Cognitive impairment and cardiovascular disease related to alexithymia in a well-controlled HIV-infected population

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SUMMARY

Both cognitive diseases and alexithymia may be associated with HIV. Moreover, alexithymia has been linked to cardiovascular (CV) diseases. Our aim was to explore the prevalence of alexithymia and its associations with neurocognitive disorders (HAND) and CV risk factors in a well-controlled HIV-positive population. We consecutively enrolled 140 HIV-positive individuals on antiretroviral therapy and 35 healthy subjects matched for age, education and gender. In all participants alexithymia was explored by the 20-item Toronto Alexithymia Scale. For HIV-positive subjects also data about CV risk factors were collected, and a comprehensive neuropsychological examination was administered; HAND was defined according to Frascati criteria.

Patients and controls did not differ in the proportion of alexithymic status (10% vs. 11%; p=0.761). Among HIV-positive patients, alexithymic participants presented a higher prevalence of diabetes (21% vs. 3%, p=0.035) and hypertension (36% vs. 13%, p=0.037) compared to non-alexithymic. About 30% (n=41) of HIV-positive patients met criteria for asymptomatic HAND. Alexithymia was not independently associated with a higher risk of HAND (p=0.189). Analyzing each cognitive domain, alexithymia showed an independent association with an abnormal performance (OR 1.08; p=0.037) only in psychomotor speed. In conclusion, in the context of a well-controlled HIV infection, we found a low prevalence of alexithymia comparable to healthy controls. Alexithymia was linked to higher risk of CV disease in the HIV-positive population, but with a rate similar to that previously estimated in the HIV-negative alexithymic. Finally, alexithymia was clearly associated to cognitive impairment only in the psychomotor speed domain, suggesting a common fronto-striatal system dysregulation.

Keywords: Alexithymia; HIV; cardiovascular risk factors; cognitive impairment.

INTRODUCTION

The core characteristics of alexithymia are remarkable difficulties in the identification and expression of emotions, along with an externally orientated thinking style that lacks fantasies, that might be related to dysfunction of the prefrontal cortex as confirmed by neuroimaging studies [1-5]. Alexithymic characteristics are thought to reflect deficits in the cognitive processing and regulation of emotions and seem to contribute to the onset or maintenance of several medical and psychiatric disorders [6].

In the general population, around 9% of people may be affected by alexithymia which is assumed to represent a longstanding risk factor for imbalances in the autonomic nervous sys-

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tem and the neuroendocrine system, and a relevant risk factor for cardiovascular (CV) diseases [7-10].
Facial emotion recognition deficits have been reported also in HIV-infected individuals, as well as alexithymia with a higher rate in comparison to healthy people [11, 12]. It has been suggested that alexithymia might be related to the typical fronto-striatal networks damage observed in HIV infection, including the prefrontal and anterior cingulate cortices, regions whose malfunctioning might also be associated to HIV-Associated Neurocognitive Disorders (HAND) that persist in the combined Antiretroviral Therapy (cART) era [12-14]. Consistently with this hypothesis, some studies found a negative correlation between alexithymia (assessed by the 20-item Toronto Alexithymia Scale; TAS-20) and cognitive performance, especially in executive functions [12].
Moreover, HIV-infected individuals also show a higher prevalence of CV risk factors when compared to healthy people, because of the direct effect of virus on the vasculature, the frequent HCV co-infection that also may produce vascular damage as well as the direct effects of specific antiretroviral drugs and immune activation, that can lead to persistent inflammation, endothelial dysfunction and metabolic disorders [15-17]. A recent longitudinal study suggests that alexithymic personality could be another strong predictor of CV diseases also in this population, in line with the hypothesis that HIV may disrupt sub-cortical brain regions involved in cognitive-emotional regulation and the relative autonomic response mediating vascular damage [18].
However, in countries where cART is widely available, most HIV-positive patients are successfully treated, and they might approach a normal life expectancy [19]. There are evidences that many confounding factors (*i.e.* comorbidities) might lead to overestimate the prevalence of HAND [20, 21]. Thus, also the prevalence of emotional disorders in successfully treated HIV-positive patients needs to be better investigated.
Our aim was to investigate the prevalence of alexithymia in a well-controlled HIV-positive population, and to assess the proportion of HAND and CV risk factors on the basis of alexithymic status.

PATIENTS AND METHODS

Subjects
We performed a cross-sectional single cohort study. HIV-infected individuals on cART, with no active opportunistic infection or other acute clinical conditions, were consecutively enrolled during routine outpatient visits within five months at our Infectious Diseases Institute. Exclusion criteria were age less than 18 years, active or known past Central Nervous System (CNS) opportunistic infections, history of neurologic disorders, active psychiatric disorders, active alcoholism or drug abuse and linguistic difficulties for non-native patients.
At the time of the neuropsychological examination, the following demographic, clinical and laboratory variables were collected for each subject by patient interview and chart review: gender, age, education, risk factors for HIV infection, history of AIDS-defining events, current and past antiretroviral regimen, nadir and current CD4 cells count, HIV-1 plasma viral load, HCV co-infection (positive anti-HCV antibodies). CV risk factors included history of previous CV events (*i.e.* myocardial infarction, peripheral vasculopathy, coronary heart disease), diabetes (fasting glucose plasma levels above 126 mg/dL and/or treatment with glucose lowering agents), hypertension (blood pressure above 140/90 mmHg and/or treatment with antihypertensive medications) and dyslipidemia (LDL cholesterol levels ≥130 mg/dL and/or total cholesterol ≥200 mg/dL and/or tryglicerides ≥150 mg/dL and/or treatment with lipid lowering drugs) [22].
We selected also an age-, gender- and education-matched HIV-negative healthy population. Control subjects had a recent (≤6 months) negative blood test and no HIV risk factors, no history or risk factors for neurologic impairment and were not taking any medication deemed to affect cognitive abilities. They were recruited among hospital personnel, or patients' caregivers or relatives. All subjects were volunteers. They did not receive any financial remuneration for participating.
This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Institutional Ethics Committee. All subjects provided written informed consent prior to enrolment.

Alexithymia and neuropsychological examinations
In all participants (both patients and controls) alexithymia was assessed by TAS-20 [3] (see Figure 1). Responses to each item were rated on a 5-point Likert scale ranging from 1 (complete disagreement) to 5 (complete agreement); higher scores reflect greater alexithymia burden. Based on the total score, individuals were categorized as non-alexithymic (scores ranging from 20 to 51), borderline alexithymic (scores ranging from 52 to 60), or alexithymic (scores ≥61). Borderline alexithymic participants were included in non-alexithymic group in order to avoid an overestimation of alexithymia. The scale has good internal consistency and test-retest reliability, and a factor structure that reflects three separated, yet conceptually related, facets of the alexithymia construct:

1. I am often confused about what emotion I am feeling
2. It is difficult for me to find the right words for my feelings
3. I have physical sensations that even doctors don't understand
4. I am able to describe my feelings easily
5. I prefer to analyze problems rather than just describe them
6. When I am upset, I don't know if I am sad, frightened, or angry
7. I am often puzzled by sensations in my body
8. I prefer to just let things happen rather than to understand why they turned out that way
9. I have feelings that I can't quite identify
10. Being in touch with emotions is essential
11. I find hard to describe how I feel about people
12. People tell me to describe my feelings more
13. I don't know what's going on inside me
14. I often don't know why I am angry
15. I prefer talking to people about their daily activities rather than their feelings
16. I prefer to watch "light" entertainment shows rather than psychological dramas
17. It is difficult for me to reveal my innermost feelings, even to close friends
18. I can feel close to someone, even in moments of silence
19. I find examination of my feelings useful in solving personal problems
20. Looking for hidden meanings in movies or plays distracts from their enjoyment

Notes: Item responses were rated on a 5-point Likert scale ranging from 1 (complete disagreement) to 5 (complete agreement); higher scores reflect greater alexithymia burden. Items 4, 5, 10, 18 and 19 are negatively keyed.

Figure 1 - The 20-item Toronto Alexithymia Scale.

1) difficulty identifying feelings and distinguishing them from the somatic sensations that accompany emotional arousal,
2) difficulty communicating feelings to other people,
3) externally oriented thinking [3].

Due to high sub-scales intercorrelation, we preferred to use only the total score in all planned analyses.
All HIV-positive patients underwent also a comprehensive neuropsychological battery; the following four cognitive domains were investigated:
1) Memory by means of the Immediate and Delayed recall of Rey Auditory Verbal Learning [23].
2) Psychomotor Speed by means of the Wechsler Adult Intelligence Scale (WAIS-III) Digit Symbol [24] and the Grooved Pegboard Test (dominant and non-dominant hand) [25].
3) Attention by means Digit and Spatial (forward) Span [26].
4) Language by means of the Phonological Fluency [23].

Individual scores on each test were transformed into standardized Z scores using means and standard deviations of Italian normative data and averaged to calculate a composite domain-specific Z score. According to Frascati criteria [27], HAND was defined as a performance below the normative mean (≤1 SD) in at least two cognitive domains among those explored, taking into account also the functional capacity assessed by the Instrumental Activities of Daily Living (IADL) scale [28].
The Italian version of Zung Self-Rating Depression Scale was also administered [29]. Scores range from 20 to 80; scores above 49 suggest the presence of clinically significant depression.

Statistical analysis
Comparisons between HIV-positive patients and healthy controls were based on the Student t test (for continuous variables) and the Chi^2 test or, when appropriate, Fisher exact test (for categorical variables).
Moreover, HIV-positive subjects were classified according to the alexithymic status in two sub-groups (alexithimic vs. non-alexithimic) in order to explore differences between them, in particular about the prevalence of HAND and CV risk factors.
The independent association between HAND (dependent variable) and alexithymia (independent

continuous variable) was further explored by a multivariate logistic regression model including clinical variables showing a significant association with HAND at univariate analyses, and controlling for education and depression that have shown to impact cognition in HIV infection [30, 31].
The same logistic regression model was performed entering domain-specific impairment as the outcome.
A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics
Overall, we enrolled 140 HIV-infected individuals with a median age and education of 47 and 13 years, respectively (Table 1). All participants were on cART and most of them with undetectable plasma viremia (n= 123, 88%). Among 17 patients with detectable plasma viremia, 2 were newly diagnosed and had started treatment during the last month; in 7 of them viral load was <200 copies/mL and only 2 had CD4 cells count <200 cells/mmc.
The most represented CV risk factors were dyslipidemia (n=58, 41%) and hypertension (n=21, 15%); only 4 patients (3%) had previous CV events.
The HIV-negative control group included 35 subjects (25 men and 10 female), matched for age (median 47 years; IQR 39-55; p=0.143), education (median 13 years; IQR 13-14; p=0.261) and gender (p=0.836) with HIV-positive patients.

Alexithymic status
Patients and healthy controls did not differ both in the median score at TAS-20 (45 vs. 44; p=0.856) and in the proportion of abnormal score (TAS-20≥61) [14/140 (10%) vs. 4/35 (11%); p=0.761]. No difference emerged also including subjects in the borderline range [44/140 (31%) vs. 9/35 (28%); p=0.681].
Among controls, no differences in age emerged between alexithymic and non-alexithymic subgroups (p=0.745), however alexithymic one showed a lower median education [11 vs. 13 years; p=0.055].
Among HIV-positive participants, differences between alexithymic and non-alexithymic subgroups are shown in Table 1. In particular, alexithymic participants showed a lower median education [10 vs.13 years, p=0.008] and a higher median Zung depression score (43.55 vs. 34.32, p=0.003). With regard to CV factors, alexithymic participants had a higher prevalence of diabetes (21% vs. 3%, p=0.035) and hypertension (36 % vs. 13%, p=0.037). No differences were found for other clinical or demographic variables.

Cognitive status
Overall, 29% (n=41) of HIV-positive patients met criteria for Asymptomatic Neurocognitive Impairment (ANI); no patient showed functional impairment (all IADL scores >6) [27].
The most affected cognitive domains were Attention and Memory, with 38% (n=54) and 27% (n=38) of the participants showing an abnormal performance, respectively. Twelve patients (8.6%) obtained a pathological score on the Zung depression scale (Table 1).
The proportion of individuals meeting research criteria for HAND was higher in the alexithymic group compared to the non-alexithymic one (57% vs. 26%, p=0.021). Moreover, alexithymic participants showed worse performance on psychomotor speed functioning compared to non-alexithymic individuals (50% vs. 11%, p=0.003), while the two groups did not show a significant difference regarding cognitive performance in other domains.

Factors associated with cognitive impairment
Alexithymia (TAS-20 score) showed a significant association with a higher risk of ANI at univariate analysis (OR 1.05; p=0.016). However, this association was not confirmed at multivariate analysis (adjusted Odds Ratio (aOR) 1.03; p=0.189], while HCV co-infection (aOR 3.61; p=0.021) showed an independent positive association with ANI and education emerged as protective factor (aOR 0.78; p=0.001), after controlling for Zung depression score; no CV risk factor or other clinical variables were associated with ANI at univariate analysis (Table 2).
Analyzing each cognitive domain, at univariate analysis alexithymia showed a significant association with abnormal psychomotor speed (OR 1.06; 95% CI 1.01-1.11; p=0.010) and language (OR 1.04; 95% CI 1.00-1.08; p=0.036), while no associations were found with pathological memory (p=0.318) or attention (p=0.725) domains.
At multivariate analysis, alexithymia (aOR 1.08; 95% CI 1.00-1.17; p=0.037), HCV co-infection (aOR 6.23; 95% CI 1.21-32.11, p=0.029), and a history of previous CV events (aOR 43.31; 95% CI 2.20-

853.00; p=0.013) showed an independent association with a higher risk of abnormal psychomotor speed, while education confirmed its role as a protective factor (aOR 0.71; 95% CI 0.54-0.93; p=0.012), after controlling for male gender (aOR 0.78; 95% CI 0.06-1.02; p=0.052) and Zung depression score (aOR 0.97; 95% CI 0.89-1.07; p=0.565).
With regard to language domain, at multivariate analysis alexithymia did not confirm a significant association (aOR 1.01; 96% CI 0.96-1.07; p=0.647) with pathological performance, while to be non-Italian born emerged as risk factor (aOR 28.27; 95% CI 1.86-430.93, p=0.016), probably for a cultural bias, after controlling for male gender (aOR 3.25; 95% CI 0.91-11.65; p=0.070), education (aOR 0.78; 95% CI 0.61-0.99; p=0.047) and Zung depression score (aOR 0.98; 95% CI 0.91-1.05; p=0.597).

Table 1 - Characteristics and cognitive evaluation in the total patients' group and according with alexithymic status. Significant p-value in bold.

	Total sample (N=140) N (%) or Median (IQR)*	*Non-alexithymic group (N=126) N (%) or* Median (IQR)*	*Alexithymic group (N=14) N (%) or* Median (IQR)*	*P*
Age, years*	47 (41-53)	47 (40-52)	47 (43-53)	0.686
Education, years*	13 (8-16)	13 (8-16)	9.50 (8-13)	**0.008**
Male gender	102 (73)	92 (73)	10 (71)	0.559
Non Italian born	7 (5)	6 (5)	1(7)	0.530
Past injecting drug users	18 (13)	15 (12)	3 (21)	0.260
Time from HIV diagnosis, years*	14 (6-19)	14 (6-20)	11 (5-18)	0.448
Time from first cART initiation, years*	9 (4-13)	10 (4-13)	8 (3-12)	0.628
Past AIDS-defining events	30 (21)	26 (21)	4 (29)	0.349
CD4 cell count, cells/µL*	611 (482-719)	624(504-720)	523 (382-644)	0.249
CD4 cell count at nadir, cells/µL*	192 (71-300)	205(75-301)	166 (29-300)	0.228
Viral Load <50 copies/mL	123 (88)	110 (87)	13 (93)	1.000
Abnormal Zung score	12 (10)	9 (9)	3 (27)	0.091
HCV coinfection	28 (20)	24 (20)	4 (29)	0.488
CV risk factors				
Previous CV events	4 (3)	4 (3)	0 (0)	0.653
Diabetes	7 (5)	4 (3)	3 (21)	**0.035**
Hypertension	21 (15)	16 (13)	5 (36)	**0.037**
Dyslipidemia	58 (41)	52 (41)	6 (43)	0.601
Neuropsychological evaluation N (%) of HAND and impairment in each cognitive domain				
HAND	41 (29)	33 (26)	8 (57)	**0.021**
Memory	38 (27)	32 (26)	6 (43)	0.154
Psychomotor speed	18 (13)	12 (11)	6 (50)	**0.003**
Language	20 (14)	17 (13)	3 (21)	0.320
Attention	54 (39)	48 (38)	6 (43)	0.470

*Median (IQR)
Abbreviations: HAND (HIV-Associated Neurocognitive Disorders ≥2 abnormal domains); IQR: interquartile range; N: number; cART: combined Antiretroviral Therapy; HCV: hepatitis C Virus; CV: Cardiovascular.

Table 2 - Factors associated with HAND. Significant p-value in bold.

	Univariate analysis OR (95%CI)	*p*	*Multivariate analysis OR (95%CI)*	*p*
Alexithymia (TAS-20 score, per 1 more point)	1.04 (1.01-1.07)	**0.015**	1.03 (0.98-1.07)	0.189
To be non-Italian born	0.96 (0.18-5.18)	0.966		
Education (per 1 more year)	0.75 (0.66-0.84)	**<0.001**	0.79 (0.68-0.91)	**0.001**
Male gender	0.68 (0.29-1.60)	0.376		
Duration of HIV Infection	1.03 (0.98-1.08)	0.225		
Duration of cART treatment	1.03 (0.95-1.11)	0.445		
CD 4 cells count (per 100 cells increase)	1.02 (0.87-1.19)	0.806		
CD 4 cells count at nadir (per 100 cells increase)	0.99 (0.10-1.00)	0.237		
Past AIDS-defining events	0.85 (0.34-2.10)	0.722		
Viral Load <50 copies/mL	0.99 (0.10-1.00)	0.265		
To be HCV co-infected	5.15 (2.13-12.46)	**<0.001**	3.61 (1.21-10.77)	**0.021**
Zung depression score (per 1 more point)	1.05 (0.99-1.08)	0.058	1.02 (0.97-1.07)	0.453
CV risk factors				
Previous CV events	2.49 (0.34-18.28)	0.371		
Diabetes	2.57 (0.50-13.29)	0.261		
Hypertension	1.62 (0.61-4.30)	0.332		
Dyslipidemia	1.63 (0.77-3.45)	0.198		

Abbreviations: HAND= HIV-Associated-Neurocognitive Disorders; OR= Odds Ratio; CI= Confidence Interval; TAS-20= 20 item Toronto Alexithymia Scale; cART= combined antiretroviral therapy; HCV: hepatitis C virus; CV= Cardiovascular.

DISCUSSION

The findings of this study reveal a very low prevalence of alexithymia in a well-controlled HIV-infected population (about 10%) comparable to that observed in a healthy age, gender and education-matched group. This result is not consistent with previous evidence showing a higher prevalence (about 18%) of alexithymia in the context of HIV infection in an Italian cohort [18]. The difference across studies might be due to different inclusion criteria; in fact, in our study we excluded patients with major psychiatric disorders since these latter are closely related to alexithymia and cognitive impairment [32]. Moreover, the other study included a lower proportion of individuals with suppressed plasma viremia (67% vs. 86%) and a higher frequency of patients with AIDS diagnosis (38% vs. 21%) in comparison to our survey. Thus, it is possible that, in a successfully treated HIV-positive cohort with no active psychiatric patient, the risk of alexithymia is comparable to the one of the general population.

Despite the overall good immunological condition, approximately 40% of HIV-positive patients showed dyslipidemia, a rate significantly higher to that one described in the normal population; anyway, also other studies showed a high prevalence of dyslipidemia in HIV-infected patients [17, 33-35]. When we split our HIV-positive sample according with alexithymic status, we found a higher prevalence of diabetes (21% vs. 3%) and hypertension (36% vs. 13%) in alexithymic subgroup compared to the non-alexithymic one; however, this higher rate was similar to the one previously observed in HIV-negative alexithymic people [9]. Taken together, these results suggest that in our HIV positive cohort the burden of alexithymia on CV disease was similar to the one observed in the general population, and concur to CV comorbidities in association with other factors, such as the direct effect of virus on the vasculature, as well as direct effects of specific antiretroviral drugs, including inflammation, endothelial dysfunction and metabolic disorders [17]. Anyway, our analysis was cross-sectional in nature and could indi-

cate only associative relations between alexithymia and CV risk factors.

Overall, we found about 30% of HIV-positive participants affected by HAND but all showed an ANI profile; this proportion was similar to that one observed in previous studies conducted on populations constituted prevalently by virologically-suppressed patients [27, 35-37]. However, until now, the clinical relevance of identifying ANI conditions is not fully understood and appropriately designed longitudinal studies are needed [38]. Interestingly, the frequency of ANI varied based on alexithymia status, with a higher frequency among alexithymic partecipants; however, when we carried out multivariate regression model adjusting for other key-factors, alexithymia did not confirm its association with ANI, that was significantly associated only with education, considered a proxy for cognitive reserve, and with HCV co-infection, confirming previous evidence showing a higher risk of cognitive impairment in HIV-HCV co-infected patients in comparison with mono-infected ones [31, 39-40]. Nevertheless, analyzing each cognitive domain, we found that alexithymia was independently associated with abnormal psychomotor speed, a function that relies especially on prefrontal cortex, in particular on anterior cingulate cortex and dorsolateral prefrontal cortex region, confirming that both deficts might be secondary to the typical dysregulation of frontostriatal system [12, 41, 42].

We acknowledge that our study can have some limitations because uncontrolled biases can occur in cross-sectional surveys performed in routine clinical practice, and the generalizability of our findings is limited to neuro-asymptomatic HIV-infected population with very good immunological control. Moreover, the interpretation of statistical comparisons is limited by an unbalance in the number of alexithymic vs. non-alexithymic participants in both study groups, due to the low prevalence of alexithymia. Definitively, we need to carry out follow-up studies to assess changes in alexithymia over time in relation to the history of illness, and additional surveys enrolling HIV-positive patients with higher proportion of detectable plasma viremia could help to better understand the association between HIV replication and alexithymia [43].

In summary, in the context of a well-controlled HIV infection, we found a low prevalence of alexithymic status, comparable to that one observed in the HIV-negative matched sample. Alexithymia was also associated to a higher risk of CV disease in HIV-positive population but with a rate similar to that one previously estimated in HIV-negative alexithymic people. Cognitively, only abnormal psychomotor speed was significantly associated to alexithymic status, confirming that cognitive and emotional processing might share some specific brain networks**.** Thus, the optimum care of HIV-positive patients seems to significantly reduce the risk of clinically relevant emotional and cognitive disorders. Anyway, in patients affected by HAND, the screening for alexithymia could help clinicians to better detect brain dysfunction especially among patients not successfully treated or those with comorbidities such as HCV co-infection or CV diseases.

Conflicts of interest

MF received speakers' honoraria and support for travel to meetings from Bristol-Myers Squibb (BMS), Gilead, Merck Sharp & Dohme (MSD), ViiV Healthcare, Janssen-Cilag, and fees for attending advisory boards from BMS and Gilead; RC has been an advisor for Gilead, JC and Basel Pharmaceutical, and received speakers' honoraria from ViiV, BMS, MSD, Abbott, Gilead and JC; SDG received speakers' honoraria and support for travel to meetings from Gilead, Bristol-Myers Squibb (BMS), Abbott, Boehringer Ingelheim, Janssen-Cilag (JC) and GlaxoSmithKline. All other authors: none to declare

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