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Neurocognitive Impairment in the Combined Antiretroviral Therapy Era in a Romanian Cohort of Young Adults with Chronic HIV Infection

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Abstract

HIV-associated neurocognitive disorders (HAND) continue to be reported even in patients with successful antiretroviral treatment. We investigated the prevalence of neurocognitive impairment and possible HIV-associated determinants of cognition in a Romanian cohort of young adults, parenterally infected with HIV during their first years of life. Two hundred fourteen treatment-experienced HIV-positive individuals [median age: 24 years, males: 48%, median duration on combined antiretroviral therapy (cART): 12 years] underwent standard immunologic and virological monitoring and antiretroviral resistance testing using pol gene sequencing in both plasma and, when available, cerebrospinal fluid (CSF) paired samples. Neurocognitive impairment was assessed using a comprehensive neuropsychological test battery, and a global deficit score (GDS) was calculated (cutoff ≥0.5). Cognitive impairment was detected in 35% of the study participants, without any association with sex, median age, CD4 cell count (actual or nadir), CSF and plasma viral load (actual or zenith), AIDS diagnosis, duration of HIV infection, and cART characteristics. Participants carrying resistant viruses tended to be more frequently cognitively impaired ($p = 0.36$), with a higher median GDS value ($p = 0.06$) compared with participants harboring wild-type HIV, although the figures did not reach statistical significance. No signs of virological compartmentalization were observed based on CSF versus plasma viral load and on the profile of pol sequences. A moderate rate of mild neurocognitive impairment is still present in young adults with chronic HIV infection acquired in early childhood despite successful cART, without any association with classic markers of HIV infection. New biomarkers reflecting persistent central nervous system inflammation and neuronal injury may be more relevant for the development of HAND.

Keywords: HIV infection, neurocognitive impairment, HIV disease markers, young adults

Introduction

DESPITE THE INTRODUCTION of combined antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) remain prevalent, with rates ranging from 20% to 50% in treated individuals.[1] HAND is associated with poor HIV outcomes and increased mortality.[2,3] Currently, the frequency of HAD (HIV-associated dementia) declined dramatically, but asymptomatic (ANI) and mild (MND) neurocognitive disorders are reported more frequently, even in patients with successful antiretroviral treatment.[2–4]

HIV invades the central nervous system (CNS) through monocytes and lymphocytes that cross the blood–brain barrier, and persistent infection is established within perivascular macrophages and microglia.[5] HIV replication in macrophage-derived cells leads to immune activation and the production of neurotoxic and inflammatory viral proteins.[2,3] The pathogenic mechanisms involved in the development of HAND are not completely understood and persist despite effective HIV suppression.[6] The risk factors associated with neurocognitive disorders in the cART era may include: (1) host factors—genetic predisposition, metabolic disorders, aging, and vascular disease; (2) HIV-related factors—advanced HIV infection (AIDS), immune activation, neurotropic subtype, drug resistance, CD4^{+} nadir; and (3) comorbidity factors such as hepatitis C virus co-infection, depression, and drug use.[3]

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Romania has a high number of patients now aged 25–29 years who were parenterally infected with HIV during their first years of life, before completion of the brain myelination process.[7] This cohort of young adults growing up with HIV, with a similar genetic background and a similar length of exposure to antiretroviral treatment ($\sim$15 years), provides a unique opportunity to explore the effect of chronic HIV infection on the developing brain.

We investigated the prevalence of neurocognitive impairment and possible clinical and HIV-associated determinants of cognition in a group of patients from this highly homogenous cohort of long-term survivors, with lifelong HIV infection since early childhood.

Materials and Methods

Study participants

This is a cross-sectional study involving 214 antiretroviral therapy (ART)-experienced participants with chronic HIV-1 infection, recruited between 2012 and 2014. Paired cerebrospinal fluid (CSF)/plasma samples were available for 72 subjects. The study was approved by the ethics committees of the participating institutions, and written informed consent was provided by all participants.

Immunologic and virological assessments

CD4 and CD8 cell counts were determined by flow cytometry (4-colors MultiTest and FACSCalibur; Becton Dickinson).

HIV viral loads in plasma and CSF were tested by quantitative RT-PCR (Cobas TaqMan HIV-1 Test; Roche Molecular System, Branchburg), with a lower detection limit of 20 copies of HIV RNA/mL and a linear range between 34 and 10,000,000 copies HIV RNA/mL. Pol gene sequencing was performed using the ViroSeq HIV-1 Genotyping System (Abbott Laboratories) in samples with more than 1,000 copies HIV RNA/mL.

Drug resistance interpretation was undertaken using the Stanford University HIVdb (http://hiv.db.stanford.edu). Data regarding CD4 nadir, HIV RNA zenith, and antiretroviral treatment history were collected from all study participants.

Adherence to antiretroviral treatment was assessed by self-reported AIDS Clinical Trials Group 4-Day Adherence Questionnaire (ACTG).[8] Inadequate adherence was considered if participants admitted missed doses on at least one question. CNS penetration effectiveness (CPE) scores of current and past cART regimens were calculated, as an estimate of the CNS penetration of cART.[9]

Neurocognitive assessment

Participants underwent neurocognitive testing using an internationally validated comprehensive neurocognitive test battery covering seven cognitive domains: verbal fluency, speed of information processing, executive functioning, learning, memory, attention/working memory, and motor skills.[10] Demographically corrected (age, education, gender) T scores (mean of 50, standard deviation of 10) were developed based on an age-matched control group. Individual test deficit scores, determined via demographically adjusted

T scores, ranged from 0 (T score of ≥40) to 5 (T score of <20). Neurocognitive impairment was assessed using the global deficit score (GDS), calculated as the average of deficit scores across all neuropsychological test.[11] The cutoff for neurocognitive impairment (NCI) was a GDS score of ≥0.5.

Statistical analysis

Statistical analysis was performed using SPSS v.20.0.0 for Windows. Spearman's rho coefficient was calculated to assess correlations between nonnormally distributed continuous variables. Comparisons were performed using the chi-squared test or Fisher's exact text (for sparse data), t test (for continuous, normally distributed variables), or Mann–Whitney test (for continuous, nonnormally distributed variables). p-Value <0.05 was considered statistically significant.

Results

Cohort characteristics

The study group had a median age of 24 years (range: 19–29 years), 48% were males. The median duration of HIV infection was 22 years, the median time since HIV diagnosis was 15 years, and 50% of the participants had an AIDS-defining event (stage C). Current median CD4 cell count was 478 cells/mm^3 (range: 2–1,768 cells/mm^3), despite a low median CD4 nadir of 88.5 cells/mm^3 (range: 1–714 cells/mm^3), and only 17% of the subjects presented severe immunosuppression (CD4 cell count <200 cells/mL). The median plasma viral load was 2.11 $\log_{10}$ HIV-1 RNA copies/mL (range: 1.53–5.65 $\log_{10}$); more than half of the subjects (59%) have achieved viral suppression and only 23% had HIV-1 RNA >1,000 copies/mL, despite a viral load zenith of 5.14 $\log_{10}$ copies/mL (range: 2.1–6.7 $\log_{10}$ copies/mL). In CSF, the vast majority of participants (84%) had undetectable HIV viral load, only 8% had a CSF HIV RNA level >1,000 copies/mL, all in patients with higher plasma viral load.

The median duration of antiretroviral treatment was 12 years, the median number of previously used antiretrovirals was 8. Currently, 91.1% of the participants are on cART. The median CPE of the current ART regimen was 8.0 (range: 4.0–14), with 29% of the patients having CPE rank >8.0. Sixty two percent of the participants were exposed to regimens containing neurotoxic dideoxynucleoside antiretrovirals (stavudine, didanosine, and zalcitabine; d-drugs) for a median period of 29 months (range: 0–545.8), and 12.6% were taking d-drugs at the time of evaluation. According to ACTG adherence self-report, 39.7% of the participants admitted treatment adherence problems.

Only two participants had chronic hepatitis C infection. No significant medical or psychiatric confounding conditions and no other significant confounders (severe depression, substance use, etc.) were registered.

Neurocognitive impairment

Overall 35% of the study participants had cognitive impairment. Patients had a median of 11.6 years of education. As shown in Table 1, there were no significant differences between the impaired and nonimpaired individuals in terms of sex, median age, education level, CD4 cell count (actual or

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF NEUROCOGNITIVELY IMPAIRED VERSUS NONIMPAIRED
HIV-INFECTED PARTICIPANTS

Plasma Number of participants = 214	Nonimpaired participants (GDS ≤0.5), n = 139	Impaired participants (GDS >0.5), n = 75	p
Males, n (%)	64 (46)	39 (52)	0.40
Age, years	24 (23–25)	24 (23–25)	0.28
Education, years	11.7 (10.3–12)	11.4 (10–11.6)	0.21
Current CD4, cells/mm^3	473 (231–678)	509 (273–809)	0.24
Time with <200 cells/mm^3, days	4,225 (2,273–5,319)	3,842 (2,447–5,195)	0.53
Current CD4:CD8	0.6 (0.3–0.9)	0.6 (0.3–0.9)	0.55
Nadir CD4, cells/mm^3	87 (31–180)	95 (16–225)	0.86
Median time from nadir CD4, years	8 (2–13)	7 (3–12)	0.74
HIV RNA, log$_{10}$ copies/mL	1.5 (0–2.7)	1.5 (0–3.1)	0.97
HIV RNA undetectable, n (%)	81 (58.2)	46 (61.3)	0.66
Time with HIV RNA detectable, days	3,657 (1,950–4,454)	3,348 (2,327–4,522)	0.81
Viral load zenith, log$_{10}$ copies/mL	5.1 (4.5–5.5)	5.2 (4.5–5.6)	0.54
Time from viral load zenith, years	6 (3–10)	7 (3.5–12)	0.45
Duration of follow-up for HIV-1 infection, years	15 (9.7–17.2)	15.6 (10.6–19.5)	0.26
Previous AIDS diagnosis, n (%)	72 (51.7)	35 (46.6)	0.44
ART characteristics			
Duration of ART, months	142.9 (101.9–177.3)	133.9 (80–167.1)	0.37
Number of antiretroviral agents/patient	8 (5.75–10.25)	8 (5–10)	0.93
No. of participants ever exposed to d-drugs, n (%)	85 (61.6)	48 (64)	0.72
Total duration of exposure to d-drugs, months	29.5 (0–89.5)	27 (0–89)	0.80
No. of participants currently exposed to d-drugs, n (%)	17 (12.2)	10 (13.3)	0.81
cART status			
Currently taking cART, n (%)	124 (89.9)	71 (94.7)	0.22
No. of participants with admitted adherence problems, n (%)	55 (39.5)	30 (40)	0.98
CSF			
Number of participants = 72	48 (66.6)	24 (33.3)	
CSF HIV RNA, log$_{10}$ copies/mL	0 (0–0)	0 (0–0)	0.94
CSF HIV RNA undetectable, n (%)	42 (87.5)	19 (79.2)	0.35
CSF HIV RNA >3 log$_{10}$ copies/mL, n (%)	3 (6.3)	3 (12.5)	0.36
CPE score of current ARV regimen	8 (7–8)	8 (7–9)	0.24
CPE score >8, n (%)	10 (20.8)	7 (29.1)	0.36

Data are expressed as median (interquartile range), unless otherwise specified.
ART, antiretroviral therapy; cART, combined antiretroviral therapy; CPE, CNS penetration effectiveness; CSF, cerebrospinal fluid.

nadir), CSF and plasma viral load (actual or zenith), median time from nadir CD4 count and zenith viral load, AIDS-defining events (stage C), and duration of HIV infection. No association was found between antiretroviral treatment characteristics: median duration on ART, median number of antiretroviral agents, treatment adherence, d-drugs exposure, and cognitive dysfunction.

Paired CSF/plasma samples

Overall, CSF HIV-1 RNA was positively correlated with plasma HIV RNA levels in the paired sample (rho = 0.666; $p < 0.001$). The mean level of HIV RNA was 0.62 log$_{10}$ copies/mL (range: 0–4.61) in CSF and 1.47 log$_{10}$ copies/mL (range: 0–5.62) in plasma, and the proportion of detectable HIV RNA was 15% in CSF and 31% in plasma. None of the patients had CSF HIV RNA level higher than their plasma HIV RNA level.

CNS penetration effectiveness (CPE) score was not correlated with CSF HIV viral load (rho = −0.047; $p = 0.71$). The median CPE of the current treatment regimen was the same in the group of participants with detectable CSF HIV-1 RNA versus the group of subjects with undetectable HIV RNA

(8 vs. 8; $p = 0.62$). No association was found between CPE and GDS (rho = 0.160; $p = 0.202$). Neurocognitive impaired individuals had similar CPE with unimpaired individuals ($p = 0.24$).

Neurocognitive impairment and HIV-associated markers

Viral load. Cognitive impairment was present in 36% of the participants with controlled HIV replication in plasma versus 33% of those with detectable HIV RNA ($p = 0.66$) and in 31% of those with viral suppression in CSF versus 45% of those with detectable HIV CSF levels ($p = 0.35$). No correlation was found between the GDS and the presence of an active viral replication. There were no significant differences between subjects with and without successful HIV suppression in terms of functional deficits for the seven evaluated domains (verbal fluency, speed of information processing, executive functioning, learning, memory, attention/working memory, and motor skills).

CD4 cell count. Neurocognitive performance did not differ between participant groups with and without current

severe immunosuppression (with CD4 cell count <200 cells/mm^3) (median GDS value 0.30 vs. 0.39, $p = 0.63$) and was independent of the nadir CD4 cell number.

HIV drug resistance.   The overall prevalence of HIV drug resistance in plasma was 13%. In CSF, the prevalence of drug resistance was 2.77%; none of the patients with CSF HIV-resistant viruses was cognitively impaired. The anti-retrovirals' resistance profiles were identical in the paired CSF/plasma samples, with predominant mutations associated with HIV resistance to reverse-transcriptase inhibitors.

Participants carrying resistant viruses tend to be more frequently cognitively impaired (42% vs. 30%, $p = 0.36$), with a higher median GDS value 0.40 vs. 0.21 ($p = 0.06$), when compared with participants harboring wild-type HIV, but the figures did not reach statistical significance. There were no significant differences between individuals having resistant HIV and those with wild-type virus in term of neurocognitive deficits for the individually assessed functional domains.

Discussion

We report a moderate rate of mild neurocognitive impairment in a cohort of young HIV-infected Romanian subjects, parenterally infected in early childhood, heavily ART-experienced. More than one-third of the young adults growing up with HIV had neurocognitive dysfunction, despite the currently well-controlled HIV infection and the absence of significant comorbidities. The rate of cognitive dysfunction found in the present study is consistent with the one reported by our group on a smaller sample from the Romanian cohort during 2007–2009.[10] In the CHARTER study, the largest work on the cognitive effects of HIV, the overall impairment rate was 52% and 45% in the group of patients without severe confounders.[12]

No correlation was recorded between the virological or immunologic markers of HIV infection and the cognitive performance. Although previous studies have shown the relationship between neurocognitive performance and HIV viral load,[13–15] more recent reports reveal that controlled HIV replication on cART is not sufficient to avoid the development of neurocognitive disorders.[1,16] Simioni et al. recorded a high prevalence of HAND in a group of 200 HIV-infected patients despite long-standing suppression of viral load.[6] In the CHARTER study,[12] involving 1,525 HIV-positive patients on cART, 30% of the individuals with suppressed viral load and CD4$^+$ counts >200, and without substantial comorbidities, continued to have neurocognitive impairment. Moreover, in a recent European multicenter study, lower plasma HIV RNA was independently associated with worse cognitive performance in highly active antiretroviral therapy (HAART)-naive HIV-infected subjects.[17]

There was no correlation between the current or nadir CD4 count and the presence of neurocognitive impairment. Nadir CD4$^+$ T cell count has been linked to neurocognitive performance in the CHARTER study,[12] but other reports did not confirm this correlation.[18] In a cross-sectional study involving HIV-positive individuals from Botswana, current CD4 count did not affect cognitive function.[19] Also, the current CD4 count was not associated with neurocognitive performance change among 101 HIV-infected HAART-treated patients with advanced HIV infection.[20]

No association between neurocognitive impairment and drug resistance or treatment adherence was found in the present cohort, although such correlations were previously suggested, with neurocognitive deficits causing suboptimal adherence,[21] that can in turn lead to continuous viral replication and the subsequent selection of drug-resistant HIV variants.[22]

It has been suggested that CNS and plasma are two virologically distinct compartments, poor penetration of CNS by antiretrovirals leading to suboptimal drug pressure and thus HIV genetic variants can occur.[23] In our study, a positive correlation was recorded between CSF and plasma viral load, a finding supported by other studies[24–26] and the drug resistance profiles were identical in both compartments.

A higher antiretroviral distribution into the CNS was reported to be associated with lower CSF HIV RNA levels and lower frequency of neurocognitive impairment,[27] but again, we found no association. Similar results were noticed by Giancola et al. who showed that neuroactive ART does not influence neurocognitive performance in HIV-infected patients on cART.[28] The only randomized trial of antiretroviral drugs with good penetration into the CNS showed no benefit of a CNS-targeted therapy on neurocognitive performance.[29]

Several reports suggested a possible neurotoxic effect of ART, thus contributing to the persistence of neurocognitive impairment in the cART era.[16] However, we did not find an association between the cognitive function, duration of therapy, and the current treatment regimens, nor with the ones administered during childhood (nucleoside reverse-transcriptase inhibitors that have been associated with mitochondrial DNA depletion).[30]

One possible explanation for the presence of cognitive impairment in our cohort is that neurological damage may have occurred during the early stages of HIV infection, before initiation of antiretroviral treatment. Our cohort has grown-up with untreated HIV for at least 10 years. Uncontrolled HIV replication in the CNS during the early years in life might have caused developmental disturbances, leading to cognitive dysfunction, despite the presently well-controlled HIV infection. We should also take into account that neurocognitive tests might overestimate the prevalence of cognitive impairment.[31] A recent study reported inconsistencies between different neuropsychological tests batteries and the possibility of overestimating cognitive impairment using the GDS method.[32] Moreover, a high prevalence of attention deficits and minor personality disorders was recorded in subjects who acquired or were exposed to HIV in early childhood, which could significantly impact the performances in several analyzed neurocognitive domains.[33]

Our findings show that markers of HIV viral infection are no longer significant indicators of risk for NCI in cART era, and new predictive biomarkers should be identified. On a related note, we previously reported some subtle gender-related differences in the psychomotor domain, with lower performances for HIV-infected women, which were linked to low current CD4 and time spent with low CD4 count.[34] cART causes immune reconstitution, which may lead to increased lymphocytic infiltration into the CNS, to the production of proinflammatory cytokines and sustained neuroinflammation—implicated in the pathogenesis of HAND.[35] The significant immune improvement on treatment recorded in our cohort (current CD4 count was 481 cells/mm^3 and nadir CD4 count

was 88.5 cells/mm^3) may also have contributed to neurocognitive impairment. cART effectively targets viral replication and increases T cell count, but it does not have an effective control of macrophage activation, brain infection, or inflammation.[36] Eden *et al.* reported that an important number of individuals still show signs of macrophage/microglia activation even after 4 years of viral suppression with cART.[37] Thus, a combination of biomarkers reflecting persistent CNS inflammation and neuronal injury may be more relevant for the development of HAND.[38]

Further longitudinal studies are needed to establish reliable biomarkers that would allow a better understanding of the neurocognitive impairment's mechanisms in HIV patients and address them.

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