Study of HIV-related neuropsychological impairment: a review of methodological aspects

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Estudio de la afectación neuropsicológica asociada al VIH: revisión de aspectos metodológicos

Summary

Research on the HIV-related neuropsychological impairment has been marked by the variety and discrepancy of results, mainly in regards to asymptomatic phases. These discrepancies have been associated with the different types of methodology used in these studies. In this article, we review the main methodological problems present in studies about HIV-related neuropsychological impairment. Our aim is to gather the suggestions contained in the literature, to help overcome these problems in future studies in the field. These suggestions consider the samples used, the way in which they are selected, their size, the sampling methods used, the risk group studied, the criteria for inclusion/exclusion applied, or the selection of the control group. References are also included for the measuring instruments or neuropsychological tests used, statistical methods and criteria for defining the presence of neuropsychological impairment, and for dealing with confounding factors. There can be no doubt that a precise and thorough examination of these issues will make it possible to achieve more conclusive results on the incidence and nature of HIV-related neuropsychological impairment, and the factors that are associated with it.

Key words: *Neuropsychological impairment. HIV infection. Methodological problems. Methodological recommendations.*

Resumen

En la investigación sobre la afectación neuropsicológica asociada al VIH destaca la variedad y discrepancia de resultados, principalmente por lo que respecta a las fases asintomáticas. Estas discrepancias se han asociado a diferencias entre los estudios en distintos aspectos de la metodología empleada. En el presente artículo revisamos los principales problemas metodológicos que presentan los estudios sobre afectación neuropsicológica asociada al VIH. Nuestro objetivo es recoger las recomendaciones que se han ofrecido en la literatura al respecto y que permitirán abordar esos problemas en la realización de futuros trabajos en este ámbito de estudio. Estas recomendaciones atienden a las muestras estudiadas, su selección, tamaño, los procedimientos de recogida utilizados, el grupo de riesgo estudiado, los criterios de inclusión/exclusión seguidos o la selección del grupo control. También se incluyen referencias a los instrumentos de medida o pruebas neuropsicológicas a utilizar, los enfoques estadísticos y criterios para definir la presencia de afectación neuropsicológica, así como el manejo de variables extrañas. Sin duda, atender con rigor y precisión a estos aspectos en la investigación permitirá alcanzar resultados más concluyentes sobre la incidencia y naturaleza de la afectación neuropsicológica asociada al VIH y los factores a ésta asociados.

Palabras clave: *Afectación neuropsicológica. Infección por VIH. Problemas metodológicos. Recomendaciones metodológicas.*

INTRODUCTION

Humman inmunodeficiency virus (HIV), causal agent of the acquired inmunodeficiency syndrome (AIDS), is associated both to the inmmunological system as well as nervous system diseases. As a consequence of the virus action in the brain, HIV infection may lead to the development of neurological complications and neuropsychological impariment whose most serious manifestation is HIV dementia complex[1-4].

Association between HIV infection and neuropsychological impairment was observed very early in the history of the infection, shortly after the description of the first AIDS cases. Since then, there has been continous and numerous research on HIV related neuropsychological impairment, and these have been collected in reviews such as those of Grant and Atkinson[5], Grant and Heaton[6], Markowitz and Perry[7], Grant and Martin[8], Marcotte et al.[9] or Neufeld and Bornstein[10]. The variety and discrepancy of the results, principally in regards to asymptomatic phases, stand out in the analysis of this scientific literature[11]. These discrepancies have been

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associated to the differences between the studies on different features of the methodology used, that constitute an important obstacle in the comparison of the results obtained by different research groups, thus explaining its inconsistencies[12-14].

Thus, in relationship to the samples studied, there is dissimilarity in their selection, both in size as well as collection procedures used, in the risk group studied, inclusion/exclusion criteria followed, or selection of control group. On the other hand, there is no agreement on the measurement instruments or neuropsychological tests to be used. Furthermore, different statistical analysis methods and different criteria to define the presence of neuropsychological impairment have been used. Finally, control of a complete series of confounding variables, other than that of the infection itself, that may coexist in the seropositive subject and that may potentially increase or attenuate the risk of developing neuropsychological involvement, has sometimes been neglected[12].

In this article, we review the principal methodological problems presented by the studies on HIV related neuropsychological involvement, especially when clinically asymptomatic phases are studied. Our objective is to collect the recommendations offered in the literature in this regards that would make it possible to approach these problems in future studies on this study scope.

METHODS

Samples

In the studies on neuropsychological impairment in HIV seropositive patients, the characteristics of the subjects making up the sample must be taken into account and subjects with similar clinical and sociodemographic characteristics should be compared, above all in those variables that may affect neuropsychological performance, such as the infection phase or educational level. In this sense, it is also essential to keep in mind that the different HIV risk groups present differential characteristics. Thus, for example, in the case of the risk group of parenteral drug users, chronic consumption of psychoactive substances could make it easier for the neuropsychological impairment to present greater seriousness and an earlier onset than in other risk groups[15]. Furthermore, the homosexual group generally has a higher educational level, so that they tend to score much better in most of the measurements when compared with the mediocre performance of drug dependents[16]. The fact that both risk groups are included in the same sample would introduce an important bias, that would complicate the assessment and interpretation of the results of this evaluation. In any event, it would also be recommendable to specify the risk group studied in the studies performed.

Inclusion and exclusion criteria of the subjects who participate in this type of studies should be carefully specified. It may be of interest to exclude from the sample the seropositive subjects who present some characteristics that may influence negatively in their performance on the neuropsychological tests, such as the presence of neurological impairments secondary to HIV infection and other CNS conditions. However, it should be remembered that application of some very strict exclusion criteria gives rise to experimentally adequate groups, but ones that are not very representative of the population studied[12].

Given the complex interrelationship of variables that may be involved in the neuropsychological impairment in seropositive patients, adequate selection of the control group becomes an essential feature. The best group to use as control would be that which only differs from the study group in regards to its HIV seropositivity. However, when other relevant variables are introduced as factors in the study, it may be necessary to use more than one control group. A clear example would be when we attempt to assess the weight that drug consumption as well as the HIV itself may have in the neuropsychological performance of drug dependents; in this case, it becomes necessary to use not only a control group of seronegative subjects without a history of drug consumption but also another group of seronegative subjects with a history of drug consumption. This double use of control group will help to discern between those neuropsychological results related with consumption and with HIV[17]. In relationship with these considerations, we also should stress the advantages of resorting to the use of a control group more than making comparisons with the existing set of criteria for the neuropsychological tests, since the HIV risk groups, especially the parenteral drug users, despite their seropositivity, seem to have a general performance below the normative data[18]. Finally, we should not forget the importance of performing longitudinal studies that allow us to use the subject as control, comparing his/her performance over time, which makes it possible to control the confounding variables, know what the evolution of cognitive deterioration is and identify the factors that predict its appearance.

In regards to the sample size studied, the scarce statistical reliability offered by small sample sizes is a basic notion of experimental research that exceeds the content of this present review. The sample size is also a feature that is directly related with the large number of neuropsychological measures used to evaluate seropositive subjects, especially when asymptomatic phases are studied. Thus, given the relationship that some authors have established between the sensitivity to detect neuropsychological impairment and the sample size, it is recommended that extensive samples, of no less than 100 subjects, be studied[11]. Following this line, performance of multicenter studies will have important advantages as they make it possible to accumulate an extensive number of subjects in a relatively short time; however, we should not forget the possible disadvantages presented by this type of studies, such as the «intercenter or interrater reliability», or the differences between subjects enrolled in different geographic or cultural regions.

Related with this feature, we would find another methodological question related to the samples studied: sub-

ject screening or enrolment. The review of existing studies shows us how different enrolment systems have been used, however, the lack of studies using patients who have not been selected previously and who have come to consultation consecutively stands out. Although it may be more expensive in time, it would be, in principle, the recommended enrolment form as it is the most valid way for the rates and characteristics of the neuropsychological impairment of the general population to be reflected in the subjects who enter into the study.

Neuropsychological measures

One of the important questions faced by researchers when studying the neuropsychological impairment associated to HIV infection is the choice of measurement instruments.

The design of the neuropsychological assessment of seropositive subjects should follow procedures similar to those used for any other clinical condition. A wide range of cognitive functions should be assessed to outline which are altered and which remain conserved, paying special attention to those functions that are more vulnerable according to the literature[19]. Following this line, most of the investigations have performed the neuropsychological assessment with batteries made for this purpose and that have been elaborated from the selection of tests that are assumed to be sensitive to HIV related neuropsychological deficits.

We will not stop here to make an extensive review and assessment of the neuropsychological assessment process in the HIV infection and of the specific characteristics of the battery or tests to use, but rather we will give brief indications regarding these features that the reader can consult in an extensive review published recently in Spanish[20].

It has been pointed out that the neuropsychological tests that are sensitive to the HIV related dementia complex, while compatible with the subcortical dementia process, have three common traits: they are tests with a limited time, they require concentration and attention, and they evaluate rapid and precise motor performance[21,22]. When the evaluation is aimed at the assessment of earlier neuropsychological deficits, there is less agreement on the tests to use and how extensive the examination should be, although it is recommended that more extensive battery be used with these patients[23], that include computerized neuropsychological measurements, for example, measurement of reaction times, since different studies have related them with greater sensitivity to detect neuropsychological impairment in the asymptomatic subjects[24-26].

In regards to the performance of the follow-up studies, it is of great importance to take the effect of practice in the performance of the tasks into account. If frequent evaluations are carried out, brief batteries whose tests have parallel forms should be used. A feasible solution to control the effects of practice intraindividually consists in performing several evaluations during the initial phase of the study, using the same tests. The effects of practice would be produced at the beginning of the study and the subject could be evaluated by comparing their initial optimum performance with performance in later evaluations[13,27,28].

In every case, and although it seems to be obvious, it is important to mention the need to choose the neuropsychological tests and other measurement instruments based on the experimental design and especially the specific questions of the investigation.

Data analysis-impairment criteria

Another methodological feature to stress is that regarding the analysis of the data and the different criteria that are used to infer the presence of neuropsychological impairment.

Statistical questions regarding the type of analysis to use according to the sample battery sizes are especially important when asymptomatic seropositive subjects are studied. The exploratory nature of the studies on the possible early neuropsychological alterations associated to HIV requires adequate evaluation of many cognitive functions, since it is most likely that only some are affected. The large number of statistical analyses to be performed, in the case of extensive neuropsychological batteries, increases the risk that a type I error will be produced, that would lead to the conclusion that there are significant differences between the groups when such differences really do not exist, thus it becomes necessary to use adequate statistical methods for multiple comparisons[29]. However, at the same time, using a more restricted criterion could increase, in turn, the probability that a type II error would be produced, that is, the conclusion could be reached that there are no differences between the groups when there really are. Thus, the studies should weigh the possibilities and risks of committing these mistakes when choosing the number of subjects and the measurements to be used[13].

Above all at the beginning of the investigation on the HIV related neuropsychological impairment, most of the studies performed an analysis of comparison of the mean scores obtained in the neuropsychological tests by seronegative and seropositive subjects in different stages of the infection (asymptomatic, AIDS related complex, AIDS), using the neuropsychological measurements as continuous variables. However, due to the variability in the neuropsychological performance of the seropositive subjects, especially the asymptomatic ones, and the heterogeneity in the nature of the impairment, the importance of performing an analysis of the proportion of subjects whose performance in different functions or in the battery as a whole exceeds some criterion or cut off defined as condition is being recognized more and more. This type of analysis helps to define the condition patterns association with HIV infection better and prevents each specific performance from being obscured by the general performance of the group[12,30].

The definition given to «neuropsychological impairment» is of crucial importance for the results, making this feature a question that is not only methodological but also conceptual. Some authors have used this term as synonymous of dementia, while others use it as indicative of the presence of neuropsychological abnormalities that do not fulfill the formal criteria of dementia, so that the conceptual model used as a base is going to outline the operative criterion to determine the impairment. Most of the studies have interpreted neuropsychological impairment in terms of the deviation presented by the subjects in regards to some type of normative score, while others[31] have used clinical opinions given by the researchers. In the former, the definition is based on three principal factors: reference with which the subjects are compared, degree of deviations required in regards to the reference, number of measurements or tasks with deviation needed to infer condition[12]. There has been a variety of criteria in the three features in the different studies carried out, which implies an added difficulty to adequately determine the prevalence of the neuropsychological impairment associated to the HIV infection[13].

The recommendations given to establish the presence of an impairment in a seropositive subject indicate that combined measurements of neuropsychological functions are used better than individual scores of tests and that criteria of condition are used in two or more of these functions[12,32]. It is important to state that, independently of the specific criterion used to define the presence of neuropsychological condition, comparisons between studies would be made easier if the instruments of measurements used and the number of subjects who present deficits of one or two typical deviations in each test would be indicated[33].

Confounding factors

The variability of the data on neuropsychological impairment in HIV infection observed when reviewing the literature may also be due to the fact that contaminating factors or confounding variables are not strictly controlled. In this line, in a study carried out to assess the influence of different contaminating factors in the neuropsychological deficits described in asymptomatic seropositive patients, it was seen that the early stages of infection were associated with a 30% prevalence of neuropsychological impairment when the confounding variables were controlled, however, when the effect of these factors were not controlled, 61% of the asymptomatic subjects presented neuropsychological impairment[16].

It is obvious to recommend that before attributing the presence of neuropsychological impairment to HIV infection, it must be discarded that it is due to other causes. Thus, especially in the initial phases of the infection, there is the possibility that the neuropsychological impairment observed is due to confounding variables and not to HIV itself, or, at least, that it is modulated by their influence[6,16]. Thus, we will pay attention to all the possible relevant variables, manipulating those that are introduced as factors in the study and controlling the rest.

Different investigations have been performed in order to identify what variables can increase or attenuate the risk of developing neuropsychological impairment in the course of the HIV infection[34,35]. Some of these variables are associated to the course and management of the HIV infection, such as antiretroviral treatments, immunological deterioration suffered by the patient as the infection advances, viral load and infection phase[36]. Others, although they are not directly related with the infection, are related with the seropositive patient, with importance being given to sociodemographic features such as age, gender, and HIV risk group; clinical features such as history of neurological and psychiatric disease, mood state, and drug consumption, and sociocultural features such as educational level, and in relationship with the latter, the so-called cognitive reserve[37].

The most present recommendations mention the interest in evaluating the weight of these factors, and not limiting oneself to controlling them by examining the differences between seropositive and seronegative subjects, and nothing more. This promising approach permits us to verify the data of some studies that maintain that the HIV infection *per se* is not associated with the presence of neuropsychological impairment unless the seropositive patients present other risk factors such as history of brain damage[38], or low cognitive reserve[17].

CONCLUSIONS

As can be concluded from the review performed up to here, assessment of neuropsychological impairment associated to the HIV infection is a complex task that is made difficult by methodological features, and by the large number of neuropsychologically relevant factors that are associated to the disease and to the subjects suffering it.

Although investigation in this regards has made it possible to establish certain bases on the incidence, prevalence, nature and course of the neuropsychological impairment associated to HIV as well as the factors associated to its presence, the discrepancy of results observed in the literature leave many questions still unresolved. There are a series of methodological variables that make it possible to determine the correctness with which the investigation was carried out in this study scope and the treatment given to these methodological features in the studies carried out have varied greatly.

In the scientific literature, different recommendations have been given to resolve methodological type problems and to unify the treatment given to these features. The review that we have presented here leads us to propose that the recommendations regarding inclusion/exclusion criteria of the samples to study, their selection

method, size or characteristics in the performance of future studies in this study scope should be followed. Precise attention should also be given to the adequate selection of the measurement instruments, to being strict in the criteria used to infer the presence of neuropsychological impairment, and finally control of the associated factors that can be of interest must not be neglected. However, strictly heeding these features will make it possible to eliminate possible sources of error to reach more conclusive results on the incidence and nature of HIV related neuropsychological impairment and associated factors. Consequently, this will also allow us to improve the clinical and therapeutical characteristics of this complex disease which is the HIV infection.

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