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ORIGINAL PAPER

Vitamin D deficiency is associated with neurocognitive impairment in HIV-infected subjects

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Abstract

Purpose Low vitamin D levels are associated with higher odds of cognitive dysfunction in the older population, and in subjects with mental disorders or with chronic neurologic diseases. With combination antiretroviral therapy (cART), incidence of HIV-associated dementia has reduced, while the prevalence of milder forms of neurocognitive impairment (NCI) persisted stable over time. Hypovitaminosis D is often found in HIV infection but its association with NCI has not been investigated yet. The aim was to explore this association in a clinic-based HIV-positive population.

Methods A retrospective, cross-sectional analysis of an existing monocenter dataset obtained from patients undergoing neuropsychological assessment in routine clinical care between January, 2011 and December, 2016 was carried out. NCI was assessed through a standardized battery of 13 tests on 5 different cognitive domains and HIV-associated neurocognitive deficit (HAND) was classified according to Frascati's criteria. Vitamin D deficiency was defined by 25 hydroxy-vitamin D 25(OH)D levels < 10 ng/mL. Logistic regression was adjusted for main associated covariates and seasonality.

Results 542 patients were included: 96.7% were receiving cART, median CD4 count was 611/mmc (IQR, 421–809), HIV RNA was < 40 cp/mL in 85.8%. Median 25(OH)D was 23.2 ng/mL (IQR, 15.6–29.2), with vitamin D insufficiency 67.7% and deficiency in 9.4%. Overall, NCI was found in 37.1% and HAND in 22.7%. Compared to patients with higher vitamin D levels, subjects with vitamin D deficiency had increased proportions of NCI (52.9% versus 35.4%; $p = 0.014$) or of HAND (42.9% versus 24.9%; $p = 0.012$). Median NPZ-8 scores were significantly different based on vitamin D levels ($p = 0.021$). At multivariable analyses, vitamin D deficiency was the only risk factor of NCI (OR 2.05; 95% CI 1.04–4.05; $p = 0.038$) or of HAND (OR 2.12; 95% CI 0.99–4.54; $p = 0.052$).

Conclusions In HIV-positive persons, severe hypovitaminosis D was independently associated with a higher risk of neurocognitive impairment in general, and of HIV-associated neurocognitive disorders in particular. Future studies are needed to elucidate causal relationship and whether vitamin D supplementation may reverse this risk.

Keywords Neurocognitive impairment · HAD · Vitamin D · HIV

Introduction

Increased life expectancy in HIV-infected persons due to combination antiretroviral therapy (cART) enhances the risk of age-related comorbidities associated with chronic infection and mediated by inflammation, immune activation and long-term treatments [1]. Particularly, neurocognitive impairment (NCI) remains prevalent among HIV-positive persons also in the cART era, with frequencies ranging from 21 to 50% [2]. With the introduction of cART, the incidence of HIV-associated dementia has reduced among HIV-associated neurocognitive disorders (HAND), while the prevalence of milder forms of impairment, such asymptomatic neurocognitive impairment and mild neurocognitive disorders, persist stable over time. Despite slighter clinical presentation, asymptomatic neurocognitive disorders also can have an impact on the patient's quality of life and on medication adherence, with the potential of evolving into more severe pictures of neurocognitive impairment [3].

Multiple factors are associated with neurocognitive deficits in HIV-positive patients: Afro-American ethnicity, lower

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education, worse mental health, use of recreational drugs, longer duration of HIV infection and increasing HIV disease stage, exposure to detectable plasma HIV RNA with concurrent viral replication in the central nervous system (CNS), antiretroviral neurological toxicity, deep immune depression (CD4 cell nadir less than 200/mm^3) or high viral load, and metabolic comorbidities [4–9]. Therefore, NCI is most commonly observed in advanced stages of HIV/AIDS, but also can occur in earlier phases of infection [3, 6].

Recently, a growing body of evidence shows that low serum vitamin D levels are associated with higher odds of prevalent cognitive dysfunction in the older general population, and in subjects with mental disorders or with chronic neurologic diseases [10–16]. The majority of the cross-sectional and prospective studies found that vitamin D deficiency is associated with a statistically significantly worse outcome in one or more cognitive function tests, or with a higher frequency of NCI and of dementia. Several pathogenetic mechanisms, such as modulating of nerve growth production, decreasing L-type calcium channel expression, regulating the toxicity of reactive oxygen species, stimulating neurotrophic factors, amyloid phagocytosis and clearance, as well as vessel protection, have been suggested to explain the contribution of 25(OH)D to neuroprotection [10].

In HIV-positive patients, hypovitaminosis D is often found at various levels of severity and has been linked to low bone mineral density and related disorders, subclinical vascular disease, kidney function decline, endocrine disorders, liver fibrosis, preterm delivery, and HIV disease outcomes [17–25].

Since to date, no information is available regarding the possible role of hypovitaminosis D in HIV-positive persons with neurocognitive impairment, our aim was to explore this association in a clinic-based HIV-positive population undergoing neuropsychological testing within routine care.

Methods

For this retrospective analysis, we used an existing monocenter database collecting information on all consecutive HIV-positive patients who undergo neuropsychological assessment for clinical purposes in routine clinical care. Clinical data, information on antiretroviral therapy, laboratory parameters and neuropsychological test scores were collected in a prospective manner within a study protocol, that was previously approved by the Institutional Ethics Committee (IEC): "Pre-IMP" (approved on January 15, 2018; *n*. 4/2018). Patients signed informed consent at enrolment in these two study protocols and were given an anonymous code for data collection. As requested by national guidelines for retrospective noninterventional research, use of the dataset for retrospective analysis of the hypothesis on association between neurocognitive impairment and hypovitaminosis D to be performed on patients observed between January 2011 and December 2016 has been notified to the IEC.

Plasma levels of 25 hydroxy-vitamin D (25(OH)D) were prospectively tested by ChemiLuminescence ImmunoAssay (CLIA) test and samples were obtained within a 6-month period around neuropsychological assessment. 25(OH) D levels were used to classify subjects into the following groups: normal > 29.6 ng/mL, "Vitamin D insufficiency" 10–29.6 ng/mL; "Vitamin D deficiency" < 10 ng/mL (to convert from ng/mL to nmol/L multiply by 2.496) [26, 27].

Neuropsychological assessment was carried out through a standardized battery of 13 tests on 5 different cognitive domains: concentration and speed of mental processing (Trail Making Test-A, WAIS-R Digit Symbol, Stroop color and word), mental flexibility (Trail Making Test-B, Stroop color-word, Controlled Oral Word-FAS, WAIS-R Digit Span backward), working memory (WAIS-R Digit Span forward and backward, Corsi's Block-Tapping Test), memory (RAVLT- Rey Auditory Verbal Learning Test, immediate and delayed recall) and fine motor functioning (Grooved Pegboard Test, dominant/non dominant hand). Subjects were classified as neurocognitively impaired or unimpaired based on the finding of values below one standard deviation (SD) of the normative mean on at least two neuropsychological tests or below two SDs of the normative mean on one test. Frascati's criteria were used for HAND classification [28]. Each test score was normalized and expressed as *z* score. A global measure was used by calculating the mean of *z* scores (NPZ-8) found at eight domains (Trail Making Test-A, Trail Making Test-B, WAIS-R Digit Span forward, RAVLT-Rey Auditory Verbal Learning Test, immediate and delayed recall, Grooved Pegboard Test, dominant/non dominant hand, WAIS-R Digit Symbol). A cumulative mean *z* score was calculated also for each tested domain (NPZ).

Patients who resulted in being neurocognitively impaired but showing confounding conditions (i.e., history of opportunistic CNS infections, non-HIV-associated neurologic disease, major psychiatric disorder, current alcohol abuse or substance use, remote traumatic brain injury) were not included among subjects with HAND.

Comorbid conditions, such as cardiovascular events, diabetes, dyslipidemia and hypertension were identified by: (1) patient self-report, (2) prescription of co-medications, (3) fasting glucose ≥ 125 mg/dL at laboratory tests for diabetes, (4) at least two of the following: fasting total cholesterol ≥ 200 mg/dL, LDL ≥ 100 mg/dL, HDL ≥ 40 mg/dL for females or ≥ 50 mg/dL for males, triglycerides ≥ 150 mg/dL for dyslipidemia. Renal function was evaluated by the estimated glomerular filtration rate (eGFR) calculated by Cockroft–Gault formula.

In the statistical analyses, two different outcomes were assessed: NCI or HAND. Chi squared test was used for

the comparison of categorical variables (gender: M, F; age: < 45, 45–54, ≥ 55 years; HIV transmission route: men having sex with men [MSM], intravenous drug user [IVDU], heterosexual contact, other/unknown; years of HIV infection: < 5, 5–10, ≥ 10; cART exposure: yes, no; nadir CD4 cell count: < 200/mmc, ≥ 200/mmc; current CD4 cell count: ≤ 500/mmc, > 500/mmc; current HIV RNA: ≤ 40 copies/mL, > 40 copies/mL; BMI: < 18 kg/m^2, 18–25 kg/m^2, 25–30 kg/m^2, > 3 kg/m^2; HCV antibodies: negative, positive, unknown; dyslipidemia: yes, no; previous cardiovascular event: yes, no; diabetes: yes, no; vitamin D: < 10 ng/mL, ≥ 10 ng/mL) and Wilcoxon–Mann–Whitney test was employed for the comparison of continuous variables (years of education, CD4/CD8 ratio, sGOT, sGPT). Multivariable logistic regression models estimated the odds ratio (OR) and 95% confidence interval (95% CI) of NCI or of HAND by retaining variables from the univariable analysis if the p value was < 0.1 and adjusting all models for seasonality. Unimpaired subjects were employed as control group for separated analyses carried out with two different outcomes: (1) subjects with NCI, (2) subjects with HAND. All analyses were performed using the statistical software STATA10.1.

Results

A total of 542 patients were included in the analysis: 81% were males, 97.6% were Caucasians, median age was 49 years (IQR, 42–56), and years of education were on average 13 (IQR, 8–16). cART was prescribed to 96.7% of patients and median CD4 cell count was 611/mmc (IQR, 421–809) with HIV RNA < 40 cp/mL in 85.8% of cases. Overall, median 25(OH)D levels were 23.2 ng/mL (IQR, 15.6–29.2). "Vitamin D insufficiency" and "Vitamin D deficiency" were detected in 367 patients (67.7%) and in 51 cases (9.4%), respectively. Overall, NCI was diagnosed in 201 patients (37.1%). Among these, after excluding 78 patients with NCI and confounding factors, HAND was found in 123 cases (22.7%): ANI in 88 (16.2%), MND in 31 (5.7%), HAD in 4 (0.7%).

Compared to patients with higher vitamin D levels, subjects with vitamin D deficiency had significantly increased proportions of NCI (52.9% versus 35.4%; $p = 0.014$) or of HAND (42.9% versus 24.9%; $p = 0.012$) (Fig. 1a). Accordingly, lower median NPZ-8 scores were found in patients with severe hypovitaminosis D than in those with higher 25(OH)D levels (OR − 0.51; IQR − 1.19 to (− 0.06) versus − 0.20; IQR − 0.83 to 0.28; $p = 0.021$) (Fig. 1b).

When considering single domains, median NPZ score for working memory was lower in subjects with Vitamin D deficiency [− 0.74; IQR − 1.45 to (− 0.01)] than in those with higher vitamin D levels (− 0.18; IQR − 1.01 to 0.37; $p = 0.004$). Further, a significant difference in median NPZ score for fine motor functioning was found when comparing subjects with 25(OH)D ≤ 10 ng/mL to those with levels above (− 0.48; IQR − 1.71 to 0.37) versus > 10 ng/mL (− 0.14; IQR − 0.92 to 0.44; $p = 0.047$).

At univariable analysis among several other variables, 25(OH)D < 10 ng/mL was significantly associated with NCI (OR 2.05; 95% CI 1.15–3.66; $p = 0.015$) or with HAND (OR 2.26; 95% CI 1.18–4.34; $p = 0.014$) (Table 1). Diabetes as well, was significantly associated with NCI (OR 2.63; 95% CI 1.27–5.46; $p = 0.009$) or HAND (OR 3.29; 95% CI 1.24–8.72; $p = 0.017$).

At multivariable regression after adjusting for potential confounders and seasonality, vitamin D deficiency remained an independent risk factor for NCI (OR 2.05; 95% CI 1.04–4.05; $p = 0.038$) or for HAND (OR 2.12; 95% CI 0.99–4.54; $p = 0.052$). Furthermore, the risk of NCI increased with age > 55 compared to 18–44 years (OR 2.98; 95% CI 1.68–5.29; $p < 0.001$) and with HIV RNA > 40 compared to ≤ 40 copies/mL (OR 1.87; 95% CI 1.03–3.38; $p = 0.039$). Besides by hypovitaminosis D, HAND risk was increased with age > 55 years (OR 2.41; 95% CI 1.26–4.61; $p = 0.008$) and CD4 nadir < 200 cells/mmc (OR 1.64; 95% CI 0.98–2.75; $p = 0.060$). Higher education in respect to lower significantly reduced the risk of NCI (5–8 years: OR 0.48; 95% CI 0.30–0.77; $p = 0.002$; > 8 years: OR 0.14; 95% CI 0.08–0.27; $p < 0.001$) or of HAND (5–8 years: OR 0.45; 95% CI 0.26–0.77; $p = 0.003$; > 8 years OR 0.16; 95% CI 0.08–0.32; $p < 0.001$).

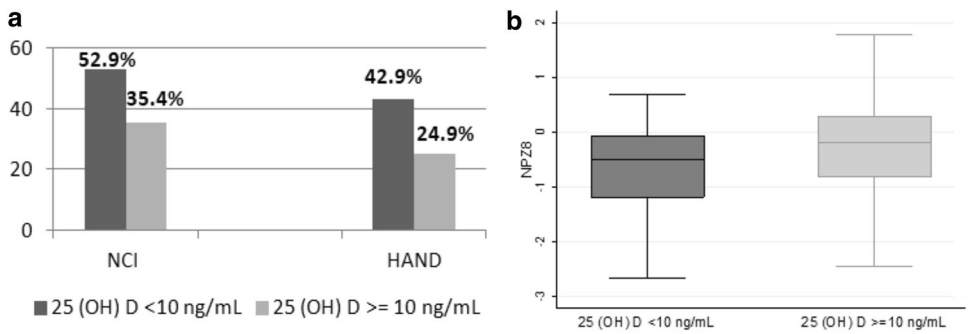

Fig. 1 Based on 25(OH)D levels, the following are shown: **a** proportion of subjects with NCI and HAND; **b** median NPZ-8 value (central horizontal line) and first/third quartiles (upper/lower side of the box)

Table 1 Odds ratio and 95% CI estimating the association of each variable with neurocognitive impairment (NCI) or with HIV-associated neurocognitive disorder (HAND) at univariable analysis ($n = 542$)

	NCI				HAND			
	OR	95% CI		*p*	OR	95% CI		*p*
Gender								
Female	1.00				1.00			
Male	0.85	0.55	1.32	0.471	0.85	0.51	1.44	0.551
Age								
18–44	1.00				1.00			
45–54	1.83	1.18	2.83	0.007	1.95	1.04	3.67	0.037
≥ 55	4.30	2.69	6.87	< 0.001	2.63	1.42	4.87	0.002
Ethnicity								
Caucasian	1.00				1.00			
Not Caucasian	2.01	0.67	6.08	0.214	2.86	0.91	9.05	0.073
Education (for each year more)	0.80	0.76	0.85	< 0.001	0.81	0.76	0.86	< 0.001
Mode of HIV transmission								
MSM	1.00				1.00			
IVDU	2.55	1.45	4.49	0.001	1.96	1.00	3.87	0.051
Heterosexual contact	2.10	1.42	3.11	< 0.001	1.88	1.19	2.98	0.007
Other/unknown	1.77	0.73	4.30	0.210	1.52	0.56	4.12	0.409
Years of HIV infection								
0–5	1.00					1.00		
5–9	0.87	0.52	1.43	0.575	0.87	0.76	0.43	1.41
≥ 10	1.84	1.23	2.76	0.003	1.84	1.52	0.95	2.44
cART								
No	1.00				1.00			
Yes	2.84	0.99	8.15	0.053	3.77	1.24	11.41	0.019
Nadir CD4 cell count/mmc								
> 200	1.00				1.00			
≤ 200	2.21	1.54	3.16	< 0.001	2.68	1.76	4.09	< 0.001
Current CD4 cell count/mmc								
0–500	1.00				1.00			
> 500	0.47	0.33	0.67	< 0.001	0.40	0.26	0.61	< 0.001
CD4/CD8 ratio								
≥ 1	1.00				1.00			
< 1	0.55	0.37	0.83	0.004	0.40	0.24	0.68	0.001
HIV RNA								
< 40 copies/mL	1.00				1.00			
≥ 40 copies/mL	1.60	0.98	2.60	0.058	1.85	1.02	3.35	0.042
BMI (kg/m^2)								
18–25	1.00				1.00			
< 18	2.00	0.71	5.64	0.191	1.90	0.59	6.14	0.286
25–29	0.93	0.63	1.39	0.739	0.68	0.41	1.13	0.136
≥ 30	1.54	0.74	3.20	0.244	1.72	0.77	3.82	0.185
HCV antibodies								
Negative	1.00				1.00			
Positive	2.11	1.34	3.33	0.001	1.71	0.99	2.94	0.927
Not tested/unknown	2.18	1.00	4.76	0.051	1.42	0.52	3.84	0.490
SGOT (for each 10 UI/mL higher)	1.13	1.03	1.25	0.014	1.15	1.03	1.28	0.013
SGPT (for each 10 UI/mL higher)	1.00	0.94	1.07	0.926	1.00	0.93	1.08	0.927
eGFR mL/min/1.73 m^2								
> 60	1.00				1.00			
< 60	1.81	1.19	2.75	0.006	1.60	0.98	2.63	0.061

Table 1 (continued)

	NCI				HAND			
	OR	95% CI		*p*	OR	95% CI		*p*
Dyslipidemia								
No	1.00				1.00			
Yes	1.14	0.69	1.89	0.616	1.31	0.74	2.33	0.356
Previous cardiovascular event								
No	1.00				1.00			
Yes	2.62	0.92	7.46	0.072	0.92	0.18	4.63	0.922
Hypertension								
No	1.00				1.00			
Yes	1.40	0.90	2.20	0.137	0.85	0.47	1.54	0.595
Diabetes								
No	1.00				1.00			
Yes	2.63	1.27	5.46	0.009	3.29	1.24	8.72	0.017
Vitamin D								
≥ 10 ng/nL	1.00				1.00			
< 10 ng/nL	2.05	1.15	3.66	0.015	2.26	1.18	4.34	0.014
Seasonality								
November–March	1.00				1.00			
April–October	1.11	0.78	1.58	0.547	1.07	0.70	1.62	0.758

NCI neurocognitive impairment, *HAND* HIV-associated neurocognitive disorders, *MSM* men who have sex with men, *IVDU* intravenous drug user, *cART* combination antiretroviral therapy, *BMI* body mass index, *HCV* hepatitis C virus, *SGOT* serum glutamic oxaloacetic transaminase, *SGPT* serum glutamate-pyruvate transaminase, *eGFR* estimated glomerular filtration rate

Discussion

Our results show that HIV-infected persons with vitamin D deficiency have a higher risk of NCI in general and HAND in particular. Accordingly, a significantly worse quantitative neurocognitive performance was found in presence of vitamin D levels < 10 ng/mL, when compared to that of patients with higher serum vitamin D levels. Hypovitaminosis D is a relevant condition regardless of HIV infection [30], and HIV-infected subjects the prevalence rates may vary between 14 and 52% depending on gender, season, ethnicity, lifestyle, geographic area and type of cART [29, 30]. By identifying a novel and modifiable factor associated with neurocognition, our result may add some relevant information for the management of NCI and HAND, potentially ameliorating quality of life of HIV-infected persons.

The biological plausibility that vitamin D influences neurocognition is based on animal studies [31–34] and more than one pathogenetic pathway can be hypothesized for the association of hypovitaminosis D with neurocognitive dysfunction. First, Garcion et al. [35] suggested that vitamin D, when sufficiently present, crosses the blood–brain barrier and exerts its actions through vitamin D receptors (VDR), which are expressed in neuronal and glial cells in almost all regions of the CNS, and especially in the areas essential for cognition, such as the hippocampus, hypothalamus, cortex and subcortex. The neuroprotective effects of vitamin D in the CNS include regulation of the expression of enzymes responsible (tyrosine hydroxylase) for dopamine's production, norepinephrine/epinephrine, as well as promotion of neuron survival, by inhibiting oxidative pathways responsible for free radical formation in the brain through the increase of antioxidant (γ-glutamyl transpeptidase) production and the inhibition of the synthesis of inducible nitric oxide synthase (iNOS), a harmful enzyme for the brain. Second, some studies have demonstrated an association between hypovitaminosis D and diseases promoting microvascular and endothelial damage, such as hypertension, diabetes, metabolic syndrome, hyperlipidemia and chronic kidney disease. Suboptimal vitamin D status directly influences cardiovascular health by suppressing the renin–angiotensin system and stimulating cellular proliferation and differentiation via 25(OH)D binding to VDR in the heart, endothelium and vascular smooth muscle [36]. Thus, the association between low levels of vitamin D and atherosclerosis is not surprising and supports the vascular disease contribution to NCI and HAND etiology [18, 37].

Diabetes is a well-known predictive factor of NCI, especially in older patients [38] and our findings are in line with the previous studies; of note, a study performed in the ANRS CO3 Aquitaine cohort, showed that people with HIV-1 infection and diabetes, performed significantly

worse on nine neuropsychological tests with worse cognitive performances in several cognitive domains [39].

For the sake of clarity, some limitations of our study need to be mentioned. First, the cross-sectional fashion of the study design makes causal inferences between hypovitaminosis D and neurocognition impossible. Second, evaluation of hypovitaminosis D and cerebrospinal fluid biomarker of HIV-associated neurocognitive disorder would have added information on biological plausibility, but lumbar puncture was not performed in our patient population. Third, the study does not allow to draw conclusions whether our findings are exclusive for HIV infection or not, because it focuses only on HIV-infected subjects. However, in the general population, the association of vitamin D deficiency and chronic illnesses involving neurocognitive decline has already been demonstrated. Lastly, generalizability of our findings to different clinical settings may be hampered until the gaps in standardization and harmonization of vitamin D metabolite measurements are overcome [40, 41].

In HIV-positive persons, severe hypovitaminosis D was independently associated with a higher risk of neurocognitive impairment in general, and of HIV-associated neurocognitive disorders in particular. Future studies are needed to elucidate the causal relationship, and whether vitamin D supplementation may reverse this risk.

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Author contributions Each author participated sufficiently in the work giving substantial contributions to realization; AAm, AAn, CP, SC and AV made contributions to the study conception and design, interpretation of data, drafting and revising the manuscript; ACB performed the neurocognitive assessment, RL, IM and ACB contributed to the acquisition of data, PL carried out the statistical analysis. All authors contributed to the intellectual content and gave their final approval to the submitted manuscript.

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Compliance with ethical standards

Conflict of interest Adriana Ammassari (AAm) received speaker's fees from AbbVie, BMS, Gilead, Janssen Cilag, Merck, ViiV and participated in Advisory Boards for Merck and Janssen; Andrea Antinori (AAn) received personal fees for consultancy and lectures from AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, ViiV and research institutional grants from Bristol Myers Squibb, Gilead, Janssen, ViiV. Carmela Pinnetti (CP) participated in Advisory Boards for Janssen and received speaker's fees from Gilead. For the remaining authors, none were declared.

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