ISSN 0025-7680

ORIGINAL ARTICLE

MEDICINA (Buenos Aires) 1998; 58: 411-414

FURTHER STUDIES ON HTLV-I ASSOCIATED MYELOPATHY IN ARGENTINA

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Abstract We report 10 HTLV-I virus seropositive subjects, eight of them with HTLV-I associated myelopathy (HAM), two of them also infected with HIV as well as two asymptomatic HTLV-I+ relatives of two unrelated patients. HTLV-I is endemic in several tropical areas, where it causes different neurological diseases. Only few patients have been reported in our country since 1994. We studied 8 patients, who fulfilled the clinical criteria for chronic spastic paraplegia, and 2 other non-symptomatic HTLV-I seropositive relatives, with electromyography (EMG), motor and sensory conduction velocities (NCV), somatosensory, visual and brainstem auditory evoked potentials (SSEP, VEP and BAEP), Magnetic Resonance Images (MRI) and cerobrospinal fluid (CSF) analysis. The latter was carried out only in seven symptomatic patients. In every case positive ELISA tests for HTLV-I/II were confirmed by Western Blot. The two asymptomatic persons were clinically and electromyographically assessed, one of them was also submitted to SSEPs studies. Three patients were males. Patient's ages ranged from 5 to 65 years old. All symptomatic patients showed muscular weakness, spasticity with pyramidal signs and sphincter disturbances. Five of them had paresthesias and 2 had burning pain on their feet. The EMGs and the NCVs were normal in 7 patients and in the 2 asymptomatic ones. SSEPs, obtained by stimulating the posterior tibial nerves, were impaired in 7 patients and in the asymptomatic person who received the procedure. The 7 symptomatic patients who underwent lumbar puncture had positive tests for HTLV-I in CSF, 3 out of these 7 patients had also high protein levels and 4 had increased number of lymphocytes. In 2 patients intrathecal IgG production could also be demonstrated. MRI were normal in 7 patients and in the 2 asymptomatics, the exception being a female who had bilateral hyperintense lesions in cerebral white matter in T2. In conclusion, tropical spastic paraparesis is apparently a rare disorder in Argentina. However, some cases have been reported recently. Most probably, its prevalence is currently underestimated. Its diagnosis should be considered in every patient with progressive spastic paraplegia.

Resumen ***Nuevos estudios sobre mielopatía asociada a HTLV-I en la Argentina.*** Presentamos 10 pacientes con serología positiva para HTLV-I, 8 de ellos con mielopatía asociada a HTLV-I (HAM), incluyendo 2 HIV positivos. El HTLV-I es endémico en varias áreas tropicales, donde es responsable de diferentes patologías. En nuestro país fueron comunicados unos pocos pacientes desde 1994 (Garcea et al 1994; Gutfraind et al 1995; Micheli et al 1996). Estudiamos 8 pacientes con paraplejía crónica progresiva, y dos familiares directos seropositivos asintomáticos, con electromiografía (EMG), velocidades de conducción motora y sensitiva (VC), potenciales evocados somatosensitivos, visuales y auditivos (PESS, PEV y PEAT), Imágenes de Resonancia Magnética (IRM) y estudio del líquido cefalorraquídeo (LCR). La punción lumbar (PL) fue hecha sólo en 7 de los 8 pacientes sintomáticos. Todos los resultados de ELISA positivos para el HTLV-I fueron confirmados con Western Blot. Tres pacientes eran hombres. Los pacientes tenían entre 5 y 65 años de edad. Todos los pacientes sintomáticos presentaban debilidad muscular, espasticidad, piramidalismo y trastornos esfinterianos. Cinco tenían parestesias y 2 dolor urente en los pies. Los EMGs y VCs fueron normales en 9, mientras que los PESS estimulando los nervios tibiales posteriores fueron anormales en 8 pacientes. Los 7 pacientes sintomáticos a los que se les realizó PL tuvieron serología positiva para HTLV-I en LCR, en 3 de ellos se demostró hiperproteinorraquia y en 4 pleocitosis linfocítica. Además, en 2 se pudo demostrar la producción intrathecal de IgG. Las IRM fueron normales en 9 pacientes, siendo la excepción una paciente con imágenes hiperintensas en sustancia blanca en secuencias de T 2. En conclusión, la paraparesia espástica tropical es aparentemente una enfermedad rara en nuestro país. Aunque últimamente se han estado comunicando algunos casos, probablemente su prevalencia es subestimada. Destacamos la importancia de la inclusión de este diagnóstico en todo paciente con paraplejía espástica progresiva.

Key words: HTLV-I associated myelopathy, tropical spastic paraparesis.

Chronic progressive myelopathy is defined as a paraplegia with gradual onset and variable levels of sensory loss and sphincter disturbances, without evidences of lower motor neuron involvement, spinal cord compression, or supramedullary disseminated lesions[1-5]. This disease has usually been reported in high HTLV-I endemic areas; mainly the Caribbean, Southern Japan, Central and South America[6-11]. In Argentina, as far as we know, surveys done in blood donors in Buenos Aires

Received: 31-III-1998 Accepted: 3-VI-1998

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yielded a low prevalence, similar to that of non endemic countries[12, 13]. We report our experience in 8 cases of slowly progressing spastic paraplegia, with positive HTLV-I antibodies in sera and cerebrospinal fluid (CSF) and in two non-symptomatic relatives, also infected with the mentioned retrovirus. Because in Argentina, HAM/TSP is not a frequently reported illness[14, 15], the aim of this work is to present epidemiologic data and the clinical features, the neurophysiology, the imaging and the CSF findings in this group of patients.

Material and Methods

Altogether we studied 8 patients, 6 females and 2 males, aged between 24 and 65 years, who fulfilled the clinical criteria for chronic spastic paraplegia (#1 to #8). Once the diagnosis was made, we summoned the patient's relatives and made a serological screening looking for HTLV-I subclinical infection. We could only assess 4 relatives and found two of them (#9 and #10) who disclosed positive serological tests. Those two persons were investigated through clinical and laboratory studies and included within this communication. The rational for doing this is to show that some findings can be achieved in people who may have the infection but remain clinically asymptomatic.

Electromyography (EMG) and nerve conduction studies (NCV) were performed in every patient and in the asymptomatic persons, somatosensory evoked potentials (SSEP) were carried out in 9 subjects including one of the asymptomatic persons, brainstem auditory evoked potentials (BAEP) were investigated in 7 patients and visual evoked potentials (VEP) in the 8 patients. Brain and cervical spinal cord magnetic resonance images (MRI) were obtained in all symptomatic subjects. Blood profiles were analyzed in every subject. Lumbar puncture was performed in 7 symptomatic patients, and CSF glucose, proteins, and cell content were determined. Immunoglobulin G and oligoclonal bands were searched for in 3 patients. The presence of IgG antibodies against HTLV-I was always confirmed by Western Blot. CSF and serum VDRL were studied in every patient who received lumbar puncture.

Results

Epidemiologic data: Three patients were from northern provinces, located within the subtropical regions of the Country, 5 patients were in downtown Buenos Aires and currently living in the city. Two patients were also infected with HIV, (intravenous drug abusers). Another patient had had blood transfusion several years before the beginning of the symptoms. Two out of the four relatives investigated had positive serological tests, and were the wife and one son of two different symptomatic patients; these two persons were born in Buenos Aires and lived there at the time of their assessment.

Clinical Features. (Table 1). Patients were aged between 24 and 65 years. Symptomatic patients had muscular weakness in both lower limbs, without atrophy, but with moderate to severe spasticity and sphincter disturbances. Sensory symptoms, described as paresthesias or hypoesthesias, were frequently found, 2 patients also had burning pain on their feet. Onset of their complaints at the time of their clinical aseessment ranged from 5 months to 30 years; the shortest interval was observed in one female patient who also was HIV infected. Monoparesis was the first symptom in 4 patients

TABLE 1.– *Clinical features*

Patient	Onset Symptom	Time from onset	Paraparesis	ASS.	Sph. D.	Sen. D.	Pain
#1	RL weakness	5 years	Moderate	4/5	Yes	No	No
#2	RL weakness	2 years	Severe	4/5	Yes	Paresthesia	No
#3	Paraparesis	4 years	Moderate	4/5	Yes	Paresthesia	Yes
#4	Pain+RL weakness	9 months	Moderate	4/5	Yes	Paresthesia Hypesthesia	Yes
#5	Urinary retention	10 years	Mild	3/5	Yes	No	No
#6	Paraparesis	11 years	Moderate	4/5	Yes	Paresthesia Hypoesthesia	No
#7	Paraparesis	30 years	Moderate	2/5	Yes	No	Yes
#8	LL weakness	5 months	Mild	2/5	Yes	No	No
#9	No symptoms	-	No	1/5	No	No	No
#10	No symptoms	-	No	1/5	No	No	No

RL: right leg; LL: left leg; ASS: Aschworth spasticity score;
Sph. D.: Sphincter disturbances; Sen. D.: Sensory disturbances
Note: All the symptomatic patients had pyramidal signs but none had muscular atrophy

TABLE 2.– *Lower limbs SSEPs latency and amplitude values*

	N (ms)	P (ms)	Ampl (μV)
#1	49	53	1,5
#2	No response	No response	No response
#3	No response	No response	No response
#4	59	64,4	3,75
#5	38	40	3
#6	No response	No response	No response
#7	No response	No response	No response
#8	46	52	2,50
#9	48	53	2
#10	ND	ND	ND

Normal ranges: N: 32-34 ms; P: 40-42 ms; Ampl: > 1,25 μV
ND: not done

and bladder dysfunction in one. Ashworth score[16] was 4/5 in 5 patients, 3/5 in 1 and 2/5 in the remaining 2. The asymptomatics were 40 and 5 years old. (Table 1).

CSF Findings. All patients studied had normal glucose, negative VDRL reaction, and positive tests for antibodies against HTLV-I. Lymphocytic pleocytosis was found in 4 patients and intrathecal IgG was elevated in 2 out of 3 patients tested. We did not perform lumbar tap in the asymptomatics.

Neurophysiology. All patients and the asymptomatic subjects had normal EMGs and motor and sensory NCVs, except patient #7 who lacked muscle response when stimulating the right peroneal nerve. VEPs were bilaterally prolonged only in 1 patient (#2), while BAEPs showed a prolonged I-III conduction time in 1 patient (#2) and could not be obtained in another (#4). Finally, SSEPs were impaired in 7 patients out of the 8 tested. The asymptomatic subject who received this procedure also showed impairment of this evoked potential. We studied only one limb because there were no clinical differences between right and left lower limbs. (Table 2).

Images. Only 1 out of the 8 patients had brain MRI abnormal findings consisting of non-specific high-signal white matter lesions in T2 sequences. The other patients had normal brain and cervical spinal cord MRIs.

Discussion

As previously described in the literature[5] our patients had the typical clinical picture of gradual onset spastic paraplegia with pyramidal signs, developing, in the course of the illness, sphincter disturbances. Intrathecal IgG synthesis and elevated IgG index have been described in most patients reported in the literature[17, 18]; we could document these features only in 2 subjects of our series. Peripheral nervous system involvement has been described in the literature in about 25% of the patients[5, 19], in our series we only found one patient with focal abnormal NCVs studies in one of her lower limbs. In the literature, abnormal VEP latencies were seen in 30% of the patients, and BAEPs prolonged latencies were also found in 25% of them[5, 20]. We found only one patient with abnormal VEPs latencies and 2 who showed abnormal BAEPs.

Although lower limbs SSEPs had delayed latencies in 7 of the 8 patients who were tested and in the asymptomatic subject who was submitted to the procedure, the figures obtained bore no relationship with the severity of their clinical involvement. Pathologic findings in brain images have been described in almost 60% of the patients by other authors[5, 19]; we found non-specific high-signal white matter lesions in T2 sequences in only one patient. All the spinal MRI were normal, including the one belonging to the patient who showed brain MRI abnormalities.

It can be concluded that HAM/TSP is a rare disorder in our country although some cases have been reported in recent years[14, 15]. Probably, its prevalence is currently underestimated. Its diagnosis should be considered in every patient with progressive spastic paraplegia.

References

1. Osame M, Usuku K, Izumo S, Ijichi N, Amitani HI, Gata A, et al. HTLV-I associated myelopathy, a new clinical entity (Letter). *Lancet* 1986; 1: 1031-2.
2. Román GC, Osame M. Identity of HTLV-I associated myelopathy (Letter). *Lancet* 1988; 1: 651.
3. Bartholomew C, Cleghorn F, Charles W, Ratan P, Roberts L, Maharaj K, et al. HTLV-I and tropical spastic paraparesis (Letter). *Lancet* 1986; 2: 99-100.
4. Osame M, Matsumoto M, Usuku K, Izumo S, Ijichi N, Amitani H, et al. Chronic progressive myelopathy associated with elevated antibodies to human T-lymphotropic virus type 1 and adult T-cell leukemia-like cells. *Ann Neurol* 1987; 21: 117-22.
5. Gessain A, Gout O. Chronic myelopathy associated with human T-Lymphotropic virus type 1 (HTLV-I). *Ann Intern Med* 1992; 117: 933-46.
6. Román GC. The neuroepidemiology of tropical spastic paraparesis. *Ann Neurol* 1988; 23 (Suppl. 7): 113-20.
7. Vernant JC, Maurs L, Gessain A, Barin F, Gout O, Delaporte JM, et al. Endemic tropical spastic paraparesis associated with human T-lymphotropic virus type 1: a clinical and seroepidemiological study of 25 cases. *Ann Neurol* 1987; 21: 123-30.
8. Delaporte E, Peeters M, Simoni M, Piot P. HTLV-I infection in western equatorial Africa (Letter). *Lancet* 1989; 2: 1226.
9. Zaninovic V, Arango C, Biojo R, Mora C, Rodgers-Johnson P, Concha M, et al. Tropical spastic paraparesis in Colombia. *Ann Neurol* 1988; 23 (Suppl. 1): S127-32.
10. McKendall RR, Oas J, Lairmore MD. HTLV-I associated myelopathy endemic in Texas-born residents and isolation of virus from CSF cells. *Neurology* 1991; 41: 448-50.
11. Newton M, Cruickshank K, Miller D, Dalgleish A, Rudge P, Clayden S, et al. Antibody to human T-lymphotropic vi-

rus type 1 in West-Indian-born UK residents with spastic paraparesis. *Lancet* 1987; 1: 415-6.
12. Gutfraind Z, Blejer JL, Saguier ML, Gómez Carretero ML, Pirola DA, Carreras Vescio LA. Evaluation of HTLV-I/II infection in blood donors in Buenos Aires. *Medicina (Buenos Aires)* 1995; 55: 295-9.
13. Del Pino N, Peral LM, Pampura S, Pimentel E, Libonatti O. HTLV-I/II seroprevalence and co-infection with other pathogens in blood donors in Buenos Aires. *J Adq Imm Def Syndr* 1994; 7: 206-7.
14. Garcea O, Rugilo CA, Diez MA, Sanz OP, Segura MJ, Rivera BI, Sica REP. Paraparesia espástica tropical. *Rev Neurol Arg* 1993; 18: 69-70.
15. Micheli F, Díaz S, Besasso O, Pozo M, Risso J, Scorticati MC. Mielopatía asociada al HTLV-I. Presentación de 2 casos en Argentina. *Rev Neurol Arg* 1995; 20: 153-8.
16. Ashworth B. Preliminary Trial of Carisoprodal in Multiple Sclerosis. *Practitioner* 1964; 192: 540-2.
17. Cerroni M, Piccardo P, Rodgers-Johnson P, Mora C, Asher DM, Gadjdusek DC, et al. Intrathecal synthesis of IgG antibodies to HTLV-I supports an etiological role for HTLV-I in tropical spastic paraparesis *Ann Neurol*; 23 (Suppl. 1): S188-91.
18. Link H, Cruz M, Gessain A, Gout O, de-Thé G, Kam-Hansen S. Chronic progressive myelopathy associated with HTLV-I: oligoclonal IgG and anti-HTLV-I IgG antibodies in cerebrospinal fluid and serum. *Neurology* 1989; 39: 1566-72.
19. Bhagavati S, Ehrlich G, Kula R, Kwok S, Shinsky J, Udani V, et al. Detection of human T-cell leukemia/lymphoma virus type I DNA and antigen in spinal fluid and blood of patients with chronic progressive myelopathy. *N Engl J Med* 1988; 318: 1141-7.
20. Paty DW, Blume WT, Brown WF, Jaatoul N, McInnis W. Chronic progressive myelopathy: investigation with CSF electrophoresis, evoked potentials, and CT scan. *Ann Neurol* 1979; 6: 419-24.
21. Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, et al. Antibodies to human T-Lymphotropic virus type-1 in patients with tropical spastic paraparesis. *Lancet* 1985; 2: 407-10.
22. Ludolph AC, Hugon J, Román GC, Spencer PS, Schoenberg BS. A clinical neurophysiologic study of tropical spastic paraparesis. *Muscle & Nerve* 1998; 2: 392-7.

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LA PORTADA

Augusto Schiavoni (1893-1942). **Con los pintores amigos.** Oleo sobre tela, 1.90 x 2.00 m. Cortesía del Museo Municipal de Bellas Artes Juan B. Castagnino, Rosario, Argentina.

Según nos relata Rafael Sendra[1], Schiavoni nació en Rosario el 18 de julio de 1893, siguió estudios de arte en esa ciudad y a los veinte años viajó a Italia. Allí conoció en medio de la guerra, a Florencia y al Renacimiento, y también a las nuevas escuelas, como el futurismo. Volvió a Rosario en 1917, donde continuó trabajando hasta el 22 de mayo de 1942, en que falleció, en su casona del barrio Saladillo. En el óleo "Con los pintores amigos" se presentan las figuras de Schiavoni mismo y de sus amigos Musto, Guido y Bikandi. El cuadro fue donado al Museo por Laura Schiavoni, en 1959.

[1]En: Obras del Museo Municipal de Bellas Artes Juan B. Castagnino, Secretaría de Cultura y Educación, Municipalidad de Rosario, 1996, pág. 50.