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Development of Subtle Neurological Signs after Systemic Illness in HIV-Infected Individuals

Key Words
HIV-1 infection
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Abstract
Thirty human immunodeficiency virus (HIV) infected individuals entered a longitudinal study without signs of dysfunction of the central nervous system (CNS). Nine of these individuals developed a systemic illness between study visits, and 7 of these 9 patients (78%) had neurological signs at the next examination (e.g., action-intention tremors, abnormal gait, release signs, abnormal deep tendon reflexes). Only 2/21 (9.5%) of the subjects who did not develop systemic illness showed such signs. These data are consistent with the hypothesis that other factors (e.g. cytokines) as well as the HIV may cause subtle CNS dysfunction.

Introduction

During the course of infection with the human immunodeficiency virus (HIV), more than 65% of the patients exhibit overt neurological dysfunction or develop multiple neurological syndromes [1–5]. Among the most common manifestations are HIV encephalopathy [2, 3] and the HIV-associated cognitive/motor complex [4]. These patients exhibit progressive cognitive and motor dysfunction that may eventually lead to dementia. The early neurological manifestations of an HIV encephalopathy are often mild; there may be no cognitive deficits, but subtle neurological signs such as abnormal eye movements, slowing of fine motor skills and brisker deep tendon reflexes in lower limbs may be present [1–3].

The relationship between neuropathological changes and HIV-related neurological signs is complex. Multinucleated giant cells, macrophages and microglia are found in less than 50% of the brains of patients with dementia at autopsy [5], but all brains of demented patients may have abnormal viral burden indicating HIV encephalitis [6]. Further, HIV encephalitis may exist for a period of time before the development of frank symptomatology [6, 7]. In addition to HIV itself, a progressive diffuse leukoencephalopathy or 'diffuse myelin pallor', or the effect of neurotoxic substances that are able to cross the blood-brain barrier (e.g., glycoprotein 120, interleukin-1 beta, tumor necrosis factor alpha, quinolinic acid) have been proposed as playing at least a partial role in the etiology of HIV-related symptomatology [1–3].

One approach that may help to understand the etiology of HIV-related neurological signs and symptoms is to determine the relationship between systemic infections and symptomatology of the central nervous system (CNS). To the extent that there is a strong association between new systemic illness and subsequent signs of neu-

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Table 1. Clinical characteristics of the patients

Case	Age/sex	CD4+ (V1/V2)[1]	CDC[2]	Systemic illness	New neurological symptoms
Patients who experienced systemic illness and developed CNS neurological signs					
1	28/M	728/NA	C	hepatitis B	snout reflex
2	32/M	726/624	B	febrile syndrome and massive GI bleeding	snout reflex
3	37/M	NA/168	B	oral candidiasis, oral hairy leukoplakia, bacterial pharyngitis	action-intention tremors, unstable tandem, snout reflex
4	42/M	582/555	A	toxoplasmosis	snout reflex, plantar response was neutral, bilaterally
5	41/M	44/15	C	exacerbation of KS, oral candidiasis, wasting syndrome	action-intention tremors, snout, glabellar and palmomental reflexes, wide-based gait, ataxic tandem
6	23/M	530/482	C	viral pneumonitis, oral candidiasis	action-intention tremors, palmomental reflex, unstable tandem
7	32/M	162/NA	C	PCP	action-intention tremors, snout and palmomental brisker DTRs, symmetric
Patients who developed systemic illness without neurological signs					
8	39/M	271/144	B	hepatitis A, oral candidiasis	none
9	46/M	555/547	C	bacterial pneumonia	none
Patients who exhibited CNS neurological signs but did not experience systemic illness					
10	29/M	769/581	A	none	snout reflex
11	43/M	202/271	A	none	palmomental reflex, ataxic tandem

NA = Not available; DTRs = deep tendon reflexes; GI = gastrointestinal; KS = Kaposi's sarcoma; PCP = *P. carinii* pneumonia.

[1] CD4+ cell count at baseline (V1) and at the visti following the illness (V2).

[2] CDC stage at study entry [9].

rological dysfunction, this would argue in favor of the role of non-HIV factors (e.g. cytokines) in the CNS symptomatology.

Material and Methods

Thirty HIV-infected individuals (29 men, 1 woman), participating in the Allegheny Neuropsychiatry Survey [8], were selected for study based on a neurological and neuropsychological exam. They were free of abnormalities at study entry. The subjects ranged in age from 22 to 49 (mean 35.4 ± 6.6). Fifteen of them were clinically asymptomatic or had lymphadenopathy only (CDC Classification System, stage A) [9]. Five had constitutional disease or minor opportunistic infections (stage B) and 10 had nonneurological acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections (stage C). Eight of the 30 patients had had AIDS-defining CD4 counts (i.e. below 200). Their CD4+ cell counts ranged from 44 to 1,568 (mean 529.1 ± 215.3) at baseline. All patients received three structured neurological and neuropsychological examinations within a 1-year interval. Psychiatric illness was assessed in each patient with the Structured Clinical Interview for DSM-III-R [10]. None of the patients met criteria for major depression, bipolar disorder or psychoactive substance abuse/dependence at study entry.

Table 2. Clinical characteristics of the patients with and without systemic illness and CNS neurological signs

	Patients with systemic illness and neurological signs (n = 7)		Patients without systemic illness or neurological signs (n = 19)	
	baseline	follow-up	baseline	follow-up
Age[1]	33.7 ± 6.8	–	35.8 ± 6.9	–
AIDS (%)[2]	3 (43)	4 (57)	4 (21)	4 (21)
CD4[3]	459 ± 294[4]	240.5 ± 295[4]	547 ± 370[5]	487 ± 322[5]
CDC staging [9] (%)				
A	1 (14)[6]	0 (0)	12 (63)[6]	11 (63)
B	2 (28.5)	3 (43)	2 (10.5)	2 (10.5)
C	4 (57)	4 (57)	5 (26)	6 (31.5)
Number of patients on medication (%)				
Antiviral	4 (57)	5 (71)	13 (68)	12 (63)
Antibiotic	2 (28)	4 (57)	4 (21)	5 (26)
Antifungal	2 (28)	4 (57)	4 (21)	5 (26)
Sedatives-hypnotics	1 (14)	0 (0)	1 (5)	2 (10.5)
Antidepressants	0 (0)	0 (0)	2 (10.5)	3 (16)

1 t test ($p > 0.05$).
2 Fisher's exact test ($p > 0.05$).
3 There was no significant difference between groups [$F(1, 17) = 0.26$, $p = 0.61$], and no interaction between groups and visits [i.e., baseline vs. follow-up; $f(1, 17) = 0.59$, $p = 0.45$].
4 4 subjects.
5 16 subjects.
6 Fisher's exact test: $p = 0.03$.

We defined systemic illness as those viral, fungal or bacterial infections which required hospitalizations and/or therapeutic intervention. These included the exacerbation or recurrence of a preexisting AIDS-defining illness such as Kaposi's sarcoma or *Pneumocystis carinii* pneumonia. One patient developed gastrointestinal hemorrhage secondary to ulcers in the duodenum, stomach and esophagus mucosa, associated with high fever. The etiology of his disease process could not be clarified, but was classified as systemic illness for this study. None of these patients developed hepatic encephalopathy during the follow-up.

Results

Nine patients developed systemic illness during the follow-up, while 21 patients did not. Seven of the 9 patients (78%) with systemic illness had new neurological signs at the study visit immediately following the illness (see table 1). Of the 21 patients who did not have systemic disease, only 2 (9.5%) developed neurological signs, which is significantly different from the rate seen among those patients who had an illness (Fisher's exact test, $p = 0.0001$). There were no significant differences in terms of age or CD4+ cell count between patients who had systemic illness and developed neurological signs (n = 7) and those who did not have any illness, and did not develop any signs (n = 19). When we compared the frequency of patients who exhibited subtle neurological signs among different stages of the CDC Classification System [10] at baseline, patients in stage A (Fisher's exact test, $p = 0.03$) developed fewer neurological signs than those in stages B or C. The frequency of patients on antiviral, antibiotic, antifungal, sedative-hypnotic or antidepressant medication was not statistically different (table 2).

Analysis of the neuropsychological data using repeated-measures ANOVAs did not yield significant differences between groups (i.e., patients with signs and systemic illness vs. patients without signs or systemic illness) on any of the neuropsychological measures at either baseline or follow-up. There were no significant differences in terms of rate of change over time between groups, except in the Visual Reproduction Task [11] [$F(1, 25) = 4.7$, $p = 0.04$]. Results of the cognitive measures are shown for both groups of patients at baseline and follow-up in table 3.

Table 3. Neuropsychological characteristics of the patients with and without systemic illness and neurological signs (means ± SD)

	Baseline score		Follow-up score	
	with signs	without signs	with signs	without signs
Free recall (total) [15]	33.7±7.5	36 ±6.4	36.7±6.4	33.8±5.3
Visual reprod. (immediate) [11]	38.1±2.7	36.8±4.1	37.2±4.6	36.8±4.4
Visual reprod. (delayed)[1] [11]	32.8±8.2	33.7±5.6	28.7±10.2	35.6±4.5
Visual reprod. (copy) [11]	40.0±1.7	39.9±1.2	39.5±2.9	39.9±1.5
Digit symbol substitution [11]	59.1±21.0	66.7±17.6	62.1±17.6	70.6±12.9
Verbal fluency (FAS) [16]	51.7±14.1	39.3±11.7	50.7±15.8	41.8±13.1
Trailmaking A (time) [17]	25.2±8.4	23.6±6.3	25.5±5.8	22.4±5.2
Trailmaking B (time) [17]	66.4±35.8	55.1±22.2	51.0±21.0	49.1±18.1
Pursuit rotor [18] (time on target)				
Block 1	17.7±5.4	25.8±17.7	26.5±20.1	24.6±11.9
Block 6	44.5±16.2	51.3±14.7	45.7±23.2	52.4±12.4

[1] Repeated-measures ANOVA showed a group-time interaction (F = 4.7, d.f. = 1,22, p = 0.04).

Discussion

Seventy-eight percent of the patients entering the study and who had no neurological signs developed them after suffering a nonneurological systemic illness. Whether these neurological signs emerged because of a direct effect of HIV on the CNS is difficult to know without pathological confirmation. However, these data are consistent with the concept that the HIV is not the single cause of CNS damage, but may trigger a cascade of events leading to subtle changes of the CNS. For example, there may be alterations in the blood-brain barrier following systemic disease; several mechanisms of blood-brain barrier dysfuncion and subsequent CNS damage have been proposed including microvasculopathy by direct involvement of the HIV itself [12], by-products of HIV or opportunistic infections (e.g., cytokines, quinolinic acid) and virus-associated polypeptides [2, 3]. This process of gradual involvement of the CNS after systemic disease appears to be related to the severity of the infection (e.g. CDC staging), but not to variations in the CD4+ cell count. However, because of the small number of patients involved in this study, this observation needs confirmation.

Neuropsychologically, patients who developed neurological signs were not different from those who did not. However, visual memory abilities did deteriorate more rapidly in the patients who developed neurological signs. Visual memory impairment is an early cognitive compromise in HIV infection [13] and can occur even in the absence of significant neurological or systemic abnormalities [14].

In spite of the limitation of this study imposed by sample size and restricted follow-up, these data demonstrate a powerful relationship between systemic and CNS manifestation of HIV infection. More careful analysis of this interaction will lead to a better understanding of the pathophysiology of HIV encephalopathy.

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Announcement

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