Cerebrospinal fluid concentration of fibronectin in patients with HIV-1 infection and central nervous system disorders

D Torre, C Zeroli, G Ferrario, G Bonetta, G P Fiori, R Martegani

Abstract

Aims—To evaluate the fibronectin concentrations in the cerebrospinal fluid of HIV-1 infected patients with central nervous system disorders.

Methods—Fibronectin was determined by an immunoturbidimetric assay in 41 HIV-1 infected patients with AIDS dementia complex, progressive multifocal leucoencephalopathy, and opportunistic infections.

Results—A significant decrease in fibronectin concentrations in the cerebrospinal fluid of patients with AIDS and dementia complex and progressive multifocal leucoencephalopathy was observed, as well as in those with opportunistic infections of the central nervous system (p < 0.0001). In particular, a significant decrease in fibronectin concentration in cerebrospinal fluid was observed in patients with cerebral toxoplasmosis and cryptococcal meningitis (p < 0.0001).

Conclusions—Because fibronectin can bind to several viruses, fungi, and protozoa, it is conceivable to suppose that the consumption of fibronectin in the cerebrospinal fluid of patients with neurological disorders may be related to the binding of fibronectin to HIV itself, or to viral proteins, or to organisms responsible for opportunistic infections.

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Fibronectin is a 420 kilodalton glycoprotein, comprising two similar subunits. It is present as a soluble dimer in plasma (circulating fibronectin) and as an insoluble multimer in the basement membrane and intercellular matrix (cellular fibronectin).1,2 Fibronectin is present in virtually all body tissues and fluids and is involved in adhesion, spreading, and phagocytosis.3,4 Decreased fibronectin concentrations have been shown in patients after burns, trauma, or sepsis.5,6 We have recently shown a significant decrease in circulating fibronectin concentrations in patients with AIDS and AIDS-related complex (ARC).7 Fibronectin concentrations were noticeably decreased in patients with Pneumocystis carinii pneumonia. Some investigators have observed that human cerebrospinal fluid contains fibronectin that is immunologically indistinguishable from the circulating form.8 Weller et al9 showed increased cerebrospinal fluid fibronectin concentrations in patients with bacterial meningitis and with tick-borne encephalitis. More recently, we observed decreased cerebrospinal fluid fibronectin concentrations in patients with aseptic meningitis.10

The measurement of fibronectin could be of some diagnostic and prognostic value in several disorders of the central nervous system and in particular in HIV-1 infected patients with neurological complications. Although fibronectin cannot be considered an acute phase protein, its determination in the cerebrospinal fluid could be of some help in the diagnosis and prognosis of central nervous system disorders in HIV-1 infected patients.

Methods

The study population comprised 41 HIV-1 infected patients with central nervous system disorders: five HIV-1 asymptomatic seropositive patients with cognitive changes and abnormalities on cerebral tomography scanning (mean (SD) age 29-8 (5-1) years); 14 patients with AIDS dementia complex (mean age 28-9 (3-9) years); four patients with suspected progressive multifocal leucoencephalopathy (mean age 28-5 (3-5) years); and 18 patients with other opportunistic infections, of whom 11 had cerebral toxoplasmosis (mean age 28-5 (3-5) years), two patients had mycobacterial meningitis caused by Mycobacterium avium-intracellulare (mean age 30-5 (2-1) years), and five had cryptococcal meningitis (mean age 35-8 (17-3) years).

Central nervous system disorders were diagnosed on various clinical, radiological, and laboratory grounds. Asymptomatic HIV-1 seropositive patients were included, and lumbar puncture was performed on admission, as they had minor behavioral and cognitive changes, together with initial signs of cerebral atrophy detected by cerebral tomography scanning. In particular, diagnosis of AIDS dementia complex was based on persistent cognitive impairment, impaired motor performance, behavioral changes, and radiological abnormalities, including progressive, severe cerebral atrophy and abnormalities of white matter or basal ganglia or thalamus. Diagnosis of progressive multifocal leucoencephalopathy was based on clinical and radiological findings. Magnetic resonance imaging scans showed large lesions of white matter, adjacent to the cortex, without enhancement, and unaccompanied by mass...
effect. Mycobacterial meningitis was diagnosed by detection of organisms in the cerebrospinal fluid. Cryptococcal meningitis diagnosis was based on direct detection of organisms in the cerebrospinal fluid and cryptococcal antigens in serum and cerebrospinal fluid.

Twenty subjects served as controls. Cerebrospinal fluid samples from control subjects were collected by lumbar puncture when myelography was carried out, which was performed in subjects with low back pain. p24 antigen was investigated in the cerebrospinal fluid of all patients using an enzyme immunoassay (Abbott Diagnostics, North Chicago, Illinois, USA). Cerebrospinal fluid samples were immediately stored at \(-20^\circ\mathrm{C}\). It should be noted that fibronectin may be considered a stable molecule, as freezing or thawing do not alter its concentration either in serum samples or in cerebrospinal fluid taken from healthy volunteers (personal data).

Fibronectin was determined in cerebrospinal fluid samples by an immunoturbidimetric assay (Boehringer Biochemica, Mannheim, Germany). Turbidimetric measurement of the antigen-antibody reaction was performed according to the principle of the endpoint method. All samples from one patient were analysed in duplicate in the same assay.

All data were expressed as mean and standard deviations. Comparisons with the various groups of patients was performed by one way analysis of variance (ANOVA). P values of \(<0.05\) were considered significant.

Results

Table 1 shows the general characteristics of patients with AIDS and central nervous system disorders. The presence of HIV antigen in the cerebrospinal fluid of these patients is also shown. Eighteen of 41 HIV-1 infected patients had central nervous system opportunistic infections, and cerebral toxoplasmosis was the most common infection. All patients were drug misusers except for two who were homosexual.

Table 2 shows the fibronectin concentrations in the cerebrospinal fluid of patients with AIDS and central nervous system disorders. A significant decrease in fibronectin concentrations was observed in patients with progressive multifocal leucoencephalopathy and in those with AIDS dementia complex (\(p < 0.0001\)). In patients with central nervous system opportunistic infections cerebrospinal fluid fibronectin concentrations were significantly decreased as well.

Table 3 shows the cerebrospinal fluid fibronectin concentrations in patients with fungal or mycobacterial infections. Decreased fibronectin concentrations were noted in patients with cerebral toxoplasmosis and cryptococcal meningitis (\(p < 0.0001\)). A smaller decrease in cerebrospinal fluid fibronectin concentrations was observed in patients with mycobacterial meningitis.

Discussion

There was a substantial decrease in fibronectin concentrations in the cerebrospinal fluid of patients with AIDS dementia complex and less noticeable decreases in patients with opportunistic infections and progressive multifocal leucoencephalopathy. The origin of cerebrospinal fluid fibronectin has not yet been clearly elucidated. Fibronectin represents about 2% of the corresponding components found in blood. Although it is not clear if fibronectin in cerebrospinal fluid is a result of local production, astrocytes produce large amounts of fibronectin. Weller et al. have shown that in bacterial meningitis fibronectin is synthesised intrathelially as a reaction by the tissue damaged during the underlying infective process. We also suggest that increased fibronectin concentrations in bacterial meningitis could be related to de novo synthesis of fibronectin by neutrophils which have accumulated in the cerebrospinal fluid. Decreased fibronectin concentrations were noted, however, in the cerebrospinal fluid of patients with aseptic meningitis. Fibronectin can interact directly with some fungi, protozoa, several viruses (influenza A virus, parainfluenza virus type 1 and mumps virus), and the envelope glycoproteins of various viruses. More recently, we have shown, in vitro, a direct binding of fibronectin to HIV-1 infected cells and to viral proteins, including glycoproteins 120

<table>
<thead>
<tr>
<th>Table 1</th>
<th>General characteristics of HIV-1 infected patients with central nervous system disorders and controls</th>
</tr>
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<tbody>
<tr>
<td>(N=)</td>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>Controls</td>
<td>20</td>
</tr>
<tr>
<td>Asymptomatic seropositives</td>
<td>5</td>
</tr>
<tr>
<td>AIDS dementia complex</td>
<td>14</td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
<td>4</td>
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<tr>
<td>Cerebral toxoplasmosis</td>
<td>11</td>
</tr>
<tr>
<td>Mycobacterial meningitis</td>
<td>2</td>
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<tr>
<td>Cryptococcal meningitis</td>
<td>5</td>
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</tbody>
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<table>
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<tr>
<th>Table 2</th>
<th>Mean (SD) fibronectin concentration in cerebrospinal fluid of HIV-1 infected patients with neurological disorders and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=)</td>
<td>Fibronectin ((\mu\mathrm{g/ml}))</td>
</tr>
<tr>
<td>HIV negative controls</td>
<td>(20)</td>
</tr>
<tr>
<td>Asymptomatic seropositives</td>
<td>(5)</td>
</tr>
<tr>
<td>AIDS dementia complex</td>
<td>(14)</td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
<td>(4)</td>
</tr>
<tr>
<td>Opportunistic infections</td>
<td>(18)</td>
</tr>
</tbody>
</table>

\(p < 0.0001\) (ANOVA)

*Normal range of fibronectin concentration in the cerebrospinal fluid of control patients was 4-0-8-0 \(\mu\mathrm{g/ml}\).
Fibronectin concentrations in HIV-1 seropositive patients with CNS disorders

and 41 (Pugliese A, et al, abstract presented at VIII International Conference on AIDS, Amsterdam, 1992). The significant decrease in cerebrospinal fibronectin concentrations in patients with AIDS dementia complex or with progressive multifocal leukoencephalopathy could be related to the ability of fibronectin to bind to HIV itself or to viral proteins. In the same way, binding of fibronectin to Toxoplasma gondii, Cryptococcus neoformans, or Mycobacterium species could increase consumption of fibronectin in the cerebrospinal fluid of patients with opportunistic infections.

As accumulation of neutrophils in patients with viral or cryptococcal, mycobacterial, and toxoplasma meningitis is rarely observed, de novo synthesis of fibronectin by neutrophils does not seem to be likely in these conditions. Thus the consumption of fibronectin caused by binding to viral, fungal, or protozoal organisms may exceed intrathecal production due to the reaction of the tissue damaged by these agents.

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