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Editorial

Mild cognitive dysfunction in physically asymptomatic HIV infection: recent research evidence and professional implications*

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Summary – Cognitive abnormalities may occur in the physically asymptomatic phases of the infection with the human immunodeficiency virus (HIV), and poor education may represent a risk factor for their development. These abnormalities are usually mild, and apparently do not affect subjects' daily living performance, although this notion should be regarded as preliminary, due to the present primitive stage of development of the instruments which assess functioning in daily living activities. The above evidence has emerged from the cross-sectional phase of the WHO Neuropsychiatric AIDS Study, carried out in the five geographic areas predominantly affected by the HIV epidemic (sub-Saharian Africa, Latin America, North America, South-East Asia, Western Europe), on subject samples that are representative of the whole population of HIV-infected persons living in those areas. The professional implications of HIV-associated early cognitive dysfunction are open to research: for example the current debate on the impact of dysfunction on aviation-related skills emphasizes the need for test batteries with a higher predictive potential than those presently available.

HIV infection / cognitive suppression / WHO Neuropsychiatric AIDS study

Introduction

Is the risk of mild cognitive dysfunction significantly increased during the physically asymptomatic stages of infection with the human immunodeficiency virus (HIV)? This remains a very controversial issue.

Although many studies have not found any significant difference in the performance on neuropsychological tests between samples of asymptomatic HIV-seropositive subjects and matched HIV-seronegative controls, others have reported significant differences in measures of attention, speed of information processing, learning/memory and sensorimotor skills (see Maj 1990; Burgess and Riccio, 1992 for reviews).

These discrepant findings support two different models of the impact of HIV on the brain. According to the first model, although the virus is frequently present in the cerebrospinal fluid during the physically asymptomatic stages of the infection, it remains non-pathogenic for the brain until significant immunosuppression occurs. When mild cognitive abnormalities are observed in the asymptomatic phases, they are likely to be related to premorbid (*eg* alcohol or drug abuse) or situational (*eg* depression or lack of sleep) factors, rather than to the effect of the virus.

According to the second model, HIV may instead affect brain functioning in a subtle way, even in the asymptomatic phases of the infection, so that there is a gradient of increasing prevalence and/or severity of cognitive deficit from the Centers for Disease Control (CDC) stage II (asymptomatic) of HIV infection to the full-blown acquired immune deficiency syndrome (AIDS). Factors

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such as poor education, advanced age and a history of head traumas with loss of consciousness may interact with the infection, producing an earlier onset and/or a more rapid progression of cognitive impairment.

Some supporters of the first model have tried to disprove on methodological grounds the evidence in favour of the second (*ie* the presence of significant differences in neuropsychological performance between asymptomatic seropositive and seronegative subjects). Their criticisms have often focused on the size of subject samples, the adequacy of matching between seropositives and seronegatives, and the treatment of potentially confounding factors (see, for instance, Selnes and McArthur, 1992, and Satz *et al*, in press). It is unlikely, however, that all of the above-mentioned discrepancies can be explained on this basis.

On the other hand, a criticism that has been addressed to all the major neuropsychological studies published to-date is that they have been carried out on subject samples that may not have been representative of the whole population of HIV-infected persons, being composed of self-selected, highly educated, middle-class, mostly white, usually homosexual men, recruited in North America, Western Europe or Australia.

These concerns about the generalizability of the available data on HIV-associated cognitive impairment, and, in general, on the neuropsychiatric complications of HIV infection, have led to the implementation of the World Health Organization (WHO) Neuropsychiatric AIDS Study.

This is the first research project focusing on the neuropsychological, neurological and psychiatric aspects of HIV infection carried out in all the five geographic areas predominantly affected by the HIV epidemic (sub-Saharian Africa, Latin America, North America, South-East Asia and Western Europe), on subject samples representing the broad population of HIV-infected persons living in those areas with respect to the distribution of the various HIV at-risk groups and the sex ratio.

The WHO Neuropsychiatric AIDS Study

The WHO Neuropsychiatric AIDS Study consists of a cross-sectional phase and a longitudinal follow-up.

The cross-sectional phase has been completed in five centres (Chulalongkorn University, Bangkok, Thailand; Mama Yemo Hospital/Projet SIDA, Kinshasa, Zaire; University of Munich, Germany; Kenyatta Hospital, Nairobi, Kenya; Emilio Ribas Hospital, Sao Paulo, Brazil). Data collection is ongoing in a sixth centre (University of California, Los Angeles, USA). These centres were selected in the above-mentioned five geographic areas predominantly affected by the HIV epidemic (one centre per area, except for sub-Saharian Africa, where two centres were selected, since that area accounts for more than 60% of all HIV infections throughout the world).

The criteria used for the selection of the centres in the five areas were the following: i) availability of at least one outpatient medical unit attended by both HIV-seropositive and HIV-seronegative persons; ii) comparability, with respect to the distribution of the various HIV at risk groups and the sex ratio, between the HIV-seropositive cases ascertained at the above-mentioned units during the last month and the whole population of HIV-seropositive persons living in the relevant geographic area (as reported by WHO); iii) availability of a laboratory unit able to perform HIV serological tests, of a microbiology unit, and of a neuroradiology unit with a functioning computerized tomography scanner; iv) availability of neuropsychiatric staff with previous research experience (including at least one professional trained in neuropsychological testing); v) ability to provide counselling for HIV-seropositive persons.

In each centre, physically asymptomatic and symptomatic HIV-seropositive subjects were consecutively recruited from the above-mentioned outpatient units. HIV-seronegative controls were enrolled from the same units on the basis of suitability for matching with seropositives by sex, age, education and HIV at-risk group.

The data collection instrument included six modules: i) sociodemographic survey; ii) cognitive/neuropsychological assessment; iii) psychiatric assessment; iv) neurological assessment; v) physical assessment; vi) laboratory tests. The cognitive/neuropsychological module consisted of: i) a brief questionnaire on subjective complaints concerning cognitive functioning; ii) a battery of neuropsychological tests; iii) a structured interview (the SIDAM, Zaudig *et al*, 1991) incorporating algorithms for the diagnosis of dementia according to ICD-10 and DSM IIIR; iv) a rating scale of performance in daily living activities (ADL).

The neuropsychological battery included six well-known tests (the Timed Gait; the Block Design and the Digit Symbol from the EIWA, Spanish version of the WAIS; the Grooved Pegboard, dominant and non-dominant; the Verbal Fluency, animals and first names; the Trail Making A) and

four newly developed tests (the WHO/UCLA Auditory Verbal Learning Test; the Color Trails 1 and 2; the WHO/UCLA Picture Memory and Interference Test), validated by means of a pre-pilot study (Maj *et al*, 1993).

The researchers involved in neuropsychological testing in all the centres underwent specific preliminary training. The feasibility of the study procedure was proved by a pilot study (Maj *et al*, 1991).

The cross-sectional phase was completed on a total of 955 subjects (almost exclusively intravenous drug users in Bangkok and heterosexuals without a history of either intravenous drug use or blood transfusions in Kinshasa and Nairobi, whereas in Munich and Sao Paulo the most represented group was that of homosexuals/bisexuals). The results will be published in detail elsewhere (Maj *et al*, in press, a,b).

In this cross-sectional phase of the WHO Neuropsychiatric AIDS Study, when physically asymptomatic seropositive subjects were compared with seronegative controls with respect to the prevalence of impairment on individual neuropsychological tests, only very few significant differences were observed. Nevertheless, the prevalence of global neuropsychological impairment (performance 2 or more SDs worse than the mean of controls on at least three of ten tests) was significantly higher in the former group than in the latter in two centres (Kinshasa and Sao Paulo).

When we performed a stepwise logistic regression analysis in asymptomatic seropositives and seronegative controls of all the centres pooled together, using global neuropsychological performance as dependent variable and several sociodemographic and clinical items as independent variables, only serostatus and education entered the model. As the interaction serostatus × education was run as an independent variable, it entered the model with an improvement χ^2 of 31.7.

Therefore, we decided to repeat, within each centre, the neuropsychological comparisons between asymptomatic seropositives and seronegative controls, performing them separately in the subsamples of subjects with high and low educational level. High educational level was defined as a number of years of education higher than the 25th percentile of the frequency distribution in the entire sample recruited in each centre.

We found that in Kinshasa and Nairobi the percentage of asymptomatic seropositives with global neuropsychological impairment was significantly higher than that of seronegative controls in the subsample of subjects with low educational level, but not in the one with high educational level. A similar trend, although not significant, was observed in the other centres.

It seems, therefore, that cognitive abnormalities may occur in the physically asymptomatic phases of HIV infection, and that low education represents a risk factor for their development.

We have interpreted this finding in the light of the "cerebral reserve" theory (Maj *et al*, in press, b; Satz, in press), according to which the cognitive deficit related to acquired brain damage may manifest itself earlier and/or develop more rapidly in subjects in whom the redundancy of cerebral neuronal networks is reduced. Low education may be itself a cause of a reduced "cerebral reserve" (since the lack of educational stimulation may limit the development of efficient synaptic connections between neurons), or it may be a correlate of a socio-environmental situation in which factors reducing the "cerebral reserve" (such as obstetric traumas, malnutrition and infectious diseases affecting the central nervous system) are at work, or it may be a consequence of a reduced "cerebral reserve" (*ie* subjects with a reduced reserve have a low educational achievement). The more pronounced effect of low education on neuropsychological performance in the two African sites may speak in favour of the second hypothesis (low education as a correlate).

The mean total score on the ADL rating scale was not significantly different in asymptomatic seropositives as compared with seronegative controls in any centre. In fact, none of the 17 items of the scale explored in the five centres showed any significant difference between the two groups.

This last finding may mean that the mild cognitive abnormalities possibly occurring in the early phases of HIV infection do not have any implication for subjects' daily living performance. We regard this conclusion, however, as very tentative: the research area dealing with the evaluation of performance in daily living activities remains, in our opinion, at a very primitive stage of development, and no largely accepted and sufficiently validated assessment instrument is currently available.

This is even more disappointing if one considers that impairment of performance in daily living activities is a pre-requisite for the diagnosis of dementia according to both ICD-10 and DSM III-R, and is crucial for the differentiation between HIV-associated dementia and HIV-associated mild cognitive/motor disorder according to the criteria recently produced by WHO (see Maj *et al*, 1993) and by the American Academy of Neurology (AAN AIDS Task Force, 1991).

Professional implications of early HIV-associated cognitive deficit

The issue of the professional implications of mild cognitive abnormalities possibly occurring in the physically asymptomatic stages of HIV infection is currently much debated.

In 1992, a report published by the American Aerospace Medical Association stated that, due to the occurrence of these abnormalities, HIV-infected airline pilots who are physically asymptomatic put the flying public at an increased, unnecessary risk. Therefore, airline pilots should be routinely tested for HIV infection, even if they do not display any physical symptom or sign, and if found to be seropositive should be disqualified from flying duties.

A group of researchers led by the American neuropsychologists O Selnes and E Miller reacted to this report by a consensus statement which was published in early 1993. I was one of those who endorsed this document, which stated that there is no justification for the use of HIV serological tests as a surrogate of neuropsychological screening for detecting functional impairment; that neurocognitive testing, if applied to all pilots, would help ensure the detection of cognitive impairments due to a variety of causes, including the far more prevalent problems of alcoholism and drug abuse; and that only on the basis of failure to pass these procedures should a pilot be excluded from flying.

It must be recognized, however, that currently available neuropsychological tests may not be adequate enough to predict deficits in aviation-related skills. Recent attempts to develop more specific batteries, based on the assessment of reaction times to different stimuli (Mapou *et al*, 1993), should be encouraged.

Concluding remarks

The clinical significance of the mild cognitive abnormalities possibly occurring in the early phases of HIV infection, and their relationship to the development of HIV-associated dementia in the later stages, will probably be clarified by the follow-up phase of the WHO Neuropsychiatric AIDS Study.

The few currently available longitudinal investigations, in fact, have been brief in duration and have been carried out on subject samples in which no significant difference in neuropsychological performance between asymptomatic HIV-seropositive and seronegative individuals was present at baseline.

The follow-up phase of the WHO Study is also expected to clarify the relationship existing between the evolution of HIV-associated cognitive impairment and the medical as well as the immunological aspects of the infection.

In conclusion, I would like to call the attention of the reader to a correlate of the cognitive abnormalities possibly occurring in the early phases of HIV infection which has been seldom, if ever, addressed up to now: the emotional implications they may have for the researchers working in the field.

It has been recently stated (Chapman and Chapman, 1988) that "scientists who build theories are notorious for selectively attending to supporting data and ignoring data that conflict with their theory". This bias may be even more insidious if the theory has social implications that elicit a strong emotional involvement in the scientist.

I believe we should all be well aware of this risk, and keep our minds as clear as possible when dealing with such sensitive issues as those discussed here.

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