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HTLV-I NEGATIVE TROPICAL SPASTIC PARAPARESIS

A scientific challenge

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ABSTRACT – We reviewed the historical, clinical and etiological aspects of the progressive chronic spastic myelopathies of unknown etiology, disserting on the clinical similarities between HTLV-I seropositive and seronegative tropical spastic paraparesis (TSP), as well as focusing on the PCR studies of the seronegative TSP.

KEY WORDS: myelopathies of unknown etiology, TSP, HTLV-I, seronegative, PCR.

Paraparesia espástica tropical HTLV-I negativa: um desafio científico

RESUMO – Fazemos uma revisão dos aspectos históricos, clínicos e etiológicos das mielopatias espásticas crônicas progressivas de causa desconhecida, dissertando sobre as semelhanças clínicas entre a paraparesia espástica tropical (PET) soro-positiva e soro-negativa para HTLV-I, focalizando também os estudos sobre PCR na PET soro-negativa.

PALAVRAS-CHAVE: mielopatias de causa desconhecida, PET, soro-negativo, PCR.

The progressive chronic spastic myelopathies of unknown etiology (MUE) is a continuous challenge in clinical neurology of the northern countries and in the tropics.

In the XIX century they were denominated as spastic tetraparesis[1], spasmodic spinal paraparesis[2] and spasmodic tabes dorsalis[3] of unknown etiology or supposedly associated with syphilis and malaria but without confirmation.

The XX century brought an increased interest for these myelopathic forms. Scott[4] (1918) described, in Jamaica, the "syndrome of central neuritis", consisting in spasticity, ataxia and gait disturbance, supposedly associated with toxic or infectious factors. Minchin[5] (1940) described, in India, the "syndrome of lathyrism without lathyrism", consisting in spastic paraparesis with pyramidal signs, normal sensibility, normal force of the upper limbs with, however, hyperreflexia. In England, Marshall[6] (1955) reported on a series of 52 cases of "spastic paraplegia of unknown etiology" and the follow-up of them allowed to define diagnosis in 27 cases as disseminated sclerosis (10), tumor (7) prolapsed disc (3), syringomyelia (1), cervical cord lesion (2) and paraplegia with dementia (4). The remaining 25 cases were further reinvestigated without determining their cause and "still defined their etiology or diagnosis 10 or more years after the onset of the illness". Cruickshank[7] (1956) described, in Jamaica, cases of progressive chronic spastic paraparesis with sphincter and sensory disturbances, and in 1964, Montgomery et al.[8] analyzed 206 cases denominated as "Jamaican neuropathy" which included a group with ataxia and another group (181 cases) with spasticity; the autopsy of 11 cases of this later group revealed a chronic meningomyelitis with perivascular lymphocytic infiltrate in the spinal cord and less involvement of the brain. They supposed it could be due to syphilis. In 1969, Mani et al.[9] described, in the South of India, 35 cases of spastic paraparesis, which they coined, for the first time, the term Tropical Spastic Paraplegia, and they thought it was possibly due to a "slow-virus".

In the 70's, Spillane, in a treatise on tropical neurology, assembled the different reports on these obscure myelopathies in Asia and Africa[10]. In the 80's, reports from South America[11-13] and South Africa[14] evidenced the presence of these conditions in these regions, supposedly associated to possible toxic factors or yaws.

Then, these previous and historical studies supposed diagnoses such as multiple sclerosis (MS), syphilis, vitamin-B deficiency, schistossomiasis, toxic factors or viral disease, without confirmation, remaining them as myelopathies of unknown etiology

Myelopathies of unknown etiology (MUE)

In order to better define the characteristics of the MUE a survey of the literature, from different countries and continents was carried out (Table 1).

In India Mani et al.[9] analyzed 35 cases of unexplained paraplegia of gradual onset. They were 23 males and 12

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females, with a mean age of 39 years. All patients presented chronic and slowly progressive symmetrical or asymmetrical stiffness or weakness with pyramidal signs in the lower limbs, associated with sensory deficit in 3/4 of the cases; these symptoms were distal in both limbs, with predominance of the lower limbs without, clear-cut segmental level. Pain was reported in 60% of the cases. The majority (80%) of cases also had sphincter disturbance and part of men had impotence. Most of them were followed-up for around 48 months and no remission or relapse occurred. The analysis of these cases excluded subacute combined degeneration of the cord, lathyrism, multiple sclerosis, syphilitic meningomyelitis, adhesive arachnoiditis, pellagra, cranio-vertebral anomalies (Table 1).

Cruickshank[15], in a neurological retrospective analysis of 206 cases of Jamaican neuropathy, showed that the spastic group with negative VDRL (60 cases) was characterized by weakness and pyramidal signs in the lower (100%) and upper (13%) limbs with less involvement of peripheral nerves (21%) than in the Indian cases. Pain was present in 30% of the patients. The sphincters were impaired in 65% of the cases (Table 1).

Steiner et al.[16] analyzed the causes and clinical features of chronic progressive myelopathy in 107 patients from Israel, based upon the presence or absence of oligoclonal immunoglobulin (Ig). The presence of it suggested a diagnosis of MS in 70 patients (65%), while the remaining 37 (35%) were considered MUE. The MUE patients differed from the MS patients in the milder disability and shorter disease course, in the former. These MUE patients were mostly males (68%) and exhibited motor weakness (100%), sensory impairment (65%) and sphincter dysfunction (57%) (Table 1).

In Spain Martí-Fabregas et al.[17] studied 264 consecutive cases of myelopathy, from which 57 cases remained undiagnosed. They were 29 males and 28 females with a mean age of onset of 37.9 years. Clinically they evidenced mostly asymmetrical weakness (71%) involving the upper (26%) and lower (72%) limbs with pyramidal signs predominant in the lower limbs. Moreover they showed disturbances of superficial and deep sensibility with dorsal (mostly), cervical and lumbar levels. Sphincter disturbance was present in 63% of them. The follow-up and subsequent exams (evoked potentials, CSF analysis, myelography and MRI) evidenced that 15 (26%) cases were definite MS, 8 (14%) probable MS, 7 (12%) acute myelopathies, and 21 (37%) remained undiagnosed. They suggested then that the clinical follow-up and MRI could help to diagnose half of the patients the majority being MS (Table 1).

Table 1. Chronic myelopathies of unknown etiology: an analysis of the literature.

	Mani et al., 1969 (n=35) India	Cruickshank, 1975 (n=60) Jamaica	Steiner et al., 1988 (n=107) Israel	Martí-Fabregas, 1989 (n=57) Spain	Merelli et al., 1990 (n=20) Italy	Abebe et al., 1991 (n=22) Ethiopia	Araújo et al., 1993 (n=26) Brazil
Weakness							
ULL	24	7	-	15	6	-	4
LLL	35	60	37	41	20	22	25
Spasticity							
ULL	19	7	-	-	-	-	2
LLL	33	60	-	26	-	22	19
Hyperreflexia							
ULL	22	-	-		6	-	9
LLL	33	60	-	37	20	22	22
Hoffmann +	17	-	-	-	03	-	08
Babinski +	30	-	-	45	16	22	15
Abdominal reflex							
Absent	27	-	-	-	-	-	8
Preserved	4	-	-	-	-	-	-
Normal	4	-	-	-	-	-	-
Clônus	16	-	-	-	-	-	-
Superfic. sensibility ↓							
ULL	10	-	-	8	2	-	-
LLL	23	12	-	28	11	4	17
Pain	21	18	14	8	-	-	
Deep sensibility ↓							
ULL	8	-	-	-	-	-	-
LLL	19	30	16	26	-	5	-
Sphincter disturbance	30	39	21	36	9	15	16

ULL, Upper limbs; LLL, Lower limbs; -, not shown

Table 2. HTLV-I myelopathy (TSP/HAM): differential diagnosis.

	TSP/HAM[1]	TSP (-)[2]	AIDS[3]	FSP[4]	PLE[5]	MS[6]	Shared %[7]
1. Muscle weakness							
- Bulbar (dysarthria/dysfagia)	(+)	–	–	–	+++	+	29.1
- Upper limbs	(+)	(+)	–	–	+++	+	33.3
- Lower limbs							
· Spasticity > Weakness	++	++	–	+++	++	++	66.6
· Weakness > Spasticity	–	–	++	–	–	–	12.5
· Symmetry	+++	+++	+++	+++	+++	+	91.6
· Asymmetry	?	–	+	–	+	+++	33.3
2. Sensitive disturbances	+	+	+++	–	–	+++	50.0
3. Autonomic involvement							
· Sphincter disturbance	+++	++	+++	–	(+ tardive)	++	66.6
· Impotence	+++	+		–	–	+++	41.6
4. Onset							
· Before 35 years-old	++	++	++	+++	(+)	+	70.8
· After 35 years-old	++	++	++	+	+++	+++	79.1
5. Disease progressive course							
· In months	+	+	+	–	–	+	33.3
· In years	++	++	–	+	++	++	58.3
· In decades	+++	+++	–	+++	++	++	75.0
6. Familial occurrence	+	–	–	+++	–	+	33.3

[1]Tropical Spastic Paraparesis / Myelopathy associated to HTLV-I; [2]TSP HTLV-I negative; [3]AIDS Vacuolar Myelopathy; [4]Familial Spastic Paraparesis; [5]Primary Lateral Sclerosis; [6]Multiple Sclerosis; +++, 100%; ++, 75%; +, 50%; (+), 25%.

Table 3. HTLV-I positive and negative tropical spastic paraparesis: comparative analysis of the literature.

	Araújo et al., 1993 (n=60)		De Castro-Costa et al., 1994 (n=31)		Andrade-Filho et al., 1996 (n=62)	
Symptoms	Pos.	Neg	Pos.	Neg.	Pos.	Neg.
Motor	21	11	6	15	17	45
Pain		7	7	6	1	-
Autonomic	6	0	1	2	17	45
Signs						
Pyramidal	34	26	13	18	17	45
Sphincter	32	16	11	17	17	45
Sensitive	15	7	4	4	13	36
Others	7	7	3	4	-	-

In Italy Merelli et al.[18] analyzed clinically 20 patients with myelopathy of unknown origin from whom 12 were males and 8 females with a mean age of 41 years. All patients had weakness and hyperreflexia of the lower limbs, with Babinski sign in 80% of the cases while only 30% had weakness and hyperreflexia of the upper limbs, with Hoffmann sign in 15% of the patients. Sensory impairment was present in the lower (55%) and upper (10%) limbs. There was as well sphincter dysfunction (45%) and impotence (25%) (Table 1).

In Ethiopia Abebe et al.[19] described the clinical features of 22 patients with tropical spastic paraparesis, from whom, only 2 had anti-HTLV-I antibodies. They were 16 males and 6 females with a mean age of 26 years at onset. All cases had pyramidal signs in the legs, touch and pain sensitivity impairment in 18% and vibration and position sense impairment in 22% of the cases. Sphincter disturbance was present in 68% of the patients (Table 1).

In Brazil Araújo et al.[20] studied 26 cases of spastic paraparesis of obscure origin for whom, other etiologies were clinically and laboratorially excluded. They were 17 males and 9 females, with a mean age of 41.6 years at onset. They showed, clinically, paresis (96%) and spasticity (73%) of the lower limbs and paresis (15%) and spasticity (7%) of the upper limbs. Seventy-six per cent of the patients had spastic gait. Hyperreflexia was evidenced in the lower (84%) and upper (34%) limbs. Bilateral Babinski (57%) and Hoffmann (30%) signs were also present. Sensory signs were evidenced in 65% of the patients. Autonomic dysfunction (bladder dysfunction, constipation, penile impotence) was evidenced in 69% of the patients (Table 1).

In this survey of the literature on series of chronic MUE

one may conclude that their presence is universal and that the analysis of different series show that most of the patients are young men with clinical signs and symptoms predominant in the lower limbs and variable sensory, sphincter and impotence disturbances, showing, this way, a clinical similarity. In addition, for part of the cases an etiology is found only after long time, and for the remaining, the diagnosis still remains unknown or obscure.

TSP/HAM: a retroviral (HTLV-I) etiology

In this context of undefined etiology for these forms of obscure myelopathies, a consistent etiological factor was finally found when Gessain et al.[21] in Martinique, and Osame et al.[22], in Japan, described the association of the Tropical Spastic Paraparesis (TSP) to the retrovirus HTLV-I for part of their cases and denominated them as TSP/HAM (Tropical Spastic Paraparesis / HTLV-I associated myelopathies).

This association became in fact important since a world meta-analysis carried out by León et al.[23] showed that among 2,811 patients with TSP or chronic idiopathic spastic paraparesis, 1,261 (44.9%) were HTLV-I positive (TSP/HAM). Moreover recently Osame[24] estimates to exist, up to now, more than 3,000 cases of TSP/HAM in the world.

TSP/HAM differential diagnosis

This way, a differential diagnosis of TSP/HAM with other clinically similar neurological entities, should be looked for. Among these the main similar neurological conditions are vacuolar myelopathy of AIDS, familial spastic paraparesis, primary lateral sclerosis, spinal form of multiple sclerosis, and HTLV-I negative TSP (Table 2). The clinical analysis of these conditions evidences that the clinical aspects which are shared by all these diseases are the predominance of spasticity on weakness in the lower limbs, symmetry of symptoms, sensitive and autonomic disturbances, age, and their chronic and progressive course. On the other hand the symptoms and signs that differentiate them are bulbar impairment, weakness of upper limbs, predominance of weakness on spasticity, asymmetry of symptoms, short course of the disease and familial occurrence (Table 2). When looked individually, some aspects should be underlined in the differential diagnosis of TSP/HAM and these specific conditions. The AIDS myelopathy is tardive and has short evolution besides the seropositivity for HIV. The familial spastic paraparesis (FSP) is rarer than TSP/HAM and, besides the "pure form", the "complicated" FSP is associated with mental retardation, optic atrophy, ataxia, distonia, dysarthria and peripheral neuropathy. The primary lateral sclerosis (PLS) is rare, presenting tetraparesis associated to accentuated spasticity of the lower limbs, pseudo-bulbar signs and absence of sphincter disturbance. The spinal form of multiple sclerosis is rarely isolated and mostly associated with, even silent, optic nerve, brainstem and cerebral lesions as shown by MRI. Moreover apart the progressive form most of them evidenced periods of relapse and remission characteristic of MS and not of TSP/HAM. In addition MS also seems to be rarer than TSP/HAM in the endemic regions of HTLV-I[25].

HTLV-I seronegative TSP: clinical studies

In the world meta-analysis of León et al.[23], it is shown that among 2,811 TSP patients 1,550 (55.1%) patients are HTLV-I seronegative and still remain without diagnosis as a group which could be called non-HAM TSP. In fact, even in the original description of Gessain et al.[21] (1985) this group appears. In Gessain's series of 17 TSP patients, 10 were HTLV-I positive and the remaining 7 (41.1%) patients were HTLV-I seronegative TSP. In a Brazilian meta-analysis De Castro-Costa et al.[26] also showed that among 433 cases of TSP, 276 (63.7%) were HTLV-I negative. More recently Zaninovic[27] reported on a surprisingly high percentage (from 56% to 100%) of HTLV-I seronegative TSP in 14 tropical and non-tropical countries.

Thus TSP/HAM and HTLV-I seronegative TSP seem to be most closesy related albeit possibly of different etiology.

Moreover a comparative analysis of some series of HTLV-I negative TSP and TSP/HAM[20,26,28] showed that there is a similitude of symptoms and signs between both forms, with a slight difference in the autonomic and sphincter symptomatology (Table 3). This similarity had already been evidenced by Bhagavati et al.[29] in a previous work.

HTLV-I seronegative TSP: molecular studies

Since TSP/HAM and HTLV-I seronegative TSP seem to be clinically similar, the etiology, however, is the critical point. In this sense, some molecular studies have been carried out to test a possible retroviral etiology for these HTLV-I seronegative cases.

Nishimura et al.[30] studied one case of HTLV-I seronegative TSP patient from South India who presented a slowly progressive paraparesis, and from whom HTLV-I pol and tax viral sequences were detected in DNA from fresh peripheral blood lymphocytes by polymerase chain reaction (PCR) and liquid hybridization techniques. In addition a long-term $CD4^+$ T-cell line was established from these lymphocytes from which the DNA was amplified and portions of the HTLV-I LTR'U3, pol, env and tax regions were sequenced with an homology of 98.8% to the prototype HTLV-I, demonstrating this way the presence of HTLV-I in this seronegative TSP patient (Table 4).

Daenke et al.[31] described one HTLV-I seronegative TSP patient from Triidad who emigrated to the United Kingdom and presented a progressive asymmetrical spastic paraparesis from whom genomic DNA and total cell RNA were extracted for PCR studies. The PCR amplification covered the entire length of the HTLV-I provirus sequence and resulted in products from gag, pol, protease, env and tax, being identified and sequenced excepting for the LTR (5' and 3') regions. This lack of LTR sequences may explain the replication incompetence and unexpression of HTLV-I antigens hence the absence of immune response. They suppose that this TSP patient carries a defective HTLV-I provirus possibly in consequence of a vigorous immune response early in the infection which successfully eradicated the infected cells, leaving only cells with defective sequences (Table 4).

Table 4. Comparative analysis of clinical and molecular approach of HTLV-I seronegative TSP series.

Nishimura et al. (India) Ann Neurol 34:867-870, 1993		Daenke et al. (Caribbean) J Infect Dis 169:941-943, 1994	Ramirez et al. (Chile) J Clin Microbiol 36(6):1811-1813,1998	De Castro-Costa et al. (Brazil) AIDS Res Hum Retrov 11(2):315-318,1995
Nº of patients	1	1	15	12
Age (x)	46	60	55.1	42.5
Age of onset (x)	21	—	—	—
Slowly progressive paraparesis RLL → LLL → ULLs No sphincter disturbance No speech and swallowing No risk factors		Progressive asymmetrical spasticity of the legs, left arm involvement, low back pain, urgency of micturition	Brain involvement (7/15): pseudobulbar, parkinsonian, dyskinesia, sphincter disturbance	Slowly progressive paraparesis
Spastic quadriparesis LLs > ULs Hyperreflexia Bilateral Babinski Brisk jaw jerking			Spasticity, hyperreflexia and weakness of lower limbs	Pyramidal symptoms in the lower limbs (12/12) and in the upper limbs (3/12)
No sensory abnormality		No sensory abnormality		
CSF normal VDRL (-) HTLV-I (-) Serum/CSF (WB) Myelogram: normal Head/Spinal cord MRI: normal ENMG: normal		Normal, except for ↑ IgG Positive Negative Multiple indent. in the cervical region Cervical MRI: normal	Negative (immunofluorescence/WB)	
Lymphocytes culture: p19, p24 $CD3^+$, $CD4^+$, CD8-, $IL2R^+$ phenotypes (long-term CD4+ T-cell lines) PCR: primers for LTR, pol, env and tax regions				
Fresh PBL – DNA PCR: primers for pol and tax regions		Fresh PBL – DNA PCR: primers for 5' LTR, gag, pol, protease, env, tax and LTR 3' Sequences amplified: gag, pol, protease, env, tax, but not LTR 3' or 5'	DNA PCR: primers for tax and LTR Only tax was amplified Homology to HTLV-I clone (ATK-1): > 98%	PCR: 10^5 cells Primers for tax/rex an pol regions
HTLV-I/II provirus		Defective provirus	Defective provirus	No HTLV-I/II provirus was detected

Ramirez et al.[32] studied 15 HTLV-I seronegative TSP patients from Chile. Clinically 8 patients presented paraparesis with spasticity, hyperreflexia, bilateral Babinski signs and some sphincter disturbances. In addition to the spastic paraparesis the other 7 patients had brain involvement. For molecular studies the DNA was extracted from purified PBMC and regions of tax and LTR genes were tried to be amplified by PCR. The results showed that only a region of the tax gene was amplified and not the LTR gene suggesting, this way, the presence of a defective HTLV-I provirus in 10 out 15 seronegative TSP patients namely those who mainly had spinal and brain involvement (Table 4).

De Castro-Costa et al.[33] studied 12 HTLV-I seronegative TSP patients from Brazil who clinically presented signs and symptoms typically of TSP without brain involvement, and tried to detected the proviral genome with PCR in the tax/rex and pol parts of the HTLV proviral genome. However, no HTLV-I or provirus was detected (Table 4).

Thus, the analysis of the molecular and clinical studies of HTLV-I seronegative TSP shows, divergent results.

In all studies the number of patients is still limited, and from the clinical point of view some studies such as in the Chilean series also show mixed cases with typical and atypical signs and symptoms of TSP. Moreover a long/term study has not yet been carried out with repetitive clinical, serological and PCR evaluations. On the other hand, the PCR studies were divergent in their results showing the presence of complete, defective or absent HTLV-I provirus.

In conclusion further studies on HTLV-I seronegative TSP cases should include a long-term clinical and laboratorial follow-up of the patients and their relatives the building-up of long-term T-cell lines and the use of repeated PCRs, the use of primers for related retroviruses or other viruses and the search for other co-factors or etiologies. So, TSP still goes on as scientific stimulus and challenge.

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