Journal of NeuroVirology
https://doi.org/10.1007/s13365-021-00944-6

Association between high proviral load, cognitive impairment, and white matter brain lesions in HTLV-1-infected individuals

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Received: 7 August 2020 / Revised: 17 December 2020 / Accepted: 12 January 2021

Abstract

The association between high proviral load (PVL) in peripheral blood mononuclear cells (PBMC), cognitive disturbance and white matter brain lesions in HTLV-1-infected individuals is still undefined. A cross-sectional study included 62 participants: 22 asymptomatic carriers (mean age 43.4 ± 13.1 years old), 22 patients with HTLV-1-associated myelopathy (HAM/TSP) (mean age 51.5 ± 8.7 years old), and 18 uninfected controls (mean age 52.3 ± 11.1 years old). All individuals fulfilled the following criteria: between 18 and 65 years of age, more than 4 years of formal education, and completed neuropsychological evaluation and HTLV-1 serology. Infected individuals underwent brain conventional magnetic resonance imaging and PVL quantitative PCR (qPCR). Statistical analysis was adjusted in the models by age and education. Cognitive deficit was observed in all groups. Patients with HAM/TSP showed higher neurocognitive deviation in attention and motor skills, higher frequency (84%) of brain white matter lesions, and higher PVL median (range) 8.45 (0.5–71.4) copies/100 PBMC. Brain white matter lesion was associated with verbal memory deficit in HTLV-1-infected individuals (HAM/TSP and asymptomatic carriers) ($p = 0.026$). In addition, there was a correlation between higher PVL and neurocognitive dysfunction score (processing speed of visuomotor information and visuoconstructive praxis) in HTLV-1-infected patients. The study demonstrates an association between HTLV-1 infection, neurocognitive disorder, and white matter brain lesions on MRI as well as a correlation with higher HTLV-1 PVL, suggesting that the central nervous system involvement by HTLV-1 is not restricted to the spinal cord but involves the whole neuro-axis. HTLV-1-infected individuals should be tested for cognitive impairment.

Keywords HTLV-1 · HTLV-1-associated myelopathy · Tropical spastic paraparesis · Cognitive impairment · Magnetic resonance imaging

Introduction

Human T-lymphotropic virus type-1 is the first human retrovirus isolated in humans (Poiesz et al. 1980). An estimated 5 to 10 million individuals are infected with HTLV-1 worldwide (Gessain and Cassar 2012). HTLV-1 infection is endemic in Africa, Japan, Central, and South America, with social impact and financial costs for infected individuals, their families, and health systems. HTLV-1-infected lymphocytes may cross

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Published online: 02 February 2021

the blood-brain barrier. One to five percent of infected individuals develop neurological disease, of which HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is the most frequent manifestation. HAM/TSP is a chronic disabling disease resulting from spinal cord inflammation (Osame 1990). Brain white matter lesions and cognitive disturbances have been reported in HTLV-1 infection (Bagnato et al. 2005; Gascon et al. 2017). However, there are few neuropsychological studies with detailed description of the procedures and instruments. Furthermore, it is not known whether any observed cognitive impairment is due to aging or is related to HTLV-1 infection.

In this study, we evaluated the neuropsychological findings of patients with HTLV-1 infection (HAM/TSP and asymptomatic carriers) and uninfected controls. In HTLV-1-infected individuals, the neuropsychological findings were compared with the presence of magnetic resonance imaging (MRI) brain white matter lesions and correlated with HTLV-1 proviral load (PVL) in peripheral blood mononuclear cells (PBMC).

Methods

Study participants

A cross-sectional, observational study of HTLV-1-infected and -uninfected individuals of known serostatus, aged between 18 and 65 years old, with 4 years of schooling and no other neurological disease or chronic viral illness.

A total of 68 individuals were recruited, 47 HTLV-1 infected from the neuroinfection outpatient clinic of Gaffrée and Guinle University Hospital (HUGG), during the period 2008–2018. The uninfected control group was randomly selected from hospital workers and patients' relatives. All patients with a diagnosis of dementia, epilepsy, psychiatric disorders, traumatic brain injury, B12/folate deficiency, hypothyroidism, alcoholism, drug addiction, arterial hypertension, stroke, diabetes mellitus, multiple sclerosis, pregnancy, viral hepatitis, HIV infection, or syphilis were excluded. All subjects underwent HTLV-1 serological screening by enzyme-linked immunosorbent assay (Murex HTLV-I + II, Diasorin, UK), and reactive sera were further tested by Western blot (HTLV BLOT 2.4-Genelabs Diagnostics, Science Park, Singapore). Six individuals whose assessments were not complete were excluded. The project was approved by the HUGG ethical committee board (47/2007). All participants gave written informed consent.

The study population ($n = 62$) was divided into three groups: uninfected group (A) (18 HTLV-1 seronegative individuals); and two HTLV-1-infected groups, composed respectively of 22 asymptomatic (B) and 22 symptomatic with neurological disorder (HAM/TSP) (C) individuals according to Osame (1990) criteria.

Neurocognitive measures

The tests were selected because they are sensitive, previously validated in HIV-infected individuals, and

Table 1 Neurocognitive tests and functions evaluated

Neuropsychological functions	Neuropsychological tests
Attention	Digit Span test, Arithmetic, Stroop Test Victoria, Trial test (A/B)
Orientation	Mini-mental State Examination (MMSE)
Language	Verbal Fluency Test; Vocabulary
Memory	Rey Auditory-Verbal Learning Test (RAVLT); Logical Memory I/II, Vocabulary; Digit Span test Mini-mental State Examination (MMSE)
Executives functions	Digit Span test, Arithmetic, Stroop Test Victoria, Trial test(A/B)
Visuospatial skills	Rey Osterrieth Complex Figure (REY), Cubes,
Visuoconstruction práxis	Rey Osterrieth Complex Figure (REY), Cubes;
Processing speed of visuomotor information	Dygit symbol (DSY)
Calculation	Mini- mental State Examination (MMSE); Arithmetic
Motor skill	Grooved Pegboard

Digits: *DSF* digit span forward, *DSB* digit span backward, *Stroop C* stroop color, *Stroop W* stoop word, *Stroop C/W* stroop color/word; Trial A/B: *MMSE* mini-metal state examination, *VFF(FAS)* verbal fluency fonemic, *VFS* verbal fluncy semantic, *RAVLT* rey auditory-verbal learning test, rol lA1,A5,A6,A7, *R/B* roll B, *%A7/A5* retention percentage A7/5, *%A7/6* retention percentage A7/6, *REC/A* remembrance A, *REC/B* remembrance B, *RFC/C* Rey figure complex/copy, *RFC/E* Rey figure complex evocation, *PI* proactive interference, *RI* retroactive interference, *LMI* logical memory I, *LMII* logical memory II, *DSY* digit symbol, *GDOMH* grooved dominant hand, *GNDOMH* grooved not dominant hand

also used in cases of HTLV-1 infection (Lezak 2004; Cartier and Gomaz 1999; Gascon et al. 2017). The tests were performed in one single session lasting 120 min by the same neuropsychologist (RSK) and included Mini-mental State Examination (MMSE) (Folstein et al. 1975); Rey Auditory-Verbal Learning Test (RAVLT) (Diniz et al. 2000) Stroop Test Victoria consisting of color (STRC) and color-word (STCW) (Strauss et al. 2006); Verbal Semantic and Phonetic Fluency (animals, fruits, letters F A and S) (Machado et al. 2009); and Rey-Osterrieth Complex Figure Rey (Rey 1999) subtests Wechsler: Vocabulary, Arithmetic, Digit Span Forward and Backward (DSF and DSB, respectively), Cubes, Digit Symbol (DSY) (Wechsler 2004) Logical Memory I/II (WMS) (Wechsler (1997) Trail Making Test (A/B), and Grooved Pegboard with dominant and non-dominant hands (GDOM and GNDOM, respectively) (Strauss et al. 2006). Additionally, participants' mood information was obtained through the Beck Depression Inventory (BDI-II) (Gorestein et al. 2012) (Table 1).

After the neuropsychological assessment, the diagnosis of neurocognitive disorder (ND) was made according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-V which is based on defined cognitive domains. (American Psychiatric Association 2013). Neurocognitive disorder was considered in the individuals with one and two standard deviations below expected standards for uninfected control in neuropsychological test performance. The neuropsychological deviation was calculated based on the z scores = individual direct score of infected (gross test value)–(mean of the values/standard deviation) of the group of non-infected individuals).

Structural neuroimaging acquisition

HTLV-1-infected individuals underwent conventional brain MRI examination on 3.0 T scanner equipment (TIM Trio, Siemmens, Germany). The protocol included the following guidelines and sequences for the brain: sagittal T1, coronal T2, and axial Fluid Attenuated Inversion Recovery (FLAIR) after intravenous gadolinium injection. All MR imaging was reported by a neuroradiologist blind to clinical status.

Laboratory assessment of proviral load quantification

Proviral load in peripheral blood mononuclear cells (PBMC) was analyzed by real-time PCR using the TaqMan system (Applied Biosystems, Foster City, CA). HTLV-1 proviral load was calculated by the formula: HTLV-1 copy number (pX) per 100 cells = (pX copy number) / (β-actin copy number/2) × 100 (Nagai et al. 1998). To generate standard curves, DNA from human mononuclear cells (uninfected for HTLV-1) was used for actin gene amplification and TARL2 cells (infected rat cell line with 1 copy of HTLV-1 per cell) for amplification of the HTLV-1 Tax gene (Nagai et al. 1998; Rosadas et al. 2013).

Statistical analyses

The descriptive analysis presented the observed data in the form of tables, expressed by measures of central tendency and adequate dispersion for numerical (quantitative) data and by frequency (n) and percentage (%) for categorical (qualitative) data.

The inferential analysis was composed by the method of Generalized Linear Models (GLM) adjusting for the age factor and education, when necessary, in order to verify the association between the scores and their neuropsychological deviations with the occurrence of symptoms, white matter lesions, and proviral load. The comparison of demographic data between the three groups of symptoms was analyzed by Tukey or Kruskal-Wallis Dunn multiple comparison tests, this for data with non-normal distribution, and by the chi-square test (χ^2) for categorical data.

The normality in the distribution of data within each group was verified by Shapiro-Wilk's and graphical analysis of the histograms. The criterion for determining significance was set at 5%. The statistical analysis was processed using the SAS 6.11 software (SAS Institute, Inc., Cary, NC).

Results

Participants

Overall, there was a predominance of women (63%). The asymptomatic infected group was younger ($p < 0.005$) in comparison with uninfected participants and patients with HAM/TSP who also had less time in education ($p < 0.005$) (Table 2).

Clinical, laboratory, and imaging features

The median duration of symptoms of patients with HAM/TSP was 9 years (range 1–33 years). According to the screening instruments, none of the participants had a neuropsychological profile suggestive of dementia (Mini-mental State Examination, MMSE) nor depression (Beck Inventory for Depression, IDB). Brain white matter

Table 2 Demographic findings

Demographic variable	Group A Uninfected	Group B Asymptomatic infected	Group C HAM/TSP	*p* = value		
	(*n* = 18)	(*n* = 22)	(*n* = 22)	A × B	A × C	B × C
Female (%)	11 (61.1%)	13 (59.1%)	15 (68.2%)	0.89	0.80	0.53
Age (years) Mean ± SD	52.3 ± 11.1	43.4 ± 13.1	51.5 ± 8.7	0.038	0.97	0.046
Schooling years Median (range)	11(11—11)	11 (8—11)	9 (6.8—11)	0.42	0.020	0.13

Sex data were expressed by frequency and percentage (%) and compared by chi-square test (χ^2); age in years was expressed as mean ± standard deviation and compared by Tukey's multiple comparison test, and education in years was expressed by the median and interquartile range (Q1–Q3) and compared by the Kruskal-Wallis Dunn multiple comparison test

lesions on MRI were most frequent (84%) in patients with HAM/TSP ($p < 0.005$). The preferential brain location was periventricular (52.9%) semioval centre and corona radiata (52.9%), frontal lobes (47.05%), occipito-parietal lobe (11.8%), and pons (1.58%). However, brain white matter lesions were also found in asymptomatic carriers (57%), predominantly periventricular (17.6%), semioval centre and corona radiata (11.7%), frontal lobes (23.5%), parietal lobes (11.8%), and hippocampus reduced (5.9%). HTLV-1 PVL was higher in the patients with HAM/TSP than in the asymptomatic group ($p < 0.005$) (Table 3).

Neuropsychological deviation

Patients with HAM/TSP had a higher frequency of cognitive deficit (Table 3). Poor performance in Stroop test word, Grooved Pegboard (GDOM), and Digit Symbol (DSY) were observed in HAM/TSP patients. The typical HAM/TSP group score on the Stroop word variable was slower. These patients needed longer time to name colors and read names of colors compared with the asymptomatic carriers ($p = 0.024$). This variable informs about the processing speed in the execution of the task. The group with HAM/TSP was also slower in the Grooved Pegboard test, in the variable regarding motor dexterity agility in the dominant hand in comparison to asymptomatic ($p = 0.028$) and uninfected individuals ($p = 0.036$) (Table 4).

Association between white matter lesions and result neuropsychological tests in the infected individuals

Sixty-six percent (24/36) of infected individuals had brain white matter lesions: 84% of symptomatic-infected (HAM/TSP) and 47% of asymptomatic-infected participants. There was a significant association between brain white

Table 3 Mini-mental State Examination, Beck Inventory Depression, HTLV-1 Proviral Load and Brain Magnetic Resonance Findings of 62 individuals

Findings	Group A uninfected (*n* = 18)	Group B asymptomatic infected (*n* = 22)	Group C HAM/TSP (*n* = 22)	*p* = adjusted value
Mini-mental State Examination* Median (Range)	27 (20–30)	26 (19–30)	28 (24–30)	0.451
Beck's Depression Inventory** Mean ± SD	7.0 ± 2.75	12.4 ± 7,87	10.9 ± 7.6	0.262
Brain white matter lesion in MRI (%)	NA	8/17 (47%)	16/19 (84%)	0.0077
HTLV PVL*** (copies number/100 PBMC) Median (IQR; min-max)	NA	1.35 (7.1; 0.03–19.0)	8.45 (9.0; 0.5–71.4)	0.0082
Neurocognitive deficit	8/18 (44%)	9/22 (41%)	14/21 (67%)	0.195

Generalized Linear Model (GLM), adjusted for age and education. Mini-mental State Examination reference values for possible dementia: < 24 points with 8 years or more of schooling; < 18 points with 4 to 8 incomplete years of schooling; < 14 points 1 to 4 incomplete years of schooling (illiterate), (Folstein, 1975). Beck's Depression Inventory reference values—11–16 points (mild mood disorder), score > 16 (depression); *MRI* magnetic resonance imaging. Neurocognitive disorders were expressed by frequency and percentage (%) and compared by chi-square test ($\chi 2$)

*Krukal-Wallis Dunn test

**One way anova test

***proviral load of 19 HAM/TSP and 20 asymptomatic, Mann–Whitney Test

Table 4 Mean and standard deviation of neuropsychological scores of 62 individuals

TESTS	Group A uninfected ($n = 18$)	Group B asymptomatic infected ($n = 22$)	Group C HAM/TSP ($n = 22$)	p = adjusted value		
				A × B	A × C	B × C
LMI	18.9 ± 6.2	19.9 ± 7.1	20.0 ± 6.3	0.99	0.86	0.72
LMII	17.4 ± 5.4	19.0 ± 7.4	16.1 ± 7.1	0.99	0.96	0.96
LM%ret	96.6 ± 28.3	97.5 ± 28.3	80.0 ± 18.7	0.99	0.15	0.12
RAVLT A1	4.89 ± 1.88	5.68 ± 1.81	5.23 ± 1.57	0.53	0.74	0.98
RAVLT A5	10.3 ± 2.9	11.7 ± 2.0	10.8 ± 2.1	0.32	0.69	0.90
RAVLT A6	8.44 ± 4.13	9.86 ± 2.29	8.73 ± 2.96	0.61	0.80	0.98
RAVLT A7	9.33 ± 3.05	11.5 ± 2.3	10.1 ± 3.8	0.14	0.58	0.95
A/Total	41.0 ± 10.0	45.5 ± 8.1	42.0 ± 8.5	0.53	0.74	0.75
R/B	4.94 ± 1.51	4.95 ± 1.70	5.00 ± 1.90	0.99	0.97	0.92
%A7/A5	91.4 ± 18.6	98.5 ± 11.3	91.3 ± 27.7	0.56	0.96	0.58
% A7/A6	126 ± 41.4	120 ± 29	120 ± 39	0.98	0.80	0.94
REC/A	12.8 ± 2.1	13.4 ± 1.8	13.0 ± 2.1	0.81	0.93	0.99
REC/B	2.89 ± 2.61	2.73 ± 2.27	2.36 ± 3.16	0.99	0.99	0.99
RFC/C	32.9 ± 4.3	32.5 ± 4.2	30.1 ± 7.7	0.96	0.85	0.54
RFC/E	16.1 ± 9.4	17.7 ± 8.6	14.5 ± 6.5	0.99	0.99	0.99
PI	1.01 ± 0.32	1.31 ± 0.72	1.12 ± 0.35	0.12	0.97	0.23
RI	1.43 ± 0.58	1,22 ± 0.25	1.36 ± 0.45	0.45	0.77	0.93
Trail A	49.1 ± 10.6	46.8 ± 16.8	55.7 ± 31.3	0.98	0.95	0.78
Trail B	87.1 ± 32.3	95.6 ± 39.7	115 ± 67.2	0.72	0.55	0.99
Arithmetic	10.7 ± 3.1	11.0 ± 3.7	11.6 ± 4.1	0.78	0.35	0.89
Digits	11.9 ± 3.6	11.8 ± 2.3	11.9 ± 3.5	0.99	0.95	0.95
DSF	5.33 ± 1.03	5.18 ± 1.18	5.50 ± 1.26	0.99	0.68	0.60
DSB	3.67 ± 0.77	3.23 ± 0.87	3.0 ± 1.0	0.39	0.25	0.99
Cubes	27.9 ± 8.1	30.1 ± 14.9	23.8 ± 9.4	0.99	0.94	0.77
Vocabulary	37.1 ± 11.8	36.1 ± 13.4	35.1 ± 15.0	0.99	0.99	0.99
DSY	49.6 ± 16,0	52.2 ± 19.2	37.2 ± 13.3	0.98	0.15	0.050
Stroop C	19.1 ± 7.8	16.9 ± 4.8	22.5 ± 6.7	0.78	0.66	0.13
Stroop W	21.6 ± 6.2	18.1 ± 4.5	23.7 ± 6.4	0.11	0.96	0.024
Stroop CW	28.5 ± 8.1	26.1 ± 9.6	34.5 ± 10.3	0.99	0.20	0.11
VFF (FAS)						
F	11.7 ± 3.5	10.6 ± 3.8	11.1 ± 3.7	0.99	0.99	0.96
A	10.4 ± 3.3	10.5 ± 4.2	9.68 ± 3.3	0.98	0.99	0.89
S	9.33 ± 3.03	10.6 ± 3.0	9,59 ± 3.96	0.18	0.42	0.93
VFS						
Animals	14.8 ± 2.9	15.9 ± 4.6	14.5 ± 3.0	0.40	0.73	0.93
Fruits	14.7 ± 3.2	15.3 ± 2.7	13.8 ± 2.9	0.99	0.79	0.59
GDOMH	58.5 ± 18.6	53.3 ± 13.1	70.7 ± 19.0	0.99	0.036	0.028
GNDOMH	42.4 ± 11.9	43.6 ± 11.9	50.2 ± 15.4	0.63	0.15	0.76

Generalized Linear Model adjusted for age and education with Sidak's multiple comparison test. Data correspond to neuropsychological score and were expressed as mean and standard deviation according to the occurrence of symptoms (HAM/TSP). Group A, uninfected; Group B, asymptomatic infected; and Group C, symptomatic infected (HAM / TSP). CN, normal controls. See abbreviations in Table 1

Table 5 Neurocognitive disorders and brain white matter (WM) injury, adjusted for age, and education

Tests	Brain WB lesion ($n = 24$)	No lesion ($n = 12$)	p = adjusted value
LMI	0.12 ± 1.08	0.51 ± 0.89	0.1
LMII	− 0.10 ± 1.36	0.36 ± 1.21	0.8
LM%ret	0.12 ± 1.80	− 0.14 ± 0.94	0.7
RAVLT A1	0.19 ± 0.77	0.68 ± 0.53	0.6
RAVLT A5	0.67 ± 1.28	0.70 ± 0.71	0.4
RAVLT A6	0.26 ± 0.62	0.67 ± 0.51	0.6
RAVLT A7	0.19 ± 0.66	0.41 ± 0.57	0.6
RAVLT/TOT	0.59 ± 0.80	0.74 ± 0.91	0.3
L/B	0.07 ± 1.32	0.23 ± 1.07	0.8
%A7/A5	0.47 ± 0.69	0.08 ± 0.90	0.03
% A7/A6	1.16 ± 1.68	0.54 ± 0.65	0.6
REC/A	0.27 ± 1.00	0.06 ± 0.87	0.2
REC/B	0.04 ± 1.33	0.20 ± 0.82	0.1
PI	1.26 ± 0.68	1.17 ± 0.44	0.9
RI	1.30 ± 0.40	1.28 ± 0.33	0.2
RCF/C	− 0.50 ± 1.62	0.29 ± 0.65	0.1
RCF/E	− 0.12 ± 0.74	0.50 ± 0.97	0.4
Trial A	0.50 ± 2.92	0.03 ± 1.79	0.8
Trial B	0.88 ± 1.94	0.10 ± 1.25	0.1
Arithmetic	0.40 ± 1.35	0.18 ± 1.15	0.6
Digits	0.09 ± 1.26	0.65 ± 0.82	0.1
DSF	0.09 ± 1.06	0.28 ± 1.51	0.3
DSB	0.93 ± 1.20	− 0.15 ± 0.84	0.5
Cubes	− 0.40 ± 1.18	0.87 ± 1.83	0.3
Vocabulary	− 0.13 ± 1.27	0.25 ± 0.81	0.5
DSY	− 0.36 ± 0.94	0.38 ± 1.15	0.4
Stroop C	0.24 ± 0.91	− 0.26 ± 0.60	0.8
Stroop W	− 0.05 ± 0.95	− 0.48 ± 1.19	0.4
Stroop CW	0.29 ± 1.34	− 0.18 ± 1.20	0.4
FVF (FAS)			
F	− 0.20 ± 0.97	0.04 ± 1.00	0.6
A	− 0.17 ± 1.19	0.43 ± 0.99	0.1
S	0.10 ± 1.3	0.28 ± 0.89	0.4
FVS			
Animals	− 0.14 ± 1.05	0.73 ± 1.57	0.2
Fruits	− 0.38 ± 0.46	− 0.04 ± 0.59	0.2
GDOM	0.55 ± 0.83	− 0.17 ± 1.24	0.6
GNDOM	0.64 ± 1.16	− 0.06 ± 1.24	0.5

Generalized Linear Model adjusted for age and education. Data correspond to neuropsychological deviations and were expressed as mean and standard deviation according to the occurrence of brain white matter lesion. A negative neuropsychological deviation expresses a score below the control and a standard positive deviation above control. See abbreviations in Table 1

matter lesion and worsening in the performance of Rey Auditory-verbal Learning Test (RAVLT) in the variable (% A7/A5) ($p = 0.026$), regardless of age, education, and the presence of symptoms (HAM/TSP) in the infected individuals. This indicates alteration in verbal memory (Table 5). The frequency of cognitive deficit in symptomatic individuals (HAM/TSP) with brain white matter lesions was 58% (11/19) and 29% (5/17) in asymptomatic individuals. Those who had brain white matter lesions show a lower memory score and percentage of information retention when compared with those who did not have such lesion.

Table 6 Correlation of proviral load with neuropsychological deviations in HTLV-1-infected individuals ($n = 39$)

Tests	MLG coefficient	p = adjusted value
LMI	− 0.0047	0.5
LMII	− 0.0057	0.5
LM%ret	− 0.0013	0.9
RAVLT A1	− 0.0073	0.4
RAVLT A5	− 0.0009	0.9
RAVLT A6	− 0.0032	0.5
RAVLT A7	− 0.0010	0.0
RAVLT/TOT	− 0.0044	0.5
L/B	− 0.0064	0.5
%A7/A5	− 0.0018	0.8
% A7/A6	− 0.0058	0.6
REC/A	− 0.0053	0.4
REC/B	− 0.0132	0.3
PI	− 0.0005	0.9
RI	− 0.0020	0.5
RCF/C	− 0.0315	< 0.0001
RCF/E	− 0.0091	0.1
Trial A	− 0.0003	0.1
Trial B	− 0.0027	0.9
Arithmetic	− 0.0041	0.7
Digits	− 0.0133	0.2
DSF	− 0.0128	0.9
DSB	− 0.0106	0.2
Cubes	− 0.0176	0.08
Vocabulary	− 0.0095	0.3
DSY	− 0.0154	0.03
Stroop C	0.0045	0.4
Stroop W	− 0.0040	0.6
Stroop CW	− 0.0082	0.4
FVF (FAS)		
F	− 0.0058	0.4
A	− 0.0008	0.9
S	− 0.0025	0.0
FVS		
Animals	− 0.0098	0.3
Fruits	− 0.0022	0.6
GDOM	− 0.0028	0.6
GNDOM	− 0.0077	0.3

GLM Generalized Linear Model adjusted for age. The GML coefficient was presented only to express the direction of the relationship between viral load and neuropsychological deviations, a positive coefficient expresses a direct relationship, and a negative coefficient expresses an inverse relationship. See abbreviations in Table 1

Inverse correlation between cognitive performance and HTLV-1 proviral load

HTLV-1 PVL was quantified in PBMC of 39 infected individuals, with a median of 4.2 copies/100 PBMC (0.03–109.2). Table 6 shows the coefficient of the generalized linear model (GLM) and the corresponding descriptive level (p value) of the adjusted and unadjusted for the age factor. The majority of neuropsychological tests had a negative coefficient (inverse correlation) in relation to the level of the PVL, although with no statistically significant value. There was a significant inverse correlation between proviral load and the Rey figure complex/copy (RFC/C) score ($p < 0.0001$) and Digit symbol (DSY) score ($p = 0.030$) regardless of age-adjusted (Table 6). This means that infected individuals with higher proviral load had worse graphical execution ability (RFC/C) and processing speed of visuomotor information (DSY).

Discussion

In this study, patients with HAM/TSP had a higher frequency of cognitive deficits, regardless of age and education level compared with uninfected and infected controls. This group had a lower performance in comparison to the reference group (uninfected controls) in the following functions: attention, information processing speed, and motor skills. Our analysis was based on the raw test scores transformed into z-score, allowing the analysis of neuropsychological deviation from the mean of the uninfected controls, adjusted for age, and education. Most of previous studies have showed deficits in the skills: attention, working memory, visual memory, information processing speed, and visuoconstructive praxis in patients with HAM/TSP, but it may also be found in asymptomatic carriers (Cartier et al. 1992; Cartier and Gomaz 1999; Silva et al. 2003; Gonçalves et al. 2017). These neurocognitive abilities have in common the activation of cortico-subcortical circuits, with high implication of the anatomical and functional integrity of the encephalic white matter. Attention and speed of information processing are largely related primarily to fronto-temporal regions that connect directly or indirectly through basal nuclei and fascicles (Cummings and Benson 1984; Cummings 1993; Aglioti 1997). Information processing speed is related to the integrity of the white matter underlying all cortical regions (Van den Heuven et al. 2006; Turken et al. 2008). It is noteworthy that the brain lesions of patients with HAM/TSP are similar to those found in healthy elderly, vascular disease, and multiple sclerosis (Melo et al. 1993). These brain lesions found in HAM/TSP patients may be related to the underlying infection as well as the aging process (Kertsz et al. 1998). HTLV-1 infection has been shown to have an impact on white matter integrity (Fukushima et al. 1994; Nakagawa et al. 1995; Kira et al. 1998; Bagnato et al. 2005; Morgan et al. 2007; Puccioni-Sohler et al. 2012) with a high frequency of white matter lesions (69–86%) in

patients with HAM/TSP as well in asymptomatic carrier (85%). Subcortical white matter lesions are predominantly located in the fronto-central regions, fronto-striated and frontal region. We also found white matter lesions with predominance in the frontal lobe, periventricular region, semioval centre, parieto-occipital and fronto-temporo-parietal lobe in HAM/TSP patients, and HTLV-1 carriers. In general, these findings were associated with verbal memory alteration.

The origin of white matter changes observed on brain MRI in HTLV-1 infection is still controversial. For hypotheses, white matter involvement between cortical and subcortical areas may be altered due to infectious and inflammatory mechanisms associated with cognitive symptomatology of HTLV-1-infected individuals. In this sense, our analysis revealed an association between subcortical white matter injury and neuropsychological performance in verbal memory ability in infected individuals (with and without HAM/TSP). Similarly, in a previous case report published by our group (Mendes et al. 2014), we observed extensive lesions arranged bilaterally in the semioval center, radiated corona, and white matter frontotemporal areas. The neuropsychological assessment revealed below average expected performance in verbal memory, suggesting a possible association between presence of brain injury and impairment of cognitive functions.

Our analysis revealed higher proviral load in PBMC in patients with HAM/TSP, consistent with the literature, although some HTLV-1 carriers also had high PVL (Rosadas et al. 2013; Morgan et al. 2007; Champs et al. 2019). Our results revealed an inverse correlation between PVL and neuropsychological tests of functions processing speed of visuomotor information and constructive praxis in infected individuals (HAM/TSP and asymptomatic carrier). The constructive praxis included an inability to graphically draw a previously indicated design or three-dimensional constructions in individuals with high PVL. This function is related to the integrity of frontotemporal circuits, including premotor cortex (Lezak, 2004). Digit symbol test allows us to verify the integrity of the information processing speed function how quickly the individual processes the visuomotor information. In neural terms it is related to the integrity of the white substance, for the functionality of different eminently cortical regions (Van den Heusen et al. 2006). PVL is one of the most relevant prognostic factors of HTLV-1 neurological associated disorders. The most evident of which is the spinal cord white matter (Nagai et al. 1998). Thus, the greater the proviral load in the PBMC, less skilled the neurocognitive function (short-term memory and episodic memory and learning). A previous study did not find any correlation between cognitive performance and high PVL (Champs et al, 2019), although only HAM/TSP patients were included in this analysis.

Patients with HAM/TSP presented cognitive performance (attention/information processing speed and motor dexterity) below that achieved by asymptomatic and uninfected infected individuals. Our results show that there is a correlation between the elevation of the HTLV-1 PVL in the PBMC and neuropsychological deviations in constructive praxis and information processing speed measurements in HTLV-1-infected individuals (HAM/TSP and HTLV-1 carriers). These findings suggest that infected individuals without HAM/TSP may present subclinical brain involvement due to the high PVL. Correlation of proviral load in PBMC and neurocognitive performance was significant in tasks requiring integrity of subcortical activation. The brain MRI revealed a significance association between subcortical white matter injury and neurocognitive impairment in verbal memory ability in symptomatic-infected individual (asymptomatic and HAM/TSP), suggestive of early involvement of the central nervous system. Despite the limitation of the sample size, our results were relevant regarding the cognitive functioning of individuals with HTLV-1 infection. Our results were pioneering in comparing white matter injury with neuropsychological skills and viral quantification performance under HTLV-1 infection (HAM/TSP and HTLV-1 carrier). Our data suggest that infected individuals without spinal cord lesion (HAM/TSP) may present brain subclinical disease, which correlates with high PVL. Since HTLV-1 does not infect neurons, persistent inflammatory activity may be the cause of the brain white matter lesion and cognitive impairment found in HTLV-1-infected individuals (Champs et al. 2019). This study suggests cognitive impairment may be a long-term clinical manifestation of HTLV-1 infection. There is evidence that the therapy introduced early (shorter time of symptoms and milder stage) can change the natural history of the HAM/TSP (Araújo et al. 2020).

Conclusions

Considering our findings, it is crucial to incorporate neuropsychological measures into early diagnostic techniques to obtain greater precision of the impact of HTLV-1 infection on the CNS. We therefore propose that cognitive function tests, brain MRI. and CSF studies for markers of inflammation are justified in high PVL carriers, to direct the use disease modifying drug therapy (corticosteroid therapy) (Araújo et al. 2020).

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