Neuropsychological impairment and the natural history of HIV-1 infection in Spanish subjects

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Summary

The authors set out to determine the rates and pattern of neuropsychological impairment shown by seropositive Spanish patients in different stages of HIV infection.

A clinical sample was recruited consisting of 115 heterosexual subjects (30 seropositive asymptomatic; 17 seropositive in stage B; 41 seropositive with AIDS; and 27 seronegative). All subjects provided written informed consent and were submitted to the same process of evaluation.

A rate of neuropsychological impairment of 33.3% was found in stage A (asymptomatic patients); of 41.2% in stage B (low symptomatology patients); and of 70.7% in stage C (AIDS patients). The pattern of neuropsychological impairment shown by the AIDS patients was qualitatively similar to that observed in the asymptomatic subjects, and consistent with fronto-subcortical-type alterations.

Clinically asymptomatic HIV infection represents a risk factor for neuropsychological impairment, even though our results reinforce the idea that the impairment seen in the asymptomatic stages cannot be interpreted as a predictor of more severe cognitive deficits as the disease progresses.

KEY WORDS: AIDS, asymptomatic HIV infection, HIV infection, neuropsychological impairment, stage of infection.

Introduction

The neurological and neuropsychological effects of HIV-1 infection on the central nervous system (CNS) are well documented (1). Involvement of fronto-subcortical structures was found in studies of cerebral metabolic function (2) and, more specifically, fronto-striatal connections (3) have been found to be implicated. The resulting neuropsychological pattern most frequently resembles that of a subcortical affection, the most frequent manifestations being a slowing of reaction times, a reduction of psychomotor speed, and decreased memory function (1,4). Although these alterations are most common in symptomatic patients, some asymptomatic subjects show a subtle slowing of reaction times and lowered performance on some neuropsychological measures (5). The neuropsychological changes in asymptomatic and in symptomatic seropositive subjects are qualitatively similar. However, it has not yet been established whether early changes observed are the prelude to more severe changes later on, that is, whether the asymptomatic subjects with neuropsychological impairment will invariably evolve towards a more severe neuropsychological picture.

Most studies focus on comparisons of mean scores between seropositive patients and control subjects in different tests; however, some studies have carried out additional analyses to determine the percentages of subjects impaired in different neuropsychological tests. Such analyses represent an important change in the way these data are treated, as there is reason to suspect that comparisons of mean scores between groups may fail to detect the real difference between the prevalence of deficits in groups of seropositive and seronegative subjects. Studies adopting this latter approach reveal that the prevalence rates of neuropsychological impairment associated with HIV infection vary according to the stage of infection (6). Most of the literature indicates that 20-30% of asymptomatic seropositive subjects may show neuropsychological deterioration (5,7), although the percentages vary between 5% (1) and 45% (8). In the advanced stages, neuropsychological impairment is not only more prevalent but, when it occurs, also likely to be more severe and to affect more abilities than in the medically asymptomatic stage (7). The prevalence of neuropsychological impairment in the advanced stages of the infection is between 50 and 70%; however, again, the range is broad: from 12% (1) to 87% (9).

Moreover, the pattern of neuropsychological impairment observed in asymptomatic HIV-positive patients shows great variability, its prevalence, as mentioned above, and its severity being very heterogeneous (10). Patients with subclinical neuropsychological disorders show deficits in attention, in memory, and in abstract thought, as well as a slowing of the speed of information process-
In general, the profile of neuropsychological impairment in AIDS patients is qualitatively similar to that of asymptomatic patients (13), becoming more evident when the subjects are faced with tasks involving a time limit, problem-solving, visual recognition and understanding, visuo-motor integration, and alternation between several series of stimuli (13). Given all these considerations, the objective of this study was to determine the rates and pattern of neuropsychological impairment shown by seropositive Spanish patients in different stages of HIV infection, taking as a reference the performance of a seronegative control group matched for age and years of education.

Materials and methods

In order to carry out this research, a sample of 115 heterosexual volunteers was recruited, all of whom gave their written informed consent. These subjects were divided into four groups: i) 30 seropositive asymptomatic subjects, in stage A; ii) 17 seropositive subjects in stage B; iii) 41 seropositive subjects with AIDS, stage C, and iv) 27 seronegative subjects. The seropositive subjects were recruited from the HIV services at hospitals in Ourense (Spain). The seronegative subjects were recruited through a special programme, run by the Provincial Office of the Red Cross in Ourense, aimed at people with HIV/AIDS or at those who have family members who are affected by the disease. We selected seronegative subjects with no history of drug abuse who belonged to the social-family setting of seropositive patients or who were family members of people at risk of infection. The seronegative subjects were matched with the seropositive patients for age and years of education. Diagnosis of seropositivity and the classification of the subjects by stage of infection was carried out according to standard procedures (14), and was based on the medical report from the hospitals where the subjects were registered.

Those subjects who presented, or had presented, neurological or medical pathologies that could affect the CNS, including HIV-associated dementia, psychiatric disturbances (psychotic symptoms), history of cranioencephalic trauma requiring hospitalisation owing to neurological complications, and antisocial personality disorder according to DSM-IV criteria (American Psychiatric Association) were excluded from the study. We also excluded intravenous drug users who, according to reports obtained from local drug abuse care units, were currently consuming psychotropic substances (illegal drugs or alcohol) other than methadone. Moreover, to be considered abstinent, the patients had to have been drug-free for at least three months.

The evaluation of each subject consisted of a semistructured interview investigating sociodemographic, clinical and toxicological aspects and a neuropsychological assessment, with a battery of tests specifically selected for this study and chosen for their validity and because they have been shown to be sensitive to neuropsychological impairment in HIV-infected patients in other studies. The tests comprising the neuropsychological battery were the following: i) the Trail Making Test (TMT) (15); ii) the Spanish version of the Toulouse-Pieron test (16); iii) the Spanish version of the Babcock Story Recall Test (17); iv) the Spanish version of the Rey-Osterrith Complex Figure Test (ROCF) (18); v) the Spanish version of the Benton Visual Retention Test (BVRT, Form C, Administration A) (19); vi) the Spanish version of the Rey Auditory Verbal Learning Test (RAVLT) (20); vii) the Spanish version of the Wechsler Adult Intelligence Scale (WAIS): digit span, arithmetic, comprehension, similarities and vocabulary subtests (21), and viii) the Edinburgh Hand edness Inventory (22).

Statistical analysis

To address the objectives of this study, different data analyses were carried out using the SPSS statistical package for Windows version 11.0 (SPSS Inc., 2002).

Results

Characteristics of the sample

A one-way analysis of variance (ANOVA), to evaluate the statistical differences between means, and a $\chi^2$ test, for statistical comparison of percentages, were performed in order to determine whether there were differences between groups in the sociodemographic and clinical variables. Tables Ia and Ib show the between-groups comparisons of these variables: no significant differences were noted (p> .05), except in the variable antiretroviral therapy, receiving $\chi^2(2)=12.27$; p< .01.

Rates and pattern of neuropsychological impairment

Using an approach previously described (7,23), a principal components factorial analysis was carried out using the direct scores obtained in the different tests. This was done to help limit type 1 error, and in order to convert the high number of scores from the battery to the general processes that it measures and obtain the domains of neuropsychological functioning. Table II shows the results of the factorial analysis and describes the neuropsychological domains and specific measurements they include. The factorial analysis yielded a five-factor model, which explained 73.34% of the variance. Each factor was given a name intended to reflect its contents and the principal neuropsychological functions it measured. However, it must be borne in mind that other neuropsychological processes, too, are involved in these factors.

In order to determine the presence of global neuropsychological impairment in the subjects evaluated, a similar procedure to that used in previous studies (5,7) was carried out. Each of the direct scores they obtained in the neuropsychological tests was transformed into a z score. Subsequently, the z scores included in each of the domains measured by the neuropsychological battery were averaged and domain scores were thus obtained. The subjects were considered to have an impaired performance in a domain if their score was two standard deviations below that of the control group. Finally, a subject was deemed to present global neuropsychological impairment if he or she had an impaired performance in two or more of the five domains measured.
Table Ia - Between-groups comparisons of demographic and clinical variables.

<table>
<thead>
<tr>
<th></th>
<th>Stage A (n=30)</th>
<th>Stage B (n=17)</th>
<th>Stage C (n=41)</th>
<th>Control Group (n=27)</th>
<th>F value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (S.D.)</td>
<td>33.07 (5.67)</td>
<td>34.76 (5.57)</td>
<td>34.00 (4.69)</td>
<td>32.70 (6.25)</td>
<td>0.601</td>
</tr>
<tr>
<td>Years of education, mean (S.D.)</td>
<td>10.30 (3.74)</td>
<td>9.47 (2.07)</td>
<td>9.39 (2.05)</td>
<td>9.89 (2.39)</td>
<td>1.61</td>
</tr>
<tr>
<td>Plasma viral loads, mean (S.D.)</td>
<td>25943.83 (54454.56)</td>
<td>69867.65 (188975.99)</td>
<td>152380.00 (398115.55)</td>
<td>–</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Table Ib - Between-groups comparisons of demographic and clinical variables.

<table>
<thead>
<tr>
<th></th>
<th>Stage A (n=30)</th>
<th>Stage B (n=17)</th>
<th>Stage C (n=41)</th>
<th>Control Group (n=27)</th>
<th>χ² value</th>
</tr>
</thead>
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<tr>
<td>Antiretroviral therapy Receiving (%)</td>
<td>63.30</td>
<td>94.10</td>
<td>92.70</td>
<td>–</td>
<td>12.27*</td>
</tr>
<tr>
<td>Not receiving (%)</td>
<td>36.70</td>
<td>5.90</td>
<td>7.30</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>53.30</td>
<td>76.50</td>
<td>68.30</td>
<td>66.70</td>
<td>3.57</td>
</tr>
<tr>
<td>Women</td>
<td>46.70</td>
<td>23.50</td>
<td>31.70</td>
<td>33.30</td>
<td></td>
</tr>
<tr>
<td>Manual dominance</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right (%)</td>
<td>93.30</td>
<td>100.00</td>
<td>100.00</td>
<td>88.90</td>
<td>4.93</td>
</tr>
<tr>
<td>Left (%)</td>
<td>6.70</td>
<td>0.00</td>
<td>0.00</td>
<td>11.10</td>
<td></td>
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<tr>
<td>Drug abuse situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used drugs (%)</td>
<td>26.70</td>
<td>17.60</td>
<td>24.40</td>
<td>100.00</td>
<td>0.692</td>
</tr>
<tr>
<td>Abstinent IVDU (%)</td>
<td>40.00</td>
<td>41.20</td>
<td>36.60</td>
<td>0.00</td>
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<tr>
<td>MMP (%)</td>
<td>33.30</td>
<td>41.20</td>
<td>39.00</td>
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Abbreviations: IVDU=intravenous drug user; MMP=methadone maintenance programme. * p<.01.

Table II - Factorial analysis of the tests comprising the neuropsychological battery.

<table>
<thead>
<tr>
<th></th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Factor 4</th>
<th>Factor 5</th>
<th>h²</th>
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<td>VISUAL MEMORY</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BVRT-correct</td>
<td>.79</td>
<td>.20</td>
<td>.23</td>
<td>.29</td>
<td>.00</td>
<td>.81</td>
</tr>
<tr>
<td>BVRT-errors</td>
<td>.76</td>
<td>-.33</td>
<td>-.22</td>
<td>-.35</td>
<td>.00</td>
<td>.88</td>
</tr>
<tr>
<td>ROCF-delay</td>
<td>.74</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>-.21</td>
<td>.61</td>
</tr>
<tr>
<td>ROCF-copy</td>
<td>.61</td>
<td>.13</td>
<td>.00</td>
<td>.00</td>
<td>.48</td>
<td>.63</td>
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<td>ATTENTION/PSYCHOMOTOR SPEED</td>
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<td></td>
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<td>Trail Making A</td>
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<td>.80</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.65</td>
</tr>
<tr>
<td>Trail Making B</td>
<td>-.23</td>
<td>.77</td>
<td>.00</td>
<td>-.15</td>
<td>-.18</td>
<td>.73</td>
</tr>
<tr>
<td>WAIS: arithmetic</td>
<td>-.18</td>
<td>.72</td>
<td>.23</td>
<td>.13</td>
<td>.23</td>
<td>.68</td>
</tr>
<tr>
<td>Toulouse-Pieron test</td>
<td>.27</td>
<td>.50</td>
<td>.18</td>
<td>.00</td>
<td>.47</td>
<td>.58</td>
</tr>
<tr>
<td>ABSTRACT REASONING/ VERBAL INTELLIGENCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS: comprehension</td>
<td>.00</td>
<td>.00</td>
<td>.87</td>
<td>.00</td>
<td>.00</td>
<td>.78</td>
</tr>
<tr>
<td>WAIS: similarities</td>
<td>.15</td>
<td>.31</td>
<td>.78</td>
<td>.00</td>
<td>.14</td>
<td>.74</td>
</tr>
<tr>
<td>WAIS: vocabulary</td>
<td>.19</td>
<td>.17</td>
<td>.76</td>
<td>.00</td>
<td>.29</td>
<td>.73</td>
</tr>
<tr>
<td>VERBAL MEMORY FOR TEXTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babcock: immediate</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.84</td>
<td>.00</td>
<td>.71</td>
</tr>
<tr>
<td>Babcock: delayed</td>
<td>.12</td>
<td>.00</td>
<td>.00</td>
<td>.81</td>
<td>.01</td>
<td>.71</td>
</tr>
<tr>
<td>VERBAL MEMORY FOR DIGITS AND WORDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT: total</td>
<td>.00</td>
<td>.17</td>
<td>.18</td>
<td>.15</td>
<td>.67</td>
<td>.53</td>
</tr>
<tr>
<td>WAIS: digit backward</td>
<td>.00</td>
<td>.16</td>
<td>.34</td>
<td>.11</td>
<td>.61</td>
<td>.53</td>
</tr>
<tr>
<td>WAIS: digit forward</td>
<td>.00</td>
<td>.21</td>
<td>-.20</td>
<td>.43</td>
<td>.54</td>
<td>.57</td>
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</table>

Abbreviations: BVRT=Benton Visual Retention Test; ROCF=Rey-Osterrioth Complex Figure; Test WAIS=Wechsler Adult Intelligence Scale; RAVLT= Rey Auditory Verbal Learning Test.
by the battery. The rate of neuropsychological impairment was determined as the percentage of subjects who showed global neuropsychological impairment with respect to the total number of subjects in the group.

None of the seronegative subjects in the control group were found to fulfill the above-mentioned criterion for global neuropsychological impairment (Fig. 1). As for the groups of seropositive subjects, a rate of neuropsychological impairment of 33.3% was found in stage A (asymptomatic patients); of 41.2% in stage B (patients with low symptomatology); and of 70.7% in stage C (patients with AIDS). Non-parametric statistics were used to compare the groups’ neuropsychological impairment rates, which showed statistically significant differences between the groups of seropositive patients \( \chi^2(3) = 31.55; p < .001 \).

![Figure 1](image1.png)

**Figure 1 - Rates of neuropsychological impairment in different stages of HIV infection.**

The rate of neuropsychological impairment in the stage C subjects was significantly higher than that in the stage A subjects \( \chi^2(1) = 7.00; p < .01 \), and control group subjects \( \chi^2(1) = 31.35; p < .001 \). The rate of impairment in the stage B subjects was significantly higher only than that recorded by the control group subjects \( \chi^2(1) = 13.22; p < .001 \). The rate of impairment in the stage A subjects was also significantly higher than that found in the control group subjects \( \chi^2(1) = 12.27; p < .001 \). However, no significant differences were noted between the impairment rates shown by the stage B and the stage A subjects \( \chi^2(1) = 0.09; p < .760 \) or between the stage C and the stage B subjects \( \chi^2(1) = 2.24; p < .151 \).

With respect to the pattern of neuropsychological impairment (Fig. 2), further analysis revealed that in the seropositive asymptomatic group, 46.6% of subjects showed neuropsychological impairment in visual memory (factor 1); 33.4% in attention and psychomotor speed (factor 2); 33.3% in verbal memory for texts (factor 4); 26.7% in abstract reasoning (factor 3); and only 6.7% in verbal memory for digits and words (factor 5).

In the stage B (low symptomatology) subjects, the domains mainly affected were visual memory (factor 1, 41.2%), attention and psychomotor speed (factor 2, 41.1%), and abstract thought (factor 3, 23.2%). Only 5.8% of the subjects showed impairment in verbal memory for texts (factor 4) with none of them impaired in verbal memory for digits and words (factor 5).

A closer analysis of the pattern of neuropsychological impairment in subjects with AIDS showed that the factors associated with the highest percentages of neuropsychologically impaired subjects were: attention and psychomotor speed (factor 2, 68.3%); visual memory (factor 1, 63.5%); abstract reasoning (factor 3, 53.6%); and verbal memory for texts (factor 4, 28.8%), whereas only 7.3% showed impairment in verbal memory for digits and words (factor 5).

**Discussion**

In this study we endeavoured to follow several methodological recommendations found in the literature: the size of the sample was greater than one hundred subjects, as recommended (24); the criteria for inclusion and exclusion were carefully selected, without disregarding the importance of representativeness of the sample (23), and in the development of the neuropsychological battery and choice of the types of test to use, we tried to bear in mind the recommendations of the principal research groups in this specific area (25,26). Finally, particular attention was paid to the statistical techniques used (described above), the choice of tests being based on recommendations in the relevant scientific literature (23,27,28). All of this was done in an effort to ensure correct analysis and interpretation of the data.

As we have pointed out, the association between HIV and the presence of neuropsychological impairment was observed quite early in the history of the infection. On the basis of the information accumulated to date, it is recognised that neuropsychological impairment and dementia are part of the spectrum of complications of the late phases of HIV infection (7). However, there is still debate over whether seropositive subjects in the asymptomatic stage show neuropsychological impairment, what its prevalence is, and what factors are associated with it (24). The variability of the data leads us to suggest that the presence of neuropsychological impairment may differ in Spanish patients compared to patients from other countries, which show other epidemiological patterns of contagion with HIV; in Spain, drug users are the main at-risk group for this infection, and
this group could be more susceptible to neuropsychological impairment compared to other risk groups. Our results indicate that 33.3% of seropositive asymptomatic subjects show neuropsychological impairment, which suggests that clinically asymptomatic HIV infection represents a risk factor for neuropsychological impairment in a Spanish population. Our results are in line with those previously obtained by other authors who have pointed out differences between the neuropsychological performances of seropositive asymptomatic and seronegative subjects (5,7,8). However, they differ from the results of similar studies in which these differences were not found and which suggested that neuropsychological impairment is rare in the early stages of the infection (1,28). The disparity in these studies can be explained mainly by methodological aspects, such as the neuropsychological battery used or the type of analyses applied.

Moreover, we found that none of the subjects in the seronegative matched group showed neuropsychological impairment. The patients with AIDS showed the highest rates of prevalence (70.7%), followed by the subjects in stage B (41.2%), and finally by the asymptomatic stage A subjects (33.3%), the differences between the groups being significant. The rates of impairment found in the present study are similar to those obtained by other authors (10,29-31) and especially to those of Heaton et al. (7), which revealed cognitive deficits in 30.5% of the asymptomatic subjects, in 44.5% of those in stage B, and in 55.6% of those with AIDS, although there are certain differences with respect to the number of functions studied and the types of test used. Other studies disclosed the presence of minor cognitive deficits in 22% of asymptomatic subjects, 50% of symptomatic subjects, and 60-90% of subjects with AIDS (12).

Summarising, the most important result of our research was the finding that the probability of neuropsychological impairment in seropositive subjects increases with the progression of the infection, and that Spanish AIDS patients, in accordance with data recorded in other countries, are twice as likely to show impairment as those who are still asymptomatic, suggesting that their increased vulnerability to neuropsychological disorders could be due to their state of immunodepression, high plasma viral loads, and symptoms of depression, all variables that may increase the risk of neuropsychological impairment associated with HIV-1 infection (32). With respect to the pattern of neuropsychological impairment and the relationship between this and the stage of the infection, the results of this research are consistent with those obtained in many studies which show that seropositivity is associated with an impairment of neuropsychological performance (7), the most frequent deficits involving attention, memory, information processing speed, psychomotor speed, learning, abstract reasoning and executive functions (3,11,12). The results allowed us to glimpse a pattern of impairment that is qualitatively similar in the different stages of the infection, with high rates of impairment in attention and psychomotor speed, visual memory, abstract reasoning and verbal memory for texts. On the contrary, verbal memory for digits and words showed a lower rate of impairment, a finding that is in agreement with other studies (9,30). This pattern of neuropsychological impairment is similar to that observed in neurological diseases affecting subcortical areas of the CNS (32).

With respect to the degree of impairment, we observed that the AIDS patients accumulated the highest rates of neuropsychological impairment and were impaired in a greater number of factors compared with the other groups of seropositive subjects. This is in accordance with other authors who have suggested that in the advanced stages of the infection, neuropsychological impairment is not only more prevalent but, when it occurs, also likely to be more severe and to affect more abilities than in the medically asymptomatic stage (7). However, we were not able to find a gradient of impairment linked to the natural history of the infection, so that, in some factors, the stage A patients showed higher rates of impairment than those in stage B. These data reinforce the idea that the neuropsychological impairment seen in the asymptomatic stages cannot be interpreted as a predictor of more severe cognitive deficits, or even of manifestations of dementia, as the disease progresses (33). Nevertheless, we should remember that the experimental design used is not the most suitable for studying this question (10,23).

In short, this research shows that seropositive subjects in all stages of HIV infection, but especially those in the more advanced stages of the disease, show high rates of neuropsychological impairment, the pattern of impairment being qualitatively similar in asymptomatic and symptomatic subjects, and consistent with fronto-subcortical type alterations, as described abundantly in the literature. Moreover, clinically asymptomatic HIV infection represents a risk factor for neuropsychological impairment, even though our results reinforce the idea that neuropsychological impairment seen in the asymptomatic stages cannot be interpreted as a predictor of more severe cognitive deficits as the disease progresses.

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