Three-year neuropsychological follow-up in a selected group of HIV-infected homosexual/bisexual men

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Objective: To evaluate changes in cognition in a selected group of asymptomatic homosexual/bisexual men over a 3-year period.

Patients and methods: Sixty HIV-infected (Centers for Disease Control stage II) subjects and 60 controls (individually matched for age and years in education) were administered neuropsychological tests evaluating attention, language, memory, logic and visuo-motor abilities. None of the patients had a history of alcohol or drug abuse, and all received the baseline cognitive evaluation within 18–24 months of seroconversion.

Results: The HIV-infected subjects differed from controls in only one of the six memory tests ($P < 0.01$). Follow-up evaluation after 18 and 36 months (available for 51 and 36 subjects, respectively) demonstrated a significant deterioration in visuo-motor ability ($P < 0.01$) only in subjects who had progressed to AIDS, without signs or symptoms of central nervous system involvement.

Conclusions: The data suggest that cognitive alterations in asymptomatic stages of HIV infection are in most subjects minor and do not develop. Percentage rates of CD4 lymphocyte decline appear to be significantly related to deterioration in visuo-motor abilities.

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Keywords: HIV infection, cognitive functions, disease progression.

Introduction

It is generally agreed that the asymptomatic stage of HIV infection is not associated with significant cognitive impairment [1–6]. If mental deficit does occur, it appears to be restricted to small subgroups of patients [7–9], and to have only a slight impact on day-to-day functioning. However, it is still not known whether these minor abnormalities constitute the same disorder as HIV-associated dementia, and whether asymptomatic subjects with mild cognitive impairment will invariably progress to a more severe condition and eventual dementia [10]. The HIV-infected population is undoubtedly highly heterogeneous in terms of age, socioeconomic status and risk factors. Therefore, appropriate comparison groups are needed, and the importance of potentially confounding factors, such as differences in life-style, use of alcohol and other drugs, and previous neurological and/or psychiatric diseases, have already been emphasized by many investigators. Moreover, the slight mnesic abnormalities reported in asymptomatic HIV infection may be related to the different neuropsychological procedures employed, especially to the different times between learning and retrieval at memory tests, as suggested by Wilkie *et al.* [7] and Lunn *et al.* [9].

Since neurological disturbances tend to be significantly associated with the onset of constitutional symptoms or AIDS-defining illnesses (i.e., increased immunosuppression), several studies have focused on the possible relationship between neuropsychological performance and various immunological and virological disease parameters [11,12]. Although conclusions have differed, faster percentage rates in the decline of CD4 lymphocyte counts have been found to correlate with poorer performance in memory and reaction time [12]. In addition to immunosuppression, a number of

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other factors, such as difference in the genetic susceptibility of the host and in the neurotropism of the virus, have also been found to play an important role in progression to severe cognitive decline [13]. Longitudinal studies have therefore become very important in determining the evolution of HIV infection.

In this study, which is a continuation of a previous study [14], cognitive changes in a selected group of asymptomatic homosexual/bisexual men were evaluated over a 3-year follow-up period.

Patients and methods

Patients

A homogeneous and self-selected group of 60 asymptomatic HIV-seropositive homosexual/bisexual men (mean age, 35.8 ± 10.7 years; range, 21–60 years; mean number of years in education, 11.7 ± 4.0 years; range, 5–17 years), without histories of substance abuse, participated in the study. They were selected from a larger group of over 400 sexually active HIV-seronegative homosexual/bisexual men, who were outpatients at the Department of Dermatology at the University of Milan and had been monitored for venereal diseases for several years [14]. Every 6 months the entire population was tested serologically for HIV-1 antibodies. After seroconversion, subjects were recruited consecutively for follow-up and given neuropsychological tests. Our research began in October 1988, and the last cases were enrolled at the end of 1991. Patients recruited for this study had seroconverted 18–24 months before baseline neuropsychological evaluation.

At baseline assessment all patients were in Centers for Disease Control (CDC) stage II, and did not present with neurological disorders. Nutritional state and body mass index were normal in all patients. The group included fully active subjects who consumed alcohol occasionally (between one and two drinks per week). Occasional benzodiazepine use (3 mg bromatepam twice a week) was detected in approximately one-quarter of patients. Subjects were instructed not to administer psychotropic substances in the 24 h before neuropsychological examination.

None of the patients included in this analysis was receiving specific retroviral therapy at baseline evaluation. Subjects who presented with persistently low ($< 400 \times 10^6$/l) CD4 lymphocyte counts during follow-up (at at least two consecutive samples in the same month) were given zidovudine therapy. Subjects with a history of head trauma and previous neurological and/or psychiatric disorders were excluded from the study. A preliminary psychiatric interview and Zung's rating scales for anxiety and depression were conducted before admittance to the study in order to exclude patients with personality or affective disorders (particularly depression), according to the Diagnostic and Statistical Manual for Mental Disorders (edition III, revised) criteria. Five seropositive subjects were thus excluded from the study.

Sixty healthy men (mean age, 35.2 ± 11.4 years; range, 20–60 years; mean number of years in education, 11.4 ± 3.8 years; range, 5–17 years), matched individually with the HIV-positive subjects for age, educational level and socioeconomic status, were selected as the control group. As in our previous study [14], controls were recruited from inpatients referred to the neurology department of the University of Pavia for neurological disorders not involving the central nervous system (CNS; such as peripheral nerve entrapment, lumbosacral pain or sciatica). None had any history of head trauma, or alcohol or drug abuse. Their personality profiles, as determined by the Minnesota Multiphasic Personality Inventory, were within the normal range.

Methods

The HIV-positive participants underwent a physical and neurological examination and assessment of immunological profile every 6 months. The neuropsychological tests were administered at baseline, and after 18 and 36 months, in different equivalent forms to avoid a learning effect. The tests included the following [14]:

(1) Digit Span Forward and Backward [15] (to determine short-term verbal memory and attention);
(2) Logic Memory [16,17], immediate and delayed recall after 30 min (to determine short- and long-term verbal memory);
(3) Visual Reproduction, immediate and delayed recall after 30 min [18] (a subitem of the Wechsler Memory Scale that determines visuoconstructive memory functions);
(4) Street Test [17] (to determine visuoperceptive ability);
(5) Number Cancellation [17] (to determine selective attention);
(6) Digit Symbol [15] (a brain-damage sensitive subitem of the Wechsler Adult Intelligence Scale (WAIS) that can be used to determine visuo-motor and attentive function);
(7) Similarities [15] (to determine logic abilities related to frontal structures);
(8) Raven's Progressive Matrices 38 (subsets A, B, C, D) [16] (to determine non-verbal intelligence and visuospatial ability);
(9) Word Fluency [17] [to determine language processes. This test requires subjects to produce as many words as possible belonging to four semantic categories (fruits, colours, animals and towns); 2 min are allowed for each category].

The neuropsychological tests were administered to all subjects under standard conditions, avoiding stress, fatigue and other factors or events influencing mental

performance, such as fever, psychotropic drugs or other neurotoxic substances. All neuropsychological tests lasted approximately 1 hour, and were selected to investigate the cognitive areas most involved in HIV infection, but were easy and quick to administer, and sensitive to acquired impairment [14].

At 18 and 36 months' follow-up, Zung's rating scales for anxiety and depression were also administered, in order to exclude significant changes of affective status.

Statistical analysis

Results were analysed using one-way analysis of variance (factorial and repeated measures).

Results

At baseline evaluation HIV-asymptomatic patients (60 cases) significantly differed from the control group only on logic memory test (immediate recall) ($P<0.01$; Table 1).

Table 1. Baseline neuropsychological evaluation: HIV-positive subjects versus normal controls.

	Mean ± standard deviation			
	HIV+	Controls	F	P
Digit span				
Forward	6.5 ± 1.0	6.5 ± 1.0	0	NS
Backward	4.5 ± 1.0	4.5 ± 0.9	0	NS
Logic memory				
Immediate recall	9.1 ± 2.5	10.3 ± 2.5	7.2	0.01
Delayed recall	10.3 ± 3.2	11.2 ± 2.8	2.7	NS
Visual reproduction				
Immediate recall	12.5 ± 1.8	12.3 ± 1.9	0.5	NS
Delayed recall	11.0 ± 2.3	11.5 ± 2.1	1.5	NS
Street test	8.8 ± 1.4	9.0 ± 1.3	0.7	NS
Number cancellation	55.1 ± 5.0	56.3 ± 4.1	2.5	NS
Digit symbol	48.8 ± 13.9	50.1 ± 14.7	0.3	NS
Similarities	16.1 ± 1.6	16.2 ± 2.7	0.1	NS
Raven's matrices	36.8 ± 4.7	36.3 ± 4.5	0.4	NS
World fluency	21.8 ± 6.4	21.0 ± 5.1	0.6	NS

NS, not significant.

Eighteen months after baseline evaluation, 51 of the 60 patients were evaluated again; two subjects did not attend the neuropsychological evaluation and six were not available because 18 months had not elapsed since their enrolment. One patient developed CNS pathology (CDC stage IVB) and was therefore excluded from the study. Forty-one of the 51 cases remained in CDC stage II, 10 developed AIDS or AIDS-related complex (ARC), and were therefore classified as CDC stage IV. There was no difference in either group between the first and the second neuropsychological evaluations (Table 2). Baseline CD4 lymphocyte counts were significantly lower in the second group ($P<0.01$; Table 2) and were between 200 and 400 × 10^6/l in five out of 10 patients.

At a second evaluation performed 1 month after baseline, low CD4 count persisted in three out of these five cases, so zidovudine (500 mg) was administered. The two groups were not homogeneous; subjects from the second group were significantly older ($P<0.01$), and had a lower number of years in education than those of the first group. Moreover, their neuropsychological performance was significantly lower, but only in those tests evaluating attention and non-verbal logic abilities (functions affected by age and education). There were no differences between older subjects and matched controls, suggesting that their worse cognitive performance can be ascribed only to differing demographic variables.

After 36 months, 36 of the 51 patients were available and retested: one patient developed CNS pathology and was excluded, two had died, one did not attend the neuropsychological follow-up, and 10 were not evaluated because 3 years had not elapsed since baseline evaluation. Twenty-six subjects remained in CDC stage II, none of whom were receiving zidovudine. Ten cases were classified as CDC stage IV, six of whom had been examined 18 months after baseline evaluation. Three-year follow-up did not reveal any change in the first group (Table 3); since a slight but not significant improvement on some neuropsychological measures could be due to a practice effect. In the second group, no significant difference was found after 3 years, except on Digit Symbol evaluation ($P<0.01$; Table 3). None of the patients presented with AIDS dementia complex according to recent criteria [10]. The two groups did not significantly differ in demographic and immunological parameters (Table 3) at baseline.

Percentage changes between baseline and 36-month values of CD4 and Digit Symbol evaluation were also calculated in all 36 cases. A significant correlation ($r = 0.60$; $P<0.01$) between these two variables was observed.

Zung's rating scales for anxiety and depression did not reveal any significant changes at 18 and 36 months of follow-up.

Discussion

Intravenous drug users form the majority (approximately 70%) of the HIV-infected population in Italy. They do not, however, represent a model for studying the epidemic because of compliance difficulties and confounding factors. In contrast, homosexual/bisexual men constitute approximately only 15% of the HIV-infected population [19], and the sociocultural situation differs from that of the United States. Therefore, despite the relatively small number of cases, we suggest that this study represents an important contribution to the knowledge of the distinctive epidemiological features of HIV infection in Italy.

Table 2. Eighteen-month neuropsychological follow-up.

	Examination (mean ± standard deviation)			
	Asymptomatic patients (n = 41)		Symptomatic patients (n = 10)	
	First	Second	First	Second
Age	33.6 ± 10.1	–	43.0 ± 12.5†	–
Educational level	12.5 ± 3.0	–	9.3 ± 4.0†	–
CD4 cell count (× 10^6/l)	701 ± 266	675 ± 241	389 ± 184†	222 ± 88‡
Digit span				
Forward	6.6 ± 0.9	6.4 ± 0.9	5.9 ± 1.0*	5.7 ± 1.1
Backward	4.7 ± 1.0	4.8 ± 1.0	4.1 ± 0.7	4.0 ± 0.5
Logic memory				
Immediate recall	9.4 ± 2.5	9.9 ± 3.2	7.9 ± 2.1	7.5 ± 2.4
Delayed recall	10.8 ± 3.1	11.3 ± 3.2	8.6 ± 3.3	8.5 ± 3.1
Visual reproduction				
Immediate recall	12.7 ± 1.6	12.8 ± 1.5	11.1 ± 2.1	10.4 ± 3.4
Delayed recall	11.5 ± 2.0	11.7 ± 2.0	10.3 ± 2.9	9.7 ± 3.9
Street test	9.0 ± 1.4	9.2 ± 1.5	7.9 ± 1.2*	7.9 ± 1.3
Number cancellation	56.6 ± 3.8	56.2 ± 4.0	52.1 ± 5.6†	51.7 ± 6.4
Digit symbol	53.3 ± 12.6	55.2 ± 12.1	39.3 ± 11.9†	37.7 ± 10.7
Similarities	16.6 ± 2.3	16.4 ± 1.5	15.0 ± 2.5	14.9 ± 3.1
Raven's matrices	38.5 ± 3.6	38.1 ± 3.9	33.0 ± 5.2†	32.0 ± 5.8
Word fluency	22.6 ± 5.8	23.2 ± 5.9	20.2 ± 8.4	21.2 ± 7.8

*$P < 0.05$ and †$P < 0.01$ at first examination: symptomatic patients versus asymptomatic patients; ‡$P < 0.01$ symptomatic patients at first examination versus second examination.

Table 3. Three-year neuropsychological follow-up.

	Examination (mean ± standard deviation)					
	Asymptomatic patients (n = 26)			Symptomatic patients (n = 10)		
	First	Second	Third	First	Second	Third
Age	34.2 ± 11.4	–	–	39.1 ± 12.2	–	–
Educational level	12.1 ± 1.8	–	–	10.4 ± 3.3	–	–
CD4 cell count (× 10^6/l)	679 ± 288	643 ± 351	658 ± 412	522 ± 215	395 ± 252	323 ± 255*
Digit span						
Forward	6.4 ± 1.1	6.2 ± 1.1	6.3 ± 1.1	6.2 ± 1.0	5.4 ± 1.0	5.5 ± 1.0
Backward	4.6 ± 1.2	4.6 ± 1.2	4.6 ± 1.0	4.5 ± 1.0	4.3 ± 0.5	4.3 ± 0.5
Logic memory						
Immediate recall	8.9 ± 2.1	9.1 ± 2.7	9.4 ± 2.0	8.5 ± 2.6	8.8 ± 4.3	9.0 ± 2.9
Delayed recall	10.3 ± 2.6	10.7 ± 3.0	10.7 ± 2.7	9.5 ± 6.0	8.5 ± 4.6	9.3 ± 3.4
Visual reproduction						
Immediate recall	12.5 ± 1.8	12.4 ± 2.1	13.0 ± 2.1	11.7 ± 1.9	11.7 ± 3.2	9.8 ± 5.2
Delayed recall	11.4 ± 2.2	11.4 ± 2.5	11.6 ± 2.5	10.5 ± 1.9	10.0 ± 3.7	8.8 ± 5.9
Street test	9.0 ± 1.4	9.1 ± 1.5	9.1 ± 1.6	8.7 ± 1.5	8.5 ± 2.4	8.7 ± 1.5
Number cancellation	55.8 ± 5.2	55.5 ± 5.6	53.4 ± 6.0	53.5 ± 5.5	51.7 ± 5.7	49.5 ± 5.7
Digit symbol	50.5 ± 14	52.8 ± 14	53.8 ± 13	43.3 ± 13	37.0 ± 12	34.5 ± 9†
Similarities	15.9 ± 2.3	16.0 ± 2.6	16.0 ± 2.4	15.5 ± 2.6	15.0 ± 1.8	13.5 ± 2.4
Raven's matrices	37.0 ± 4.7	36.7 ± 4.9	36.6 ± 5.0	34.5 ± 4.7	33.7 ± 5.1	31.3 ± 8.5
Word fluency	22.4 ± 7.3	22.8 ± 7.0	22.6 ± 7.0	18.8 ± 5.2	19.2 ± 5.4	18.7 ± 5.1

*$P < 0.05$, †$P < 0.01$; symptomatic patients: first examination versus third examination.

Our results, in agreement with both published data [1–6] and our previous study [14], suggest that the asymptomatic stage of HIV infection is not related to significant cognitive impairment. We found a slight deficit in the control group on only one verbal memory measure. This finding, however, developed in neither those subjects who remained asymptomatic nor those patients who developed the disease during a 3-year follow-up. This could be due to factors other than HIV infection, such as the type of neuropsychological measured employed. The results of other tests evaluating mnesic functions were within the normal range; it should be emphasized that none of the patients at baseline evaluation complained of memory difficulties

with everyday activities. Therefore, these findings do not necessarily imply presence of early CNS involvement or progression to more severe conditions and eventual dementia.

In contrast, patients who developed AIDS (except those cases with CNS involvement who were excluded from the study) showed, after 3 years, only a moderate impairment on Digit Symbol evaluation, in the absence of signs or symptoms indicating the presence of AIDS-related dementia. Digit Symbol evaluation has been found to be particularly sensitive to cognitive impairment in HIV infection [10]. It evaluates attentive ability and visuo-motor speed, but, because of its sensitivity to brain damage, can be considered an indicator of cerebral dysfunction in AIDS patients.

Like our previous study [14], these results indicate that, despite the small number of cases, older HIV-infected subjects with more vulnerable immunological status can develop AIDS earlier than younger patients with the same disease duration. Percentage rates of CD4 lymphocyte decline appear to be significantly related to worsening of visuo-motor abilities. Further research is needed to define the predictive significance of the decline in immune function.

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