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Memory impairment: an intermediate clinical syndrome symptom in HTLV-1-infected patients?

Comprometimento da memória: um sintoma de síndrome clínica intermediária em pacientes infectados pelo HTLV-1?

Maria Rita GASCON[1], Michel E. HAZIOT[2], Tatiane ASSONE[3,4], Luiz Augusto M. FONSECA[4], Jerusa SMID[2], Augusto César Penalva de OLIVEIRA[2], Jorge CASSEB[3,4]

Background: Although classical human T-cell lymphocyte virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis syndrome is the most frequent HTLV-1-associated neurological disorder, some "minor" neurological disorders can be seen in "asymptomatic" carriers. These disorders, including cognitive alterations already described in clinical cases and studies, may constitute an intermediate syndrome (IMS) between the asymptomatic state and myelopathy. The aim of this study was to investigate the presence of cognitive deficits in patients with HTLV-1 virus, who usually are diagnosed as asymptomatic. **Methods:** A total of 54 HTLV-1-infected patients were evaluated, 35 asymptomatic and 19 with minor neurological alterations (evaluated by a neurologist); 25 HTLV-1-seronegative individuals served as controls. The instruments used were: Beck's Depression Inventory, Lawton's Daily Life Activity Scale, and a complete neuropsychological battery. The application of these evaluation instruments was performed blindly, with the evaluator neuropsychologist not knowing the clinical condition of the patient. **Results:** Most of the participants in this cohort, including seronegative controls, were female (n = 57, 72.21%), their mean age was 52.34 years (SD = 14.29) and their average schooling was 9.70 years (SD = 4.11). **Discussion:** Participants classified with IMS had lower gross scores when compared with both the patients classified as asymptomatic and with the control group, and when tested for auditory episodic memory of immediate ($p < 0.01$), and late ($p = 0.01$), recall. **Conclusion:** Patients with IMS presented with memory impairment when compared with asymptomatic patients and seronegative individuals; this is one of the symptoms that aids in the classification of the syndrome.

Keywords: Human T-lymphotropic virus 1; neuropsychological evaluation; early neurocognitive impairment.

RESUMO

Apesar da síndrome de HAM / TSP clássica ser a perturbação neurológica mais atribuída, alguns distúrbios neurológicos denominados "menores" são vistos em portadores "assintomáticos" de HTLV-1. Esses distúrbios, incluindo alterações cognitivas já observadas em descrições de casos clínicos e estudos, podendo constituir uma verdadeira síndrome clínica intermediária (SI) entre o estado assintomático e mielopatia. O objetivo deste estudo foi investigar a presença de déficits cognitivos em pacientes portadores do vírus HTLV-1 diagnosticados classicamente como assintomáticos. **Métodos:** Foram avaliadas 54 pessoas, sendo 35 assintomáticos, 19 com alterações neurológicas menores (avaliados por um neurologista) e 25 HTLV-1 negativo. Os instrumentos utilizados foram: Inventário Beck de Depressão, Escala de Atividades de Vida Diária de Lawton e uma completa bateria neuropsicológica. A aplicação destes instrumentos de avaliação foi realizada de forma cega, ou seja, a avaliadora não sabia a condição clinica do paciente. **Resultados:** A maioria dos participantes era do sexo feminino (n = 57, 72,21%), com idade média de 52.34 anos (DP = 14,29) e escolaridade média de 9.70 anos (DP = 4,11). **Discussão:** Avaliando o desempenho cognitivo nos três grupos, foi possível observar que os participantes classificados com SI, apresentaram menores escores brutos, quando comparados, com os pacientes com classificação assintomática e grupo controle e, em relação à memória episódica auditiva de evocação imediata ($p < 0,01$) ($p = 0,01$) e tardia. **Conclusão:** Diante dos resultados foi possível concluir que os pacientes com SI apresentam comprometimento de memória quando comparado com os outros grupos, sendo possível, ser este um dos sintomas para auxiliar na classificação da síndrome.

Palavras-chave: Vírus 1 linfotrópico T humano; avaliação neuropsicológica; comprometimento neurocognitivo precoce.

The most well-known neurological disease seen in patients with human T-cell lymphocyte virus type 1 (HTLV-1) is HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), which preferentially affects the lower limbs

[1]Universidade de São Paulo, Hospital das Clínicas, Instituto Central, Divisão de Psicologia, São Paulo, SP, Brasil;

[2]Instituto de Doenças Infecciosas "Emilio Ribas" de São Paulo, São Paulo, SP, Brasil;

[3]Universidade de São Paulo, Faculdade de Medicina, Departamento de Dermatologia, Laboratório de Dermatologia e Imunodeficiencas, São Paulo, SP, Brasil;

[4]Instituto de Medicina Tropical de São Paulo, São Paulo, SP, Brasil.

Michel Haziot https://orcid.org/0000-0002-3549; Tatiane Assone https://orcid.org/0000-0003-0993-4523; Luiz Augusto Marcondes Fonseca https://orcid.org/0000-0003-3113-8558; Jerusa Smid https://orcid.org/0000-0001-95123-0964; Augusto César Penalva de Oliveira https://orcid.org/0000-0002-0488-8188; Jorge Casseb https://orcid.org/0000-0002-4553

Correspondence: Jorge Casseb; Av Dr Eneas de Carvalho Aguiar, 255 / 3° andar; 05402-000 São Paulo SP, Brasil. E-mail: jcasseb10@gmail.com

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in a slowly progressive fashion[1]. The disease usually begins between the fourth and fifth decade of life, affecting women more often than men. The Ministry of Health in Brazil[2] states that young adults also tend to be affected by HAM/TSP, but warns that no age group is spared. Myelopathy can occur after viral acquisition of HTLV-1 transmission by any manner, after a period of variable latency.

In addition to motor signs and symptoms, cognitive disorders began to be studied after a number reports describing the presence of brain abnormalities in magnetic resonance imaging (MRI) from patients with HAM/TSP. The lesions found in the white matter of those patients showed aspects similar to those observed in patients with multiple sclerosis or in HIV-infected individuals, both conditions characterized by the likelihood of presenting cognitive deficits[3]. The cognitive alterations observed were: psychomotor slowing, attention deficit and impaired visuospatial skills and working memory[3,4,5].

In a study by Silva et al.[3], HTLV-1-infected patients mild cognitive impairment, psychomotor retardation, mild difficulty in tests of verbal fluency, verbal and visual memory, selective and alternating attention, and visuoconstruction capability[3]. Another study was conducted with 111 HTLV-1-infected patients, in Belo Horizonte, Brazil, who underwent a series of brief evaluations of their cognitive performance and humor. Results disclosed a mild cognitive impairment (3.4%)[6]. A study by Gascón et al.[7], from our service, showed that HTLV-1 asymptomatic carriers and patients with HAM/TSP had poorer performance in neuropsychological tests, as well as high depression scores, when compared to healthy controls.

The major questions that this study aimed to solve were: Can neurocognitive changes indicate an early alteration in the central nervous system? Can they be viewed as part of an "intermediate syndrome" (IMS)? Or are they pointing to the onset of HAM/TSP? To answer the questions above, we searched for cognitive impairments in HTLV-1 patients who were usually considered as asymptomatic.

METHODS

This was a transversal study comparing the performance of patients with a positive serology for HTLV-1 with that from seronegative participants, all submitted to the same neuropsychological tests. We included HTLV-1-positive patients who were followed at our HTLV-1 outpatient service, according to the following criteria: they should be 18 years old or older, not infected with other viruses such as HIV or hepatitis C; and did not use illicit drugs, or have psychiatric or neurologic disturbances, or deficit of B12 vitamin and folates.

From a total of 79 participants, all of whom were evaluated by the same neurologist (MH) blinded to the HTLV-1 status of the patients, 19 had IMS and 35 were asymptomatic; the remaining 25 were HTLV-negative controls. The study was developed from 2016 to 2018, at the Institute of Infectious Diseases Emilio Ribas.

The IMS was characterized by the presence of three or more of the signs and/or symptoms: dysautonomia (erectile dysfunction, orthostatic hypotension), neurologic symptoms (impaired vibration, hyperreflexia, gait, plantar response), ocular symptoms (uveitis, dry eye), oral symptoms (dry mouth, gingivitis) (arthralgia, arthritis, polymyositis, Sjögren syndrome) and bladder symptoms (urinary urgency, incontinence, nocturia).

Neuropsychological tests were performed by the same specialist in neurology (MRG), blinded to the HTLV status.

The Beck Depression Inventory[8] was used to assess the depression frequency, and the Lawton Daily Life Activity Scale[9] was used to sort participants with minor neurocognitive disorders from major ones. The neuropsychological battery of tests included the following tests: Intellectual Functioning Estimate: subsets Vocabulary[10] and Matrix Reasoning[10]; Memory: Digits[10], Hopkins Verbal Learning Test (HVLT)[11], Rey Complex Figure[12]; Visuoconstruction: Copy of Rey Complex Figure[12]; Speed Information Processing: Codes[10]; Executive Function: Verbal Fluency (F-A-S[13] and Animals[14]); Attention: Trail Making Test (A and B)[15] and Stroop Test[15] and Motor Skill: Grooved Pegboard[16]. The application of these evaluation instruments was performed blindly, that is, the evaluator did not know the clinical condition of the patient.

After neuropsychological assessment, the following categories, adapted from the Diagnostic and Statistical Manual of Mental Disorders–V (2013)[17], were created:

- without cognitive disorder: no evidence of cognitive decline, regular neurocognitive assessment and independence in daily activities;
- minor cognitive disorder: there is evidence of modest cognitive decline from a previous performance level, in one or more of the evaluated domains, not interfering with independence, not due to delirium, not due to another mental disorder, and 1-2 standard deviations (SD) in cognitive tests;
- major cognitive disorder: significant cognitive decline, interfering with independence, not due to delirium, not due to another mental disorder and below 2 SD in cognitive tests.

Differential diagnosis was also made between neurocognitive disorders (minor or major) and cognitive impairment due to symptoms of depression. The following criteria were used for classification: the patient presents with depressed mood, moderate or severe grading in the Beck Depression Inventory, compromised performance in tasks requiring more effort, memory complaints (frequently) divergent from cognitive test results, and shows significant gains in recognition tasks in relation to late retention.

The Ethical Board of the Emilio Ribas Institute of Infectious Diseases approved the protocol of the study (number 86379218.6.1001.0061), and a signed informed consent was obtained from all participants prior to inclusion in the study.

We used one-way ANOVA for comparison of the neuropsychological performance among groups to identify potential covariates associated with neuropsychological performance of the participants (sex, age, education and depression). The chi-squared test was performed to compare the scores of the three groups comparing patients with minor neurocognitive disorder and major neurocognitive disorder. Spearman's correlation was used to verify the relationship between sociodemographic variables (age, sex and schooling) and performance in cognitive tests. All quantitative analyses were performed using the statistical software SPSS (13.0) and p = 0.05 was set as the significance level.

RESULTS

We included 126 potential participants who were identified during a medical consultation with a neurologist. From these, 47 individuals were excluded; the reasons for exclusion are shown in Figure. The remaining 79 participants were included in the study, 19 (24%) were classified as IMS, 35 (44.3%) as asymptomatic carriers, with 25 (31.6%) HTLV-1-negative individuals making up the control group.

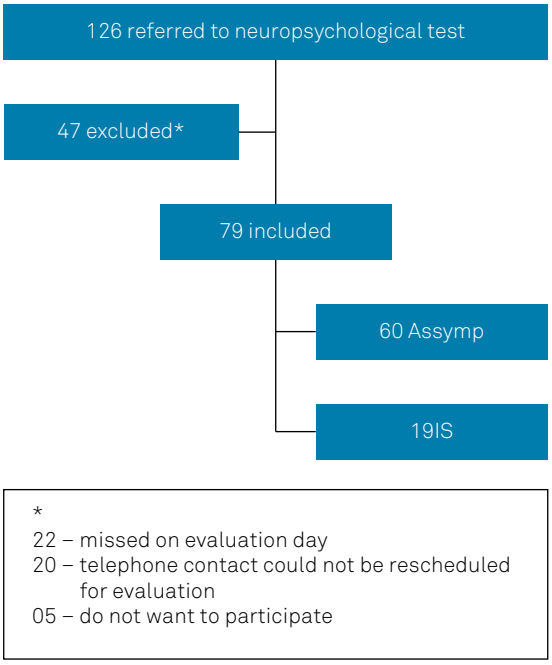

Figure. Flowchart of the participants referred for neuropsychological evaluation and included in the study the distribution of the sociodemographic data of the participants is shown in Table 1.

Of the 79 participants (including controls), 44 (55.6%) reported memory difficulties, 11 (18.98%) complained of attention deficit, one (1.26%) had psychomotor slowing and two (2.53%) had difficulty organizing and planning activities. In correlation tests, most of the patients who reported memory difficulties also complained of attention deficits ($p < 0.01$) and those who complained of psychomotor slowing had difficulty in organizing and planning ($p \leq 0.01$). Table 2 shows the frequency of cognitive complaints according to the neurological classification. Of the 79 patients evaluated, 27 (34.1%) had no cognitive impairment, 35 (44.3%) had mild cognitive impairment, six (7.6%) had major neurocognitive disorder and 11 (13.9%) had cognitive impairment. Table 3 shows the classification of cognitive impairment according to the neurological classification.

Evaluating the cognitive performance for the three groups, we observed that the participants classified with IMS showed lower gross scores when compared both with asymptomatic patients and controls; auditory episodic memory of immediate and late recall were also impaired when compared with participants in the other two groups. Participants with IMS also presented a significant difference on the general score in the Lawton Scale evaluating functionality related to basic and instrumental activities of daily life, when compared with the control group. Table 4 shows the average performance of the neuropsychological battery according to the neurological classification. The patients with IMS presented with a higher frequency of depression compared with the asymptomatic and healthy control groups.

We observed that age was inversely correlated with the following: digits test ($p = 0.01$), Rey copy ($p = 0.04$), and grooved dominant hand and non-dominant hand ($p < 0.01$) tests. In contrast, age was directly correlated with the Beck Depression Inventory score ($p = 0.05$) and Trail Making A ($p < 0.01$), and Trail Making B ($p \leq 0.01$). Schooling was directly correlated with the performance of the following tests: matrix reasoning ($p = 0.01$), estimated IQ ($p < 0.01$), digits test ($p < 0.01$), HVLT immediate recall ($p < 0.01$), HVLT delayed recall ($p = 0.01$), Animals ($p < 0.01$), Grooved ($p = 0.02$) and inversely with the Trail Making B ($p < 0.01$).

Table 1. Socio demographic data of the participants

Variable	IMS (n = 19)	Asymptomatic (n = 35)	Controls (n = 25)	p-value
Age - Mean (SD)	48.31 (8.94)	52.17 (16.53)	55.64 (10.04)	0.24
Education (years) - Mean (SD)	8.94 (4.24)	9.48 (4.54)	10.60 (3.27)	0.38
Sex				
Male	4 (21.0%)	8 (22.8%)	10 (40%)	0.25
Female	15 (79%)	27 (77.2%)	15 (60%)	

SD: standard deviation; IMS: intermediate syndrome; asymptomatic; controls: seronegative cases.

Table 2. Frequency of subjective cognitive complaints in HTLV-1 IMS patients, HTLV-1 asymptomatic carriers, and controls.

Subjective cognitive complaint	IMS (n = 19)	Asymptomatic (n = 35)	Controls (n = 25)	p-value
Memory	17 (89.4%)	17 (48.5%)	10 (40%)	< 0.01
Attention	4 (21.0%)	7 (20.0%)	4 (16.0%)	0.89
Slowing down	1 (5.26%)	0	0	0.42
Executive function	2 (10.52%)	0	0	0.03

IMS: intermediate syndrome.

Table 3. Frequency of cognitive impairment in HTLV-1 among IMS patients, HTLV-1 asymptomatic carriers, and healthy controls.

Cognitive impairment	IMS (n = 19)	Asymptomatic (n = 35)	Controls (n = 25)	p-value
Normal	4 (21.0%)	12 (34.2%)	11 (44.0%)	0.08
Minor	7 (36.8%)	15 (42.8%)	13 (52%)	0.41
Major	2 (10.52%)	4 (11.4%)	0	0.68
Cognitive depression	6 (31.5%)	4 (11.4%)	1 (2.8%)	0.04

IMS: intermediate syndrome, HTLV-1: human T-cell lymphocyte virus type 1.

DISCUSSION

This study aimed to look for the existence of early cognitive alterations present in HTLV-1 carriers, characterizing a new condition, enabling the detection of early markers of HAM/TSP. We found that patients with IMS had a poorer performance in immediate and late evoked auditory episodic memory, when compared with the two other groups (control and asymptomatic), and that the impairment found in tests corroborated the subjective complaints of patients.

Memory impairment of HTLV-1-infected patients was one of the cognitive alterations that has already been observed in other studies[4,6,7,18,19]. In the study by Gascón et al.[7] after analyzing the results of each formal neuropsychological evaluation, it was observed that all HTLV-1 patients showed some degree of cognitive impairment, regardless of their neurological condition. In that study, all 37 asymptomatic patients had a mild degree of cognitive impairment, whereas among patients with HAM/TSP, 15 (40.4%) had a more severe degree of impairment and 22, (59.6%) had a milder degree; these results are similar to those from this study. Of the patients in that study, 24% also presented with some peripheral neurological system disturbance.[20] In the Trail Making Tests, age had a direct relationship with time, that is, the longer the time required to perform the test, the older the age of the individual, and the effect of schooling was not direct but indirect.

The memory impairment observed in this and other neuropsychological studies performed on patients with HTLV-1 may be due to lesions in the white matter in the central nervous system (CNS), responsible for transporting neural signals from the subcortical regions to the cortex and from the cortex to the subcortical regions (1-4). Osame et al.[21] proposed an interesting hypothesis to explain the neurological injury occurring in patients with HAM/TSP. The presence of inflammation, measured by TNF-alpha and IFN-gamma levels, among others, would damage neural tissue[22]. These damaging effects of a primary CNS pathological change, for example, are exacerbated during the so-called secondary degeneration process. The progressive increase of the primary lesion area occurs in regions distant from the initial site of the lesion[23,24,25 (23-25)], which could lead to the cognitive impairment seen in our patients.

The main clinical and structural factors to be considered are white matter lesions found in MRIs of patients with HAM/TSP, as reported in other studies[3,26,27]. The white matter plays an important role in the complexity of neural systems, having an important role in the motor, sensory and visual systems. Injuries to this subcortical structure may contribute to a variety of behavioral syndromes (with attention, memory, wakefulness or motivation) because of the extensive connection between the frontal lobes and the posterior regions of the brain[28]. Diffuse lesions in the white matter could cause deficits in attention systems, mental flexibility, visuospatial abilities, and emotional states. One of the physiological functions of the frontal lobe is to integrate the combined networks of actions and multifocal partial lesions can interrupt this network collectively, leading to manifestations of the frontal network syndrome, characterized by psychomotor slowing, decreased verbal fluency, memory deficits, impaired waking state, deficits in selective and alternating attention, and impairment in visuoconstructive ability[29]. Clinical case reports also demonstrate the association between cognitive deficits and HAM/TSP and its possible relationship with white matter[18,19,26]. The cognitive alterations reported on these studies were: psychomotor slowing, attention deficit, impairment in visuospatial ability, executive function and memory.

Despite the fact that MRIs were not done in our patients, clinical features, such as inflammatory findings in the cerebrospinal fluid and lesions in the white matter of the brain and

Table 4. Scores on the neuropsychological battery tests among HTLV-1-infected patients (IMS and asymptomatic) and healthy controls.

Tests	IMS (n = 19)	Asymptomatic (n = 35)	Controls (n = 25)	p-value
Intellectual function				
Vocabulary	29.73 (11.02)	29.82 (7.64)	31.24 (8.87)	0.80
Matrix reasoning	8.05 (3.53)	10.77 (5.70)	9.52 (5.00)	0.16
Estimated IQ	89.63 (9.12)	93.17 (13.49)	94.68 (10.74)	0.36
Memory				
Digits test	10.31 (2.72)	11.91 (3.36)	11.68 (2.67)	0.16
HVLT – Immediate	18.84 (4.83)	20.82 (5.03)	24.20 (4.74)	< 0.01
HVLT – Delayed	6.00 (2.26)	6.25 (3.10)	8.08 (1.70)	0.01
HVLT – Recognition	9.78 (2.09)	10.00 (2.31)	10.52 (1.15)	0.43
Rey - Immediate	11.05 (6.09)	10.61 (7.41)	10.84 (7.26)	0.97
Rey – Delayed	11.47 (7.79)	11.85 (7.63)	11.60 (7.11)	0.98
Visuoconstruction				
Rey – Copy	24.68 (8.98)	28.65 (8.90)	26.58 (8.21)	0.27
Attention				
Trail Making A	54.05 (37.07)	54.58 (28.60)	49.76 (18.38)	0.79
Trail Making B	133.31 (84.46)	119.61 (83.61)	127.72(73.82)	0.82
Stroop 1	21.47 (7.44)	19.88 (7.18)	19.84 (6.48)	0.68
Stroop 2	24.73 (7.78)	24.60 (7.78)	25.80 (10.55)	0.84
Stroop 3	40.36 (18.42)	40.17 (14.69)	38.92 (14.97)	0.94
Speed of Information				
Codes	39.89 (20.28)	39.91 (18.46)	39.08 (16.16)	0.98
Executive Function				
F-A-S verbal fluency	26.05 (10.82)	28.91 (10.11)	29.80 (8.67)	0.43
Animals	13.57 (3.71)	13.91 (3.85)	14.32 (3.50)	0.80
Motor Skill				
Grooved – dominant hand	79.63 (21.73)	80.57 (20.67)	89.36 (23.98)	0.23
Grooved – nondominant hand	92.36 (36.26)	85.17 (18.69)	98.16 (28.99)	0.18
Mood Scale				
Beck – Depression	20.31 (12.97)	15.79 (13.08)	13.44 (10.11)	0.18
Daily Life Activity Scale				
Lawton	20.52 (0.61)	20.77 (0.59)	21.00 (0.0)	0.01

HVLT: Hopkins Verbal Learning Test; IMS: intermediate syndrome.

in the cervical spinal cord have been described elsewhere[27]. Despite the non-specificity of white matter lesions in association with clinical features for HAM/TSP, researchers still do not fully understand the origin and significance of white matter lesions observed in the MRIs in HAM/TSP patients. In fact, neuropsychological examination revealed changes in cognitive tests were also reported in some studies[3,18,19,26].

As expected, age and schooling influenced the performance of cognitive tests, and of the risk factors for the development of possible areas of cognitive impairment, regardless of HTLV serostatus[30]. These findings could be related to the increased exposure to deleterious environmental factors to the CNS, presumably present in those with low schooling[31]. On the other hand, formal education increased the synaptic density in the neocortical associative areas, reducing the impact of aggressions on the CNS, leading to a potential delay at the beginning of the development of dementia, that is, about four to five years[30].

Patients with IMS had greater memory impairment when compared with the other groups, and this is one of the manifestations that help in the classification of the syndrome, especially for those patients who complain of memory deficits, have a low level of schooling and are older than 50 years. The white matter plays an important role in the complexity of neural systems, especially in motor, sensory and visual systems. Injuries in this subcortical structure may contribute to a variety of behavioral syndromes (attention, memory, wakefulness or motivation) as there

are connections between the frontal lobes and the posterior regions of the brain[28]. One of the physiological functions of the frontal lobe is to integrate the combined networks of actions, and multifocal partial lesions can interrupt this network collectively, and may cause manifestations of the frontal network syndrome, characterized by psychomotor slowing, decreased verbal fluency, memory deficits, impaired waking state, deficits in selective and alternating attention, and impairment in visuoconstructive ability[29]. Clinical case reports have also demonstrated the association between cognitive deficit and HAM/TSP and its possible relationship with white matter[18,19,26].

Finally, there is no evidence in cohort studies that individuals with minor neurological impairment will progress to HAM/TSP. Does the IMS refer to minor neurological impairment only? Or does the IMS suggest a clinical course between being asymptomatic and HAM? The major point is that only a long-term clinical follow up may explain these findings in our study. These data also suggest that minor neurological impairment, including cognitive impairment, is not specific and prevalent only in individuals classified in the IMS group. Finally, our study indicates that the CNS is also affected during the early phase of the HTLV-1 infection, but further studies should be done confirm this finding.

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