitative HIV RNA amplification techniques have been recently applied to the CSF of HIV-infected patients, and have demonstrated a correlation between CSF HIV concentrations and the presence and severity of ADC, as well as potential for monitoring the effects of HAART on the nervous system [21, 22]. This relationship between CSF HIV RNA levels and HIV-related neuropathological abnormalities could represent an important aspect in the search for a pathogenetic model of ADC. In our study, the relationship between HIV load and both IFN-alpha and TGF-beta1 may play an important role in supporting the hypothesis that neurological damage associated with HIV encephalitis is secondary to productive infection of macrophages/microglia. This is also consistent with the multiple biological activities of TGF-beta1 and IFN-alpha on

macrophages. In fact, the immunosuppressive role of TGF-beta1 on T and B cell proliferation, on IL-2 receptor production, and on cytokine production is well known [23]. Furthemore, it has been shown as an important negative autocrine regulator of IL-2-induced lymphocyte responses [13, 16], and has some neuroprotective properties. In this study, the role of IFN-alpha is seemingly paradoxical: this cytokine is a critical participant in host viral processes. It has been shown to have immunomodulatory, antiproliferative and antiviral effects [24]. An open label study has shown that it can delay progression and significantly prolong survival in HIV-associated, progressive multifocal leukoencephalopathy (PML) [25]. Moreover, other authors also report the role of IFN-alpha at high and low doses in the treatment of Kaposi's sarcoma (KS) [26]. Conversely, according to our study, a potential role of IFN-alpha in the progression of ADC has been demonstrated by Rho *et al.* [27]: increased cerebral production of IFN-alpha correlated to the greatest neurocognitive dysfunction. Moreover more recently, the role of HIV amplification in the brain has been demonstrated for other substances with Th1-like activity such as monocyte chemotactic protein-1 (MCP-1) [28]. In the study of Cinque *et al.*, a possible model of ADC pathogenesis was determined by the interaction between MCP-1 and cerebral load; in particular, the effects of this chemokine in the devopment of dementia was expressed by attracting mononuclear cells to the sites of cerebral inflammation. In this context, we suggest that an inihibitory effect of TGF-beta1 on other proinflammatory cytokines that have an important role in regulating the processes of inflammation in the ADC might be possible. Moreover, the simultaneous presence of IFN-alpha and TGF-beta 1 in the brain of patients with mild ADC suggests that TGF-beta1 may play a complex role in the regulation of cytokine production, suggesting that not all patways of cytokine gene activation are susceptible to inhibition by TGF-beta1. This possibility is evident in other pathogenetic models of human diseases such as relapsing-remitting multiple sclerosis in which TGF-beta1 down regulated multiple sclerosis expression *via* a complex interaction with ICAM-1 [29]. The inhibitory effect of TGF-beta1 on the proinflammatory cytokines could explain the down-regulation of HIV production in the brain: this cytokine influences the polarization of Th2-like immune responses and induces a lower effect on HIV amplification as reported by others [30]. From these findings, it seems that viral invasion and subsequent replication are necessary, but not sufficient to induce an important clinical neurological injury, without the interaction of the immune response. On the basis of these data critical issues in the pathogenesis of ADC could be the role of the environment on individual immune responses during the course of HIV disease, and the role of new potent antiretroviral drugs in

regulating the cerebral viral load. In conclusion, our study indicates that a relationship between viral load in the CNS and the immune response can determine a dynamic process in which ADC can have different phenotypic expression. Our data also suggest a rationale for the possible control of ADC by acting on the regulatory cytokine balance, including the possible direct use of exogenous TGF-beta1 as a therapeutic tool to block the cascade of events leading to inflammation and macrophage activation.

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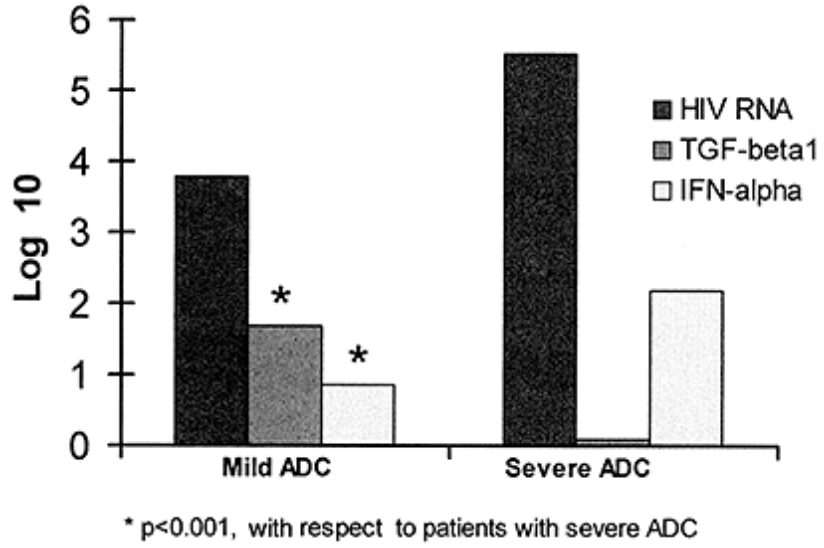


Figure 1

Mean of HIV-RNA, TGF-beta1 and IFN-alpha in the cerebrospinal fluid of patients with both mild and severe AIDS-dementia complex (ADC).

The values are expressed as log 10 for TGF-alpha and IFN-alpha as pg/ml for HIV-RNA as copies/ml.

* p < 0.001, with respect to patients with severe ADC.

Table 1
CSF and serum levels of TGF-beta and IFN-alpha in patients with mild to severe ADC and controls

	TGF-beta		IFN-alpha	
	CSF	Serum	CSF	Serum
Mild ADC	66 ± 50*	14 ± 3	30 ± 46*	1 ± 1.2
Severe ADC	UD	15 ± 2	176 ± 71	1.5 ± 1.6
Controls	UD	16 ± 3	UD	1.1 ± 1.3

* p < 0.001 with respect to patients with severe ADC.
UD: undetectable.
The values are expressed as (m ± DS).

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