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Cognitive impairment in HTLV-1-associated myelopathy, proviral load and inflammatory markers

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ABSTRACT

Objectives: Myelopathy is a well-established long-term clinical manifestation of HTLV-1 infection. Besides motor dysfunction, cognitive impairment may be another consequence of HTLV-1 infection. Moreover, inflammatory markers may be associated with cognitive impairment in these patients. The present study compared the cognitive performance of HAM/TSP patients with healthy controls and investigated the associations between cognitive performance, proviral load and blood inflammatory markers.
Methods: Eighty-three patients fulfilling diagnostic criteria for HAM/TSP were submitted to a comprehensive clinical, cognitive and functional evaluation, brain magnetic resonance imaging and determination of levels of IL-1β, IL-6, TNF-α, immunoglobulins and HTLV-1 proviral load in blood and cerebrospinal fluid. The control group was composed of 88 cognitively healthy subjects, matched for age, sex and educational level.
Results: Compared to healthy subjects, HAM/TSP patients displayed significant global cognitive impairment and executive function deficits. HAM/TSP cognitive impairment was significantly associated with altered levels of IgM, IgG, IL-6 and TNF-α in blood. There was no association between HAM/TSP cognitive impairment and HTLV-1 proviral load.
Conclusions: This study suggests cognitive impairment may be a long-term clinical manifestation of HTLV-1 infection, which seems to be linked to the persistent inflammatory activity that is found in the disease.

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) infects around 10–20 million people worldwide, although these figures may be underestimated (Gessain and Cassar, 2012). The infection is associated with neurological conditions such as myelopathy, peripheral neuropathy and myopathy (Araujo and Silva, 2006; Cooper et al., 2009). Myelopathy (HAM/TSP) is the most frequent manifestation of HTLV-1 infection, representing a serious incapacitating disease, with no currently curative option or therapies to modify the course of the disease (Champs et al., 2010; Olindo et al., 2006).

As HTLV-1 infection causes motor dysfunction, its association with cognitive impairment is a plausible hypothesis. The association between HTLV-1 infection and cognitive impairment/dementia has been described in case reports and case series (Lycke et al., 1993; Cartier et al., 1997; Champs et al., 2013; Castillo et al., 1999; Cartier et al., 1992). Compared to healthy controls, HTLV-1 infection was described as a risk factor for vascular dementia and cognitive impairment (Kira et al., 1997; Silva et al., 2003).

HTLV-1-related cognitive impairment may be associated with viral infection or its inflammatory response. Higher levels of interleukin (IL) 8, IL-1β, IL-6 and tumour necrosis factor-alpha (TNF-α) have been associated with cognitive dysfunction among

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elderly subjects and those with rheumatologic diseases (Dik et al., 2005; Mcafoose et al., 2009; Kozora et al., 2001). Higher plasma levels of IL-1β, IL-6, and TNF-α have been associated with cognitive decline in chronic hepatitis C infection, Alzheimer's disease and depression (Hilsabeck et al., 2010; Dursun et al., 2015; Spanemberg et al., 2014).

The paucity of studies motivated us to perform a comprehensive clinical and laboratory approach to investigate the association between cognitive performance, proviral load and inflammation in HAM/TSP patients. Our hypothesis was that since HTLV-1 infection causes a chronic inflammatory disease as HAM/TSP, the inflammation or the viral load may also have detrimental effects on cognition.

Methods

We conducted a cross-sectional controlled study comprising HAM/TSP patients selected from a cohort of 520 HTLV-I patients. All patients had progressive paraparesis, varying from a few months to years, neurogenic bladder symptoms and positive anti-HTLV-I antibodies in blood serum (n = 310) (De Castro-Costa et al., 2006). We excluded all patients with diagnosis of other causes of dementia, epilepsy, major psychiatric disorders, traumatic brain injury, B12/folate deficiency, hypothyroidism, alcoholism, drug addiction, HIV infection and syphilis (excluded n = 133). Patients with depression under treatment were eligible for this research, given that they were euthymic by the time of evaluation. Twenty-four individuals decline to participate, seven were missing and 32 were not found. So, 114 HAM/TSP patients were selected.

Healthy hospital workers and patients' relatives, with no history of neurological or psychiatric diseases and without cognitive complaints, composed the control group. The hospital workers were selected following a random list, in order to reduce the selection bias. It was not possible to random the patient's relatives. To reduce selection bias, we selected those patient relatives who were in the even position in the list of visitors. We excluded those who had alcohol or drug addiction. We selected 121 healthy controls. After matching for age and education, 83 patients with HAM/TSP and 88 healthy controls were eligible for this study.

The following independent variables were obtained among HAM/TSP patients: age, sex, schooling, duration of symptoms, vertical transmission, wheelchair dependence, tobacco use, presence of diabetes mellitus or hypertension and medications.

Cognitive tests were performed applied in a fixed order by a unique trained neuropsychologist in a quiet environment with good lighting and low levels of noise or other distracting stimulations. The Mattis Dementia Rating Scale (DRS) was used as a measure of global cognitive performance. The DRS evaluates different cognitive domains: attention (37 points), initiation/perseveration (37 points), construction (6 points), conceptualization (35 points) and memory (25 points) (Porto et al., 2003). The scores range from 0 to 144, with higher scores indicating better performance. Executive functioning was assessed by phonemic verbal fluency tests (F, A, S), versions A and B of Trail-Making Test (TMT) (Spreen and Strauss, 1998) and the Clock Drawing Test (CDT) (Eddy and Sriram, 1977). Version A TMT consists of 25 numbered circles randomly assigned to be united in a continuous line. The test involves connecting the numbers in ascending order without lifting the pencil from the paper. In version B, 13 letters and 12 numbers are alternately connected (1A, 2B, etc.). For the CDT, the individuals were asked to draw a clock with all the numbers and to set the hands to 11:10; the scores ranges from no impairment (0) to complete impairment (5) (Eddy and Sriram, 1977). Semantic memory was assessed by category fluency (animals/minute) (Spreen and Strauss, 1998).

Blood samples were collected after 8 h fasting. HTLV-1 proviral load was quantified using real-time PCR of DNA extracted from blood cells and was expressed as the number of copies of HTLV-1 DNA per 100,000 cells. IgA, IgG, IgM and IgE were measured using a chemiluminescent enzyme immunometric assay on a BN ProSpec system, and the IL-1β, IL-6, and TNF-α levels were measured using a chemiluminescent enzyme immunometric assay on an Immulite analyser (Siemens). We also evaluated numbers of CD4+ and CD8+T cells.

We decided to investigate our main hypothesis using routine clinical data. CSF was collected for clinical reasons and we did not collect CSF exclusively for this research. Moreover, the majority of patients had already had CSF collected for analysis before this study and we decided not to submit them to lumbar puncture again. For this reason, we only have 26 patients with HAM/TSP who had CSF collected during this research and studied HTLV-1 proviral load quantified using real-time PCR of DNA extracted from cells of CSF, IgA, IgG, IgM, intrathecal IgG synthesis rate and presence of oligoclonal IgG bands were also measured in the CSF by a chemiluminescent enzyme immunometric assay on a BN ProSpec system, as well as IL-1β, IL-6, and TNF-α levels measured using a chemiluminescent enzyme immunometric assay on an Immulite analyser (Siemens).

All HAM/TSP patients underwent a brain magnetic resonance imaging (MRI) to exclude other causes of cognitive impairment and dementia. Magnetic resonance imaging (MRI) was performed on a 1.5 Tesla whole body scanner (Signa Horizon, General Electrics Medical Systems, Milwaukee, Wisconsin), with a head coil. The imaging protocol included sagittal T1-weighted, axial fluid-attenuated inversion recovery (FLAIR), axial T2-weighted, axial gradient-echo and coronal T2-weighted sequences, all with 22–24 field of view, and 20–22 contiguous 5-mm-thick sections. All MRI scans were evaluated by only one expert radiologist (C. Mello). A lesion was defined if displaying hyperintensity on FLAIR images and if its size was > 3 mm. Brain atrophy was quantified by visual inspection.

Statistical analysis

We compared cognitive scores of HAM/TSP patients and controls. Impaired cognitive performance was defined as scores below the 95% confidence interval (CI) for all timed tests but TMT, when values higher than 95% CI were considered altered.

The *t* test or Mann-Whitney test compared data with normal or abnormal distribution, respectively. Yate's Chi-square test (X^2) was used to test for associations between the two groups and cognitive function in the univariate analysis.

Spearman's correlation coefficient measured the association between proviral load and inflammatory findings and cognitive tests. The significance level was set at 0.05.

All the independent variables with a significance level of 0.80 ($p<0.20$) were tested using multiple logistic regression.

Ethical aspects

The study was approved by the institutions' ethics committees of Sarah Network of Rehabilitation Hospitals and Federal University of Minas Gerais (ruling 664/08 COEP UFMG). A written informed consent was obtained from all the participants.

Results

The 83 HAM/TSP patients were mainly middle-aged (55.5 ± 13.1 years) women (74.6%), with a long history of disease (17.8 ± 10.4 years). Thirty-two (38.6%) patients were wheelchair-bound. Mean educational level was low (7.7 ± 3.8 years), with 75% of patients

Table 1
Sociodemographics and cognitive data of HAM/TSP patients and healthy controls.

	HAM/TSP N: 83	Healthy controls N: 88	*p*
Age (years)	55.8 ± 13.4	54.0 ± 5.1	0.54
Sex			
Female	62	54	0.06
Male	21	34	
Schooling (years)	7.7 ± 3.8	8.1 ± 3.1	0.27

having had less than eight years of schooling. Only three (3.6%) patients were smokers, 22 (26.5%) had high blood pressure, and eight (9.6%) had diabetes mellitus. The majority of patients did not use drugs with potentially deleterious effects on cognition: 12 (14.5%) used amitriptyline, six (7.2%) diazepam or clonazepam, nine (10.8%) oxybutynin and five (6.0%) reported the use of carbamazepine.

The participants from the two groups were matched for age ($p = 0.14$), sex ($p = 0.06$) and education ($p = 0.32$) (Table 1).

HAM/TSP patients performed significantly worse than healthy subjects in DRS total score and in attention, initiation/perseveration and conceptualization sub-scales, TMT-A and B and F, A and S fluencies (Table 2). Fifty (60.2%) HAM/TSP patients showed significant impairment in the DRS (total score), 71 (85.5%) in TMT-A, 41 (49.3%) in TMT-B, 43 (49.3%) in category fluency, 57 (68.6%) in F, A, S and 24 (28.9%) in the CDT, when compared with healthy subjects.

Among HAM/TSP patients, higher blood levels of IgG, IL-6 and TNF-α, and lower mean levels of IgM were significantly associated ($p < 0.05$) with decreased performance in some cognitive tests, although showing a weak correlation (Figure 1).

In the CSF analysis, most of the 26 patients showed higher levels of IgG, IL6, TNF-α, increased intrathecal IgG synthesis rate and presence of oligoclonal IgG bands (Table 3). Higher CSF levels of IL-6 were significantly associated with decreased proviral load in CSF (Figure 2).

In univariate analysis and multivariate analysis, no association was found between cognitive performance and duration of symptoms, hypertension, diabetes mellitus and the use of medications (amitriptyline, diazepam, clonazepam, oxybutynin and carbamazepine). There was no association between cognitive impairment, findings in brain MRI and the HTLV-1 proviral load or the plasma levels of IgE, IgA, IL1β and numbers of CD4+ and CD8 + T cells.

Brain MRI of participants with HAM/TSP showed twenty-two (26.5%) patients with brain atrophy and 50 (60.2%) patients with brain lesions.

Table 2
Mean and 95% CI values from cognitive tests for HAM/TSP patients and healthy controls.

Tests	HAM/TSP Mean (95% CI) N: 83	Healthy Controls Mean (95% CI) N: 88	*p*
DRS total score	124.3 (121.4–127.2)	131.7 (130.3–133.1)	<0.0001
DRS attention	34.7 (34.0–35.4)	35.8 (35.6–36.1)	0.02
DRS I/P	31.7 (30.6–32.78)	34.6 (33.98–35.2)	<0.0001
DRS construction	5.57 (5.3–5.8)	5.78 (5.6–5.9)	0.12
DRS conceptualization	29.8 (28.6–31.0)	32.1 (31.2–33.1)	0.004
DRS memory	22.4 (21.8–23.1)	23.2 (22.9–23.5)	0.54
TMT-A	107.5 (94.0–121.0)	49.6 (45.6–53.6)	<0.0001
TMT-B	203.2 (175.7–230.7)	136.9 (122.3–151.4)	<0.0001
Category fluency (animals)	15.6 (14.4–16.8)	16.7 (15.7–17.7)	0.12
Phonemic fluency (F, A, S)	25.5 (22.4–28.1)	31.5 (29.4–33.7)	<0.0001
CDT	3.7 (3.5–4.0)	3.9 (3.7–4.0)	0.45

Legend: DRS = Mattis Dementia Rating Scale; I/P = initiation/perseveration; TMT = trail making test; CDT = clock drawing text.

Discussion

In the present study, a high proportion of HAM/TSP patients displayed global cognitive impairment and executive dysfunction. Moreover, the higher levels of peripheral cytokines among patients with the worst cognitive performance suggest an inflammatory mechanism involved in the impaired cognitive function in HAM/TSP. Despite the weak correlation, it is of note that IgG, IL-6 and TNF-α have a negative correlation suggesting a chronic persistent inflammation linked to cognitive impairment. These findings may suggest cognitive impairment in HAM/TSP patients might be linked to the persistent inflammatory activity that is found in the disease.

We consider that our sample is similar to others from international (Olindo et al., 2006) and Brazilian studies (Moreno-Carvalho et al., 1992; Araujo et al., 1993; Domingues et al., 1995). HAM/TSP presents an insidious beginning and slow progression, individuals becoming symptomatic in their fourth and fifth decades of life, rarely prior to the age of 20 or after the age of 70. The disease more commonly affects women, with a sex ratio of about 2–3:1; 50% of patients are on a wheelchair after a mean time of symptom onset from 19 to 22 years.

Infected T CD4+ lymphocytes pass through the blood-brain barrier and interact with T CD8+ lymphocytes in the central nervous system, leading to parenchymal lymphocytic infiltration with the presence of macrophages and proliferation of astrocytes. This results in the production of TNF-α, IL-6, interferon (IFN)-γ and intrathecal antibody, resulting in consequent destruction of glial tissue and neurons, loss of myelin, and fibrillary gliosis. Aye et al. (Aye et al., 2000) reported brain perivascular cells infiltration in HAM/TSP and similar chronic lesions are seen in the spine and in the brain (Saito and Bangham, 2012; Futsch et al., 2018). HAM/TSP patients are characterized by elevated levels of IL-4, IL-6, IL-8, IFN-γ and TNF-α in their plasma and IFN-γ, TNF-α, IL-6, and IL-1β in the CSF (Raulino Goncalves et al., 2017). We hypothesize that a persistent inflammatory reaction is a potential aetiology for cognitive decline in HAM/TSP, because the secondary damage caused by inflammatory processes after virus infection is well known. It is possible that cytokines and other products of spinal cord inflammation could reach the brain via the CSF and affect cognitive functions.

This was not the objective of this study, but we found elevated levels of IL-6 correlated negatively with proviral load in CSF of fourteen patients with HAM/TSP. We suggest other scientists replicate this study with more HTLV-1-infected persons. It is likely that IL-6 may have some importance against this disease.

Cross-sectional studies had already detected a high frequency of cognitive impairment in patients with HAM/TSP (Gascón et al., 2017), suggesting that these alterations are an important clinical manifestation associated with myelopathy or even among asymptomatic carriers of HTLV (Craig et al., 2017). Patients presenting traumatic spinal cord injury showed 29% of impaired cognitive performance (Gascón et al., 2017), which may be related to multiple factors, such as inflammation, disability adjustment, depressive mood and medications. The results of this study

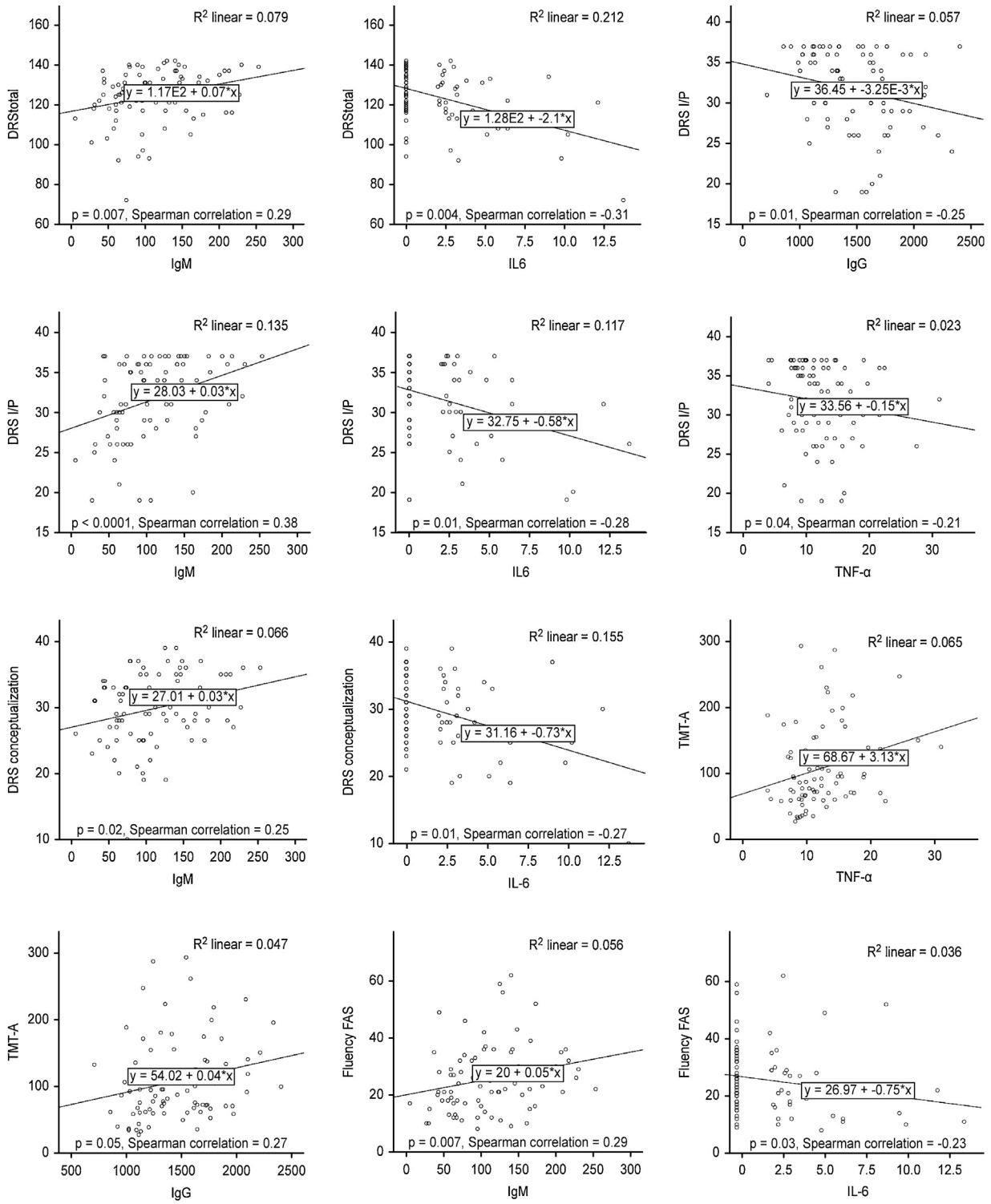

Figure 1. Blood Inflammatory findings and cognitive tests for HAM/TSP individuals.
Higher blood levels of IgG, IL-6 and TNF-α, and lower mean levels of IgM were significantly associated ($p < 0.05$) with decreased performance in cognitive tests, although showing a weak correlation.

corroborate the hypothesis that in the present study, these same factors might have contributed to cognitive impairment in HAM/TSP patients and elevated levels of the inflammatory parameters may not be directly attributable to HTLV-1 infection and CSF inflammation.

The cross-sectional controlled design of this study precludes any causal conclusion. HAM/TSP patients were recruited from a rehabilitation hospital and probably present more severe and chronic form of the disease and, it would be expected, a more severe cognitive impairment in these group of patients. Women are overrepresented in this group, since they generally seek health care more than men. The selection of controls does not allow generalization to the whole population. Besides that, there is no information about medications, diseases, laboratory tests and

Table 3
Cerebrospinal fluid analyses and MRI findings of 26 patients with HAM/TSP.

Participant	IL1β pg/ml	IL6 pg/ml	TNF-α pg/ml	Proviral Load/ 100,000cells	IgA mg/dl	IgG mg/dl	IgM mg/dl	Intrathecal IgG synthesis rate	proteins mg/dl	cells/ mm^3	Oligoclonal IgG bands	Brain Atrophy	Brain Lesions
1	<5.0	3.3	**18.5**	127246	0.48	3.22	0.02	0.66	24	3	No	**Yes**	No
2	< 5.0	< 2.0	5.4	IA	0.11	3.27	0.05	0.68	NT	N	NT	No	Yes
3	< 5.0	< 2.0	4.5	IA	0.35	3.04	0.02	0.57	25	1	No	No	Yes
4	< 5.0	< 2.0	6.3	NT	0.24	**3.52**	0.02	0.7	21	10	No	No	No
5	< 5.0	< 2.0	5.3	NT	0.54	3.9	0.02	NT	43	7	Yes	No	**No**
6	< 5.0	< 2.0	6.0	19789	0.46	**7.23**	0.05	NT	45	6	**Yes**	No	**Yes**
7	< 5.0	< 2.0	5.1	11391	**0.61**	4.42	0.03	0.69	**49**	1	**Yes**	**Yes**	**Yes**
8	< 5.0	< 2.0	6.5	NT	0.09	1.33	0.02	0.52	25	1	NT	No	No
9	< 5.0	**3.5**	7.0	5412	0.77	4.62	0.05	0.78	39	8	NT	**Yes**	Yes
10	< 5.0	**3.8**	7.5	9574	**16.10**	**19.65**	0.06	**1.28**	**80**	18	**Yes**	No	**Yes**
11	IA	IA	IA	NT	0.28	0.07	**4.75**	0.74	33	15	**Yes**	No	**No**
12	< 5.0	2.8	6.6	13261	0.5	7.0	0.04	**1.34**	23	36	**Yes**	No	**Yes**
13	< 5.0	**3.5**	6.1	12905	0.63	**18.2**	**0.15**	**1.51**	**47**	12	**Yes**	No	**Yes**
14	< 5.0	2.9	6.5	13490	0.42	**9.26**	0.02	**1.37**	41	5	NT	No	No
15	< 5.0	**8.2**	**11.2**	13	NT	NT	NT	**1.4**	**77**	75	**Yes**	No	**No**
16	< 5.0	2.4	5.2	IA	0.24	**4.56**	0.07	NT	26	12	No	No	No
17	< 5.0	**4.5**	6.8	13	0.26	**4.04**	0.02	0.78	29	20	NT	No	No
18	< 5.0	< 2.0	7.0	14	0.25	**4.24**	0.02	0.53	30	12	**Yes**	No	**Yes**
19	< 5.0	2.5	6.8	NT	0.87	**9.32**	0.04	0.76	**55**	4	**Yes**	**Yes**	**Yes**
20	< 5.0	2.4	6.8	NT	0.28	**5.42**	0.06	0.61	29	8	No	No	Yes
21	< 5.0	**4.6**	6.4	9459	0.29	**7.42**	0.04	**1.32**	31	15	**Yes**	**Yes**	**No**
22	< 5.0	3.1	5.6	NT	0.6	2.40	**0.15**	0.53	35	14	No	No	Yes
23	< 5.0	2.6	5.0	NT	**0.9**	**7.71**	0.07	0.58	45	7	No	**Yes**	Yes
24	< 5.0	**3.7**	5.8	IA	0.69	**7.2**	0.06	0.9	40	4	**Yes**	No	**No**
25	< 5.0	**4.8**	5.2	10593	NT	NT	NT	0.69	32	7	NT	No	No
26	NT	NT	NT	156083	0.46	**10.06**	0.08	0.84	**49**	5	NT	No	No

Legend: IA = insuficiente; NT = not tested.
Cut-off value or normality values: Proteins: 15–45 g/dl; IL1β: <5.0 pg/ml; IL6: <3.4 pg/ml; TNF −α: <8.1 pg/ml; IgA: <0.6 mg/dl; IgM: <0.13 mg/dl; Intrathecal IgG synthesis rate: 0.58–0.85.
Oligoclonal IgG bands: negative.

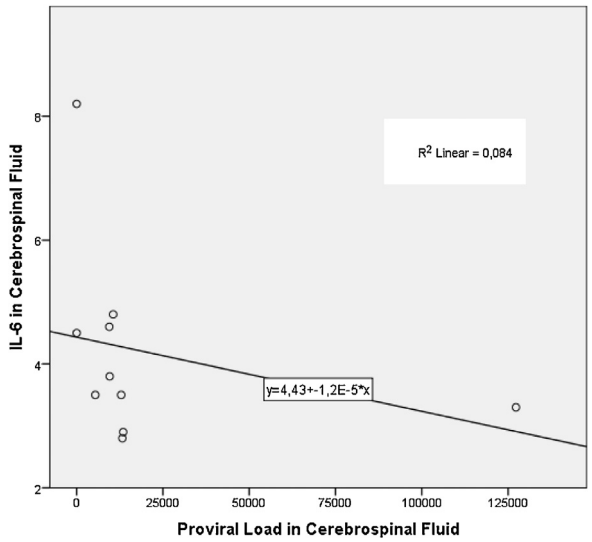

Figure 2. Spearman Correlation IL-6 and Proviral Load in Cerebrospinal Fluid of 14 patients with HAM/TSP (r: −0.73 p = 0.01).

HTLV infection among the healthy controls. It is noteworthy that if there are potentially cognitive problems among the healthy subjects, our results are underestimated and the performance of HAM/TSP patients should be even worse.

Conclusion

Our results suggest HTLV-1 infection induces a neuro zinflammatory response that causes not only a myelopathy, but also may cause cognitive impairment, at least at late stages of the disease. In HAM/TSP patients presenting more severe disease, cognitive function must be continually monitored and should receive special attention from rehabilitation professionals.

Statement of ethics

This project was approved by Ethic Committee CAEE 01413412.8.0000.5149.

Conflicts of interest

None declared.

Author contributions

These authors contributed equally to the manuscript.

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