Myelin basic protein in the cerebrospinal fluid of patients infected with HIV

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Summary. The major pathological abnormalities of HIV encephalopathy are infiltrates of macrophages, multinucleated giant cells, microglial nodules and demyelination. Elevated myelin basic protein (MBP) levels in the cerebrospinal fluid (CSF) provide a marker for central nervous system demyelination. The purpose of this study was to investigate the possible role of CSF MBP as a useful and early marker for HIV encephalopathy. The CSF of 40 consecutive patients with HIV infection of various clinical stages was investigated, including 13 patients with clinical signs of HIV encephalopathy. CSF MBP was elevated in 2 patients (5.0 and 5.3 ng/ml), both of whom had moderate to severe HIV encephalopathy. The course of the disease was rapid in both patients. In the remaining 38 patients, CSF MBP levels were marginally elevated ($n = 12$) or normal ($n = 26$). Our results suggest that CSF MBP is not a sensitive marker for the diagnosis and evaluation of HIV encephalopathy, but may be an indicator of prognosis for the course of the disease. There were only few findings of elevated CSF MBP levels in patients with HIV encephalopathy in the current study, and this may be because the disorder progressed slowly in most patients. It is possible that CSF MBP levels in HIV encephalopathy may only be elevated with acute clinical deterioration but are normal in slowly progressive forms of demyelination, as seen in multiple sclerosis.

Key words: Myelin basic protein – AIDS – HIV encephalopathy

Introduction

Neurological disorders have been reported in approximately 40% of adult AIDS patients [11, 22]. However, up to 70%–80% of adult AIDS patients have been shown to have neuropathological abnormalities in autopsy-based surveys [14, 19]. The most frequent and most important cause of neurological morbidity in HIV-infected patients is HIV encephalopathy [7]. There is increasing evidence that this disorder, which has also been referred to as subacute encephalitis [17, 19] or AIDS dementia complex [15, 16, 20], is caused by direct HIV brain infection. The white matter and subcortical structures of the cerebral hemispheres are most severely involved with relative sparing of the cortex [8, 14, 18, 19]. The major pathological abnormalities are infiltrates of macrophages and multinucleated giant cells and microglial nodules. Involvement of the white matter appears either as diffuse leucoencephalopathy with severe loss of myelin or as small paravascular foci of demyelination [5, 8, 10, 16]. De la Monte et al. [5] reported demyelination in 44% of autopsy cases with HIV encephalopathy.

Elevated myelin basic protein (MBP) levels within the cerebrospinal fluid (CSF) provide a marker for central nervous system demyelination, as has been shown in patients with relapsing-remitting multiple sclerosis [3, 13, 24]. The purpose of the present study was to investigate if CSF MBP has a role as a useful and early marker for HIV encephalopathy. We investigated CSF samples of 40 consecutive patients with HIV infection of various clinical stages, including 13 with clinical signs of HIV encephalopathy.

Patients and methods

Seven of the HIV-positive persons were clinically healthy (stage WR 1), 22 suffered from the lymphadenopathy syndrome or the AIDS-related complex (WR 2-5) and 11 had full-blown AIDS (WR 6). Clinically manifest HIV encephalopathy was diagnosed in 13 patients. Symptoms of mental deterioration ($n = 11$) and/or pontomesencephalic or cerebellar dysfunction ($n = 4$) were used as diagnostic criteria (Table 1). Opportunistic conditions, including both infections and neoplasms, were not evident in these 13 patients with HIV encephalopathy.

CSF and serum samples were collected from 40 HIV-positive patients. Oligoclonal IgG bands were detected by isoelectric focusing. The samples were concentrated and run on a polyacrylamide gel at a pH gradient of 3–9 (Phast-System; Pharmacia, Uppsala, Sweden). The gels were stained with Coomassie blue. The ratio CSF albumin/serum albumin was used as an indicator of blood-CSF-barrier permeability. A commercial ELISA was used to determine IgG antibody titres to HIV. A CSF/serum quotient of IgG-related HIV antibodies above 1.5 was considered to indicate intrathecal production of HIV antibodies [12]. MBP in CSF was determined using a commercial, competitive radioimmunoassay (Biodata; Milan,

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Table 1. Clinical data of 40 HIV-infected patients

Patient	CSF findings						Neurological findings	Neurological diagnosis
	WR-stage	MBP	Cells/μl	Albumin ratio	Oligoclonal bands	HIV antibody:IgG ratio		
1.	1	2.2	146	9.8	+	8.6	Dissociated nystagmus	Neurosyphilis
2.	1	2.8	1	1.6	−	0.1	Normal	
3.	1	3.0	4	5.5	+	3.1	Normal	
4.	1	3.0	4	7.1	−	ND	Normal	
5.	1	3.1	3	8.9	+	ND	Normal	
6.	1	3.7	5	4.8	+	1.1	Normal	
7.	1	4.1	4	3.5	−	0.8	Normal	
8.	2	2.7	4	4.0	+	6.3	Dissociated nystagmus	HIV encephalopathy
9.	2	2.8	21	3.7	+	2.7	Normal	
10.	2	2.9	13	5.5	−	0.3	Normal	
11.	2	2.9	12	3.4	+	1.6	Normal	
12.	2	2.9	2	4.0	−	1.1	Normal	
13.	2	3.0	28	6.2	+	1.7	Normal	
14.	2	3.0	6	2.5	+	3.6	Normal	
15.	2	3.0	2	3.5	−	0.1	Horizontal gaze evoked nystagmus (tranquillizer abuse)	Tranquillizer induced nystagmus
16.	2	3.1	5	4.5	+	ND	Horizontal gaze evoked nystagmus	HIV encephalopathy
17.	2	3.7	ND	7.9	+	ND	Normal	
18.	3	2.5	3	5.2	+	1.0	Peripheral facial palsy right	Aseptic meningitis
19.	3	2.8	35	7.7	+	2.1	Normal	
20.	3	3.0	12	5.4	+	2.6	Normal	
21.	3	3.2	1	2.8	+	1.7	Normal	
22.	3	3.6	7	5.4	−	0.3	Normal	
23.	4	2.9	9	7.1	+	0.1	Spontaneous nystagmus left and upward, horizontal gaze evoked nystagmus	CNS toxoplasmosis
24.	5	2.3	1	8.3	+	1.9	Motor, mental and behavioral disorder, absent tendon reflexes, pallhypaesthesia	HIV encephalopathy, polyneuropathy
25.	5	2.4	2	3.1	+	ND	Normal	
26.	5	2.7	5	4.3	+	0.9	Mental disorder	HIV encephalopathy
27.	5	2.9	3	3.1	−	3.5	Normal	
28.	5	3.1	2	7.1	−	0.3	Mental disorder, dissociated nystagmus, cerebellar ataxia	HIV encephalopathy
29.	5	3.7	18	7.7	+	18.4	Mental disorder, horizontal gaze evoked nystagmus	HIV encephalopathy
30.	6	2.1	12	5.5	−	0.7	Normal	
31.	6	3.2	20	6.8	+	1.0	Mental, behavioral disorder	HIV encephalopathy
32.	6	3.4	1	6.6	+	5.5	Normal	
33.	6	3.4	1	6.8	+	3.5	Mental disorder	HIV encephalopathy
34.	6	3.4	1	5.8	−	ND	Mental disorder	HIV encephalopathy
35.	6	3.7	1	4.4	+	ND	Mental disorder	HIV encephalopathy
36.	6	4.1	32	9.3	+	ND	Headache, stiff neck	Cryptococcal meningitis
37.	6	4.3	1	4.0	+	3.8	Mental disorder, hyporeflexia, pallhypaesthesia	HIV encephalopathy, polyneuropathy
38.	6	4.3	4	3.5	+	3.2	Convergence nystagmus	CNS toxoplasmosis
39.	6	5.0	1	17.5	+	0.3	Mental disorder	HIV encephalopathy
40.	6	5.3	1	3.8	+	1.8	Mental disorder, spastic paraparesis, urinary incontinence	HIV encephalopathy, myelopathy

ND = Not done

Italy). Fifty microlitres of a histone solution (2.5 ng/ml) was added to 500 μl fresh CSF sample to prevent adhesion. The samples were stored at −18°C until they were analysed. The reference range for MBP in CSF was defined as follows: up to 3.4 ng/ml, normal; 3.4–4.6 ng/ml, marginal; and above 4.6 ng/ml, elevated.

Results

CSF abnormalities were detected in 32 patients (80%). Oligoclonal IgG bands were found in the CSF of 29 patients (73%); 18 of 24 patients with oligoclonal IgG bands in the CSF had evidence of intrathecal HIV antibody production.

Lymphocytic pleocytosis ranging from 5 to 146 cells/μl was present in 17 patients and an elevated ratio of CSF albumin/serum albumin (> 7.5) in 8 patients.

CSF MBP was elevated in two patients (5.0 and 5.3 ng/ml), both suffering from full-blown AIDS. One of these patients presented with severe dementia and a history of oesophagitis. The other patient had a history of *Pneumocystis carinii* pneumonia and presented with moderate dementia and severe myelopathy which could not be attributed to any condition other than HIV infection. Neurological symptoms had progressed rapidly over a few months in both patients. In the remaining 38 patients, CSF MBP levels were marginally elevated ($n = 12$) or normal ($n = 26$). There was no significant correlation between elevated (including marginally elevated) CSF MBP levels and intrathecal HIV antibody production, oligoclonal IgG bands, or lymphocytic pleocytosis (chi-square test, $P > 0.05$).

Discussion

Elevated levels of CSF MBP secondary to acute myelin breakdown are present in many patients with active disease of the nervous system, e.g. multiple sclerosis, tranverse myelitis, central pontine myelinolysis [3, 25]. In the current study elevated MBP CSF levels were detected in only 2 patients, both of whom presented with moderate to severe HIV encephalopathy. In the other 11 patients with HIV encephalopathy as well as in 27 HIV patients without clinically apparent HIV encephalopathy, only marginally elevated or normal MBP levels were found. There was no significant correlation between CSF MBP levels and intrathecal HIV antibody production. Our results suggest that CSF MBP is not a sensitive marker for the diagnosis and evaluation of HIV encephalopathy.

The rapidity of demyelination seems to influence MBP levels in the CSF, as is known from studies in multiple sclerosis [2, 4, 13]. In multiple sclerosis elevated MBP was usually detected in the CSF of patients during acute exacerbations of the disease. MBP was not detected in the CSF of any patient with a slowly progressive form of multiple sclerosis. It was speculated that in slowly progressive demyelination CSF MBP might be degraded by macrophages or proteinases or inactivated by antibodies, thus preventing elevation of MBP [1, 6, 13, 21, 23]. The rare finding of elevated CSF MBP levels in patients with HIV encephalopathy in the current study may be explained by the fact that the disorder is more often chronically progressive than subacute in its evolution [20]. It must be stressed that in the current study the clinical course of HIV encephalopathy in the 2 patients with elevated CSF MBP levels differed from that of the other patients with HIV encephalopathy in that both suffered rapidly progressive dementia. Since CSF MBP is elevated in acute exacerbations of multiple sclerosis as well as in rapid progressive cases of HIV encephalopathy, we think that an elevated CSF MBP level may be a prognostic marker for the course of HIV encephalopathy.

Previous studies in patients with other neurological diseases have shown that CSF MBP is not a specific marker. Other neurological disorders affecting the CNS in HIV-infected patients, such as progressive multifocal leucoencephalopathy [25] or herpes simplex encephalitis [9], may also cause elevated CSF MBP levels. Furthermore, combinations of HIV encephalopathy and opportunistic infections may occur, which complicate the interpretation of elevated CSF MBP levels.

We conclude that CSF MBP is not a sensitive marker for HIV encephalopathy. The significance of normal and marginally elevated CSF MBP levels with respect to demyelination is unknown. Elevated CSF MBP levels may indicate a rapidly progressive course of HIV encephalopathy provided that other CNS disease is not present.

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