

Influence of Lymphocyte T CD4 Levels on the Neuropsychological Performance of Population Affected by HIV and with a Previous History of Substance Use

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ABSTRACT

The immunological markers help to know if there is a good recovery of the immunological system in patients infected with HIV. Among them, the lymphocyte T CD4 rate is the main indicator of the patient's immunological state being used for staging HIV infection, evaluating the mortality or comorbidity risk and the vulnerability to certain opportunistic infections. However, its link with the presence of cognitive alterations is not clear. Therefore, the aim of this article is to study if lymphocyte T CD4 levels are connected with the neuropsychological performance of a group of people infected with HIV and with a previous history of substance use. The sample consisted of 80 seropositive males with a previous history of substance use. They were evaluated by means of a neuropsychological battery which assesses the most affected cognitive domains in HIV population. The results showed that the patients having a higher level of immunodeficiency (CD4 <200/mm³) have a poorer performance in terms of attention, visuomotor dexterity, visual memory, visual perception, auditory-verbal learning and inhibition. Therefore, our results show a relation between the lymphocyte T CD4 rate and the neuropsychological performance in seropositive people with a previous history of substance use.

KEYWORDS

HIV, T CD4
Lymphocytes,
Neuropsychological
Evaluation.

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I. INTRODUCTION

SINCE the HIV primary infection the viral activity is continuous, and it produces the rise of a series of markers which will reflect the probability of HIV development at a certain speed. These markers show in a direct way (viral load, or lymphocytes T CD4) or in an indirect way (microglobulin β -2, neopterin, or antigen p24) the action HIV takes on the immunological system of the patient, and they have been used independently or combined to identify the risk of progression to AIDS [9] (Table I).

All these markers have a high prognostic value. In the case of lymphocytes T CD4, their number is the main indicator of the patient's immunological state. Its count is used for staging HIV infection, evaluating the risk of comorbidity or mortality, and the vulnerability to certain opportunistic infections, the need for its prophylaxis and the occasional discontinuation [1] [15]. Nowadays, the universal indication of anti-retroviral treatment (ART) is recognised for all patients, regardless of the lymphocyte CD4 count. Thus, the absolute

number and the percentage of lymphocytes CD4 must be periodically determined before initiating ART and, once it has been initiated, as a parameter of periodical monitoring of the immunological response to said treatment [15].

As far as the viral load is concerned, it must be determined during the initial assessment of the patient and before the beginning of ART, being the main parameter for the evaluation of ART's virological efficacy and to define the virological failure [7]. For all these reasons, we can conclude that the combination of these markers allows us to obtain a better overview of a patient's state, his/her prognosis and his/her response to treatment.

HIV may affect the cognitive development of these patients [10], these specific markers have been studied regarding the presence of neuropsychological affectation, although results are not very consistent. As far as immunological markers are concerned, the lymphocyte T CD4 rate of decrease is a good indicator to determine the probability of developing AIDS [2] [27] [36], however, its efficiency to predict neurological and neuropsychological affectation has not been confirmed. While some authors point out that the probability of developing neuropsychological affectation is higher among seropositive patients with low levels of lymphocytes CD4 [26] [28] [29] [15],

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others, on the contrary, claim that there is no connection between the rate of lymphocytes T CD4 and neuropsychological functioning [14] [19] [21] [34]. In the end, immunological markers of HIV infection, specifically lymphocyte T CD4 count, have been associated to the presence of neuropsychological affectation in seropositive patients, though there does not seem to be an agreement about this in literature, which suggests the need for continuing research in order to clarify this subject.

For all these reasons, the objective of this article is to study the connection between lymphocytes T CD4 levels and the neuropsychological performance of former seropositive drug addicts.

TABLE I
MAIN BIOLOGICAL MARKERS OF HIV INFECTION
(ADAPTED FROM GARCÍA SORIANO & MIRÓ, 1999)

Immunological markers	
<i>Lymphocytes T CD4:</i>	It is considered a severe immunodepression when the lymphocyte CD4 number, its percentage or the quotient CD4/CD8 is lower than 200/mm ³ , 15% or 0,3 respectively.
<i>Microglobulin β-2:</i>	It is present in all the nucleated cells, including lymphocytes and macrofages. Its serum increase reflects the activation of these cells. In homosexuals infected with HIV it has been observed a progression of the infection when the plasmatic levels are higher than 5 g/ml. The results in drug addicts are contradictory.
<i>Neopterin:</i>	It is produced by monocytes and macrofages stimulated with interferon gamma produced by the activated lymphocytes T. In HIV-infected homosexuals it has been observed a progression of the infection with plasmatic levels higher than 20 nmol/l. The results in drug addicts are variable.
Virological markers	
<i>Antigen p24:</i>	It is detected at the beginning (acute infection) and at the end (AIDS) of the infection. It is not detected when the patient has lymphocytes T CD4 higher than 500/mm ³ . Its apparition in an asymptomatic patient is a biological marker of progression. It is seldom used at present.
<i>Viral load:</i>	Measured through PCR (detection limit 200 copies/ml), bDNA (detection limit 500 copies/ml) y NASBA (detection limit 50 copies/ml) from plasma or serum. Viral load is the best prognostic and treatment-monitoring indicator.

II. METHODOLOGY

A. Subjects

This study is part of another one done on a wider population [32]. In order to conduct this research we have used a sample which comprised 80 males with a previous history of substance use, who voluntarily took part in the study, giving their informed consent. All the subjects for this study are former drug addicts with HIV infection. They were recruited at the Montecelo Hospital in Pontevedra, Xeral Cies Hospital in Vigo, Xeral de Galicia Hospital in Santiago de Compostela and Juan Canalejo Hospital in A Coruña.

For the selection of the sample the professionals in the reference centres were informed of the requirements which the subjects for our study had to meet, and once selected, they were called at the centre, where the researcher informed them of the characteristics of the research, asking for their cooperation, and offering them the presentation of a report with all the results of the evaluation once it was complete. The subjects interested in taking part gave their informed consent and were called for the evaluation at the same centre where they had been selected, although some of them preferred taking the tests at the Faculty of Psychology in Santiago de Compostela.

We excluded from the study those subjects who showed, or had shown, neurological or medical pathologies that could affect the central nervous system, including dementia associated with HIV; psychiatric disorders; history of head trauma requiring hospitalization due to neurological complications; and antisocial personality disorder according to DSM-IV criteria (American Psychiatric Association, 1995). Also, we excluded subjects with moving or sensory defects, except in the case of visual ones corrected with lenses. Finally, based on the report from the professionals at the drug addict assistance units and the self-report from the subjects itself, we excluded those patients currently using psychotropic substances (illegal, medicine or alcohol) different from methadone.

Regarding the socio-demographic characteristics of the sample, 94% of the subjects presented right-hand dominance and 6% left-handed. 60% had primary studies, and the remaining 40% secondary or higher studies. 33% had a low socioeconomic level, and 67% a medium level. In terms of work situation, 40% were working when the study took place, and 60% were unemployed or retired (see Table II).

TABLE II.
SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE

		HIV+ N(%) 80 (100)	
Age*			34 (4.9)
Hand dominance	Right	94%	73 (91.2)
	Left	6%	7 (8.8)
Level of studies	Primary	60%	55 (68.7)
	Secondary or higher	40%	25 (31.3)
Job situation	Not working	60%	57 (71.2)
	Working	40%	23 (28.8)
Economical level	Low	33%	35 (43.8)
	Medium	67%	45 (56.3)

* Mean and standard deviation

Regarding the clinical characteristics of the sample, 39% of seropositive subjects were not having any antiretroviral treatment, unlike the remaining 61%; in terms of viral load, in 44% of the cases it was undetectable, whereas in 56% it was detectable. As far as lymphocyte T CD4 level is concerned, 25% of seropositive subjects had a count higher than 500, in 29% it was 200-499, and in 46% it was under 200 (see Table 3).

TABLE III.
CLINICAL CHARACTERISTICS OF THE SAMPLE

		HIV+ N(%)80 (100)
Antiretroviral treatment	Yes	61%
	No	39%
Viral load	Detectable	56%
	Undetectable	44%
Lymphocyte T CD4	>500	25%
	200-499	29%
	<200	46%

B. Tools for Neuropsychological Assessment

The tests included in the battery for neuropsychological exploration designed for this study were chosen because of their validity, and because they appeared to be sensitive to the neuropsychological deterioration in HIV-infected patients in other studies. We present below the list of tests used (Table 4) following the order of application, and clarifying the results collected with each test.

TABLE IV.
BATTERY OF NEUROPSYCHOLOGICAL EXPLORATION USED

<ul style="list-style-type: none"> • WAIS IV: Comprehension, Similarities, Digit Span, Vocabulary, Digit Symbol, Block Design and Object Assembly • Rey Auditory Verbal Learning Test • Visual Search and Attention Test • Trail-Making Test (parts A and B) • Verbal Fluency Test 	<ul style="list-style-type: none"> • Benton's Visual Retention Test • Boston Naming Test • Stroop Test • Purdue's Pegboard Test • Rey-Osterrieth Complex Figure • Finger-Tapping Test • Wisconsin Card-Sorting Test
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1. *Wechsler Adult Intelligence Scale* [35]. We used the following subtests from the Wechsler Adult Intelligence Scale (*WAIS IV*): Comprehension, Similarities, Digit Span, Vocabulary, Digit Symbol, Block Design and Object Assembly.
 - *Comprehension* Subtest. It assesses the degree of appreciation of past experience applied to everyday situations, and of internalization of culture, especially of moral or ethical values. It consists of twelve open-ended questions, 14 common sense and practical reasoning questions, and 3 proverb questions that the subject must explain.
 - *Similarities* Subtest. It is a test for verbal formation of concepts, which assesses the ability to assimilate and classify similarities and differences between objects, facts or ideas. It requires comprehension and associative thinking skills. The subject is asked to explain what a series of word pairs presented to him/her have in common.
 - *Digit Span* Subtest. It consists of two parts: forward digit span, in which the subject must repeat some series of numbers in the same order, and backward digit span, in which the subject repeats other series of numbers in reverse order. It assesses immediate auditory memory (backward digit span), attention (forward digit span), and resistance to distraction.
 - *Vocabulary* Subtest. The subject must tell the meaning of 40 words presented to him in order of increasing difficulty, which allows us to assess classification and conceptualization skills. The score obtained in this test was also used to calculate the cognitive reserve.
 - *Digit Symbol* Subtest. It assesses the ability to learn an unfamiliar task, visuomotor skill, the degree of persistence when doing an unattractive task, and the information processing speed. It consists of a sheet which shows the subject some numbers, from 1 to 9, corresponding to a symbol, and a part where the numbers are, and in which the subject must draw the symbol corresponding to each number, as fast as possible in a limited time.
 - *Block Design* Subtest. It assesses visuomotor integration, visuospatial organization, execution speed, and non-intellectual factors such as excessive care, impulsivity, and distraction. The task consists of having the subject perform a series of constructions according to a model using blocks and in a limited time.
 - *Object Assembly* Subtest. It is a test for visuospatial organization speed and motor response, which assesses analysis skills and visual synthesis, visual and motor coordination. Sequential thinking also plays an important role in this test. The task consists of having the subject build figures from the pieces that he/she is given, in a limited time.
2. *Rey's Auditory Verbal Learning Test* [24]. It involves the reading, by the examiner, of a list of 15 words, which the subject must evoke immediately afterwards, in five different trials; and during a sixth evocation after an interference task (reading of 15 more words). It allows us to obtain seven scores, corresponding to the number of words evoked during the first five trials, a total score resulting from the addition of those, as well as the difference between the fifth and the sixth trials. This test allows us to assess immediate memory, it provides us with a learning curve, reveals inclinations towards patterns of retroactive and proactive interference, and measures the memory capacity after an interference.
 3. *Visual Search and Attention Test* [31]. It is a test of visual cancellation which allows us to obtain a measurement of visual search skills and sustained attention. It comprises 4 sheets in which the subject must recognise and point out a certain letter or symbol among a series of distracting stimuli. With this test we obtain a score corresponding to the number of hits of the last two sheets.
 4. *Trail-Making Test* [22]. It assesses skills of visual search and visuoconceptual and visuomotor exploration. It also assesses attention, mental flexibility, perceptive-motor skill and information processing speed. It consists of two tasks with separated scores, the score being the time that the subject needs to complete each task:
 - *Trails A*, consisting of 25 circles numbered from 1 to 25 that the subject must join correlatively with a pencil stroke.
 - *Trails B*, in which the 25 circles contain numbers from 1 to 13 and letters from A to L, the subject must join alternatively numbers and letters.
 5. *Verbal Fluency Test* [6]. Its main objective is to assess verbal fluency. It consists of having the subject tell us as many words as possible starting with the letters F, A and S in three trials of one minute each. We get a score resulting from the addition of the number of words which the subject names with each letter.
 6. *Benton Visual Retention Test* (Form C, Administration A) [5]. It assesses visuoconstructive skills, visual memory and visual perception, as well as spatial organization and visuospatial memory. It involves the presentation of ten sheets with printed figures for ten seconds each, asking the subject to reproduce them immediately once the stimulus sheet has been removed. This test gives us two scores: the number of sheets correctly reproduced, which measures the general efficiency of the execution, and the number of mistakes made.
 7. *Boston Naming Test* [16]. It is a broad-spectrum figure-naming test, consisting of 60 sheets in which an object is represented, which the subject must name spontaneously, or with the help of a semantic or phonetic key. The score we obtain corresponds to the total number of figures named correctly.
 8. *Stroop Test* [11]. It measures verbal fluency, cognitive efficiency, and the ability to inhibit stimuli which trigger automatic responses and, therefore, the ability to adapt perception and accommodate to new demands inhibiting a usual response in favour of an unusual one (cognitive flexibility). It consists of three sheets that the subject must read:
 - In the first sheet, he/she must read the words red, green and blue printed in black ink, and randomly arranged in columns.
 - In the second one, he/she must name the colour of ink with which some symbols "xxx" are printed.
 - Finally, in the third sheet, the words red, green and blue appear printed with ink of those same colours. The subject must say the colour of the ink regardless of the written word.
 A score is obtained for each sheet, consisting of the number of elements read in 45 seconds. We also calculate an interference score based on the score obtained in each sheet.

different neuropsychological tasks, once the direct scores have been transformed into Z scores, and its direction has been corrected.

B. Discussion

The relation of lymphocyte T CD4 levels, used as immunological markers of the progression of HIV infection, have also been studied in connection with the presence of neuropsychological affectation, although the results are not consistent. While some studies point out that the lower the level of lymphocyte T CD4 in seropositive subjects, the greater the neuropsychological deterioration [26] [29] [28], others, on the contrary, show that cognitive functioning is not connected at all with this immunological marker [14] [19] [21] [34].

As far as our research is concerned, we have noticed a selective effect of the level of immune compromise in some attention and memory tasks. Our findings show that seropositive subjects with higher immunodepression levels (CD4 <200/mm³) obtain a poorer

performance than those whose lymphocyte T CD4 levels are within the range of normality, in the Auditory Verbal Learning Test, Visual Search and Attention Test, WAIS Digit Symbol, Benton Visual Retention Test, and Stroop Test, which leads us to suggest that only the subjects with a high degree of immune compromise are neuropsychologically vulnerable.

Taking into account our findings and the fact that the immunodepression level did not show its effect in verbal and denominational tasks, concept formation and reasoning, visuoconstructive skills, manual dexterity and motor speed, and frontal functions, we can suggest that the deterioration of the immunological system does not affect the neuropsychological performance in a general way, it does so in a selective way in attention and memory tasks.

These results are in accordance with those obtained in other studies with drug addict subjects during the different stages of infection [8] [28], as well as those obtained with homosexual subjects [4] [18]

TABLE V
SCORES OBTAINED BY SEROPOSITIVE FORMER DRUG ADDICTS IN THE NEUROPSYCHOLOGICAL TESTS ACCORDING TO LYMPHOCYTE T CD4 LEVELS [MEAN (STANDARD DEVIATION)]

	HIV+			F
	Lymphocyte T CD4 level			
	> 500 n = 20	499-200 n = 23	< 200 n = 37	
WAIS Comprehension	13.40 (4.15)	14.13 (4.00)	14.19 (4.05)	.26
WAIS Similarities	12.10 (6.08)	11.78 (4.58)	13.49 (4.87)	.94
WAIS Forward Digit Span	6.00 (1.12)	5.78 (1.28)	5.95 (1.18)	.20
WAIS Backward Digit Span	4.25 (1.07)	3.83 (1.23)	4.27 (0.90)	1.43
WAIS Vocabulary	42.30 (13.88)	41.91 (13.24)	42.32 (12.00)	.00
WAIS Digit Symbol a	48.45 (14.55)	45.52 (16.31)	38.34 (12.80)	3.77
WAIS Block Design	34.55 (8.38)	29.96 (9.78)	29.43 (7.90)	2.48
WAIS Object Assembly	31.80 (5.03)	27.13 (10.54)	27.11 (8.53)	2.28
AVLT , 5-6	1.65 (1.87)	2.26 (1.60)	1.97 (2.07)	.55
AVLT, total a	45.65 (6.41)	38.91 (8.07)	36.41 (10.08)	6.35
VSAT a	129.40 (25.92)	117.43 (39.55)	102.86 (36.19)	3.91
Trails A	43.20 (14.97)	45.61 (25.51)	48.38 (23.03)	.37
Trails B	89.60 (41.28)	101.04 (59.89)	128.65 (76.96)	2.72
Verbal Fluency Test	28.95 (10.60)	29.43 (11.08)	28.03 (9.44)	.14
BVRT, correct	7.25 (1.62)	6.13 (2.40)	5.95 (1.90)	2.92
BVRT, errors a	4.05 (2.95)	6.17 (4.10)	7.41 (4.17)	4.85
Boston Naming	54.63 (2.29)	53.23 (5.47)	51.30 (6.25)	2.63
Stroop 1	99.40 (19.12)	96.26 (22.44)	90.89 (17.33)	1.37
Stroop 2 a, c	68.75 (13.95)	67.57 (16.44)	55.54 (14.83)	6.92
Stroop 3	39.35 (10.40)	37.87 (14.61)	32.54 (11.78)	2.43
Stroop: interference	-1.33 (8.31)	-1.62 (8.29)	-1.28 (7.28)	.01
Purdue dominant	13.70 (2.36)	14.09 (2.33)	12.78 (2.72)	2.08
Purdue nondominant	13.30 (2.20)	13.09 (1.76)	11.81 (2.53)	3.76
ROCF: copy	31.30 (2.25)	29.89 (4.92)	30.55 (3.66)	.73
ROCF: Delay b	17.25 (4.74)	12.96 (7.49)	15.22 (4.83)	3.17
Finger Tapping: dominant	42.81 (8.85)	41.60 (10.65)	42.24 (12.73)	.06
Finger Tapping: nondominant	38.89 (7.95)	37.87 (8.87)	37.31 (10.47)	.17
WCST Categories	4.15 (1.90)	3.83 (2.08)	3.22 (2.11)	1.50
WCST Learning	-6.39 (12.36)	-8.00 (10.45)	-3.66 (7.54)	1.05
WCST % Perseverative errors	20.39 (14.25)	19.16 (10.88)	22.94 (14.41)	.61
WCST % Nonperseverative errors	14.67 (8.40)	17.58 (13.67)	18.13 (10.98)	.64
WCST Maintain set	0.90 (1.17)	0.78 (0.95)	1.17 (1.50)	.69
WCST Conceptual response	54.06 (23.15)	50.29 (23.32)	44.68 (22.40)	1.17
WCST Perseverative response	23.49 (18.50)	21.81 (13.58)	27.22 (19.19)	.73

- a) Differences between CD4 > 500 y CD4 < 200 (p < .05)
- b) Differences between CD4 > 500 y CD4 499-200 (p < .05)
- c) Differences between CD4 499-200 y CD4 < 200 (p < .05)

[29], which describe problems of attention, verbal fluency and manual dexterity.

However, in some of the studies carried out with seropositive homosexuals, both asymptomatic and symptomatic, no connection between immune deterioration and neuropsychological performance has been described [3] [19] [21] [34], and Heaton and collaborators do not describe it either (1995) [14] with seropositive heterosexual subjects during different stages of the infection, despite having used the same neuropsychological tasks as we did.

Our hypothesis is that the differences between the results obtained in these studies and ours can be due not only to the fact of using different risk groups, but also to the classification used to determine immunodepression levels. In this regard, some authors use as an immunodepression criterion values under 400 or 500 lymphocytes T CD4/mm³ [21], whereas we have grouped together the subjects according to the current classification of HIV infection (CDC, 1992) which provides three differential levels of immunodepression. That is why when using levels of immune compromise with broader ranges the possibility of finding differences in the neuropsychological performance are reduced. On the other hand, we also must consider that some studies argue that lymphocytes T CD4 are the best immunological marker of neuropsychological deterioration in seropositive drug addicts [36], while in homosexuals the best predictor seems to be microglobulin β -2 [17]

On balance, our results support a direct relation between the lymphocyte T CD4 rate and the neuropsychological performance in seropositive people with a previous history of substance use in attention and memory tasks, whereas we do not observe this relation in the rest of skills assessed, which allows us to confirm that the processes of attention and memory decline with the deterioration of the immune system. Therefore, we consider that the deterioration of the immune system can be regarded as a risk factor for neuropsychological manifestations in seropositive former drug addicts during the different stages of the infection. These results provide necessary advances in this field, and studies in this way will have to be continued in order to keep working towards the progress of knowledge in the affectation of the lymphocyte T CD4 rate on HIV+ patients.

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