

Neuropathology of Human and Experimental TSP/HAM : a critical review

Carlos Maurício DE CASTRO COSTA¹, René DOM², Herwig CARTON³, Terezinha DE JESUS TEIXEIRA SANTOS¹ and Maria José ANDRADA-SERPA⁴

¹Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza-CE, Brazil ; ²Department of Neuropathology, Katholieke Universiteit Leuven, Leuven, Belgium ; ³Department of Neurology, Katholieke Universiteit Leuven, Leuven, Belgium ; ⁴Evandro Chagas Hospital Research Center, Oswaldo Cruz Foundation, Rio de Janeiro-RJ, Brazil

Abstract

Tropical Spastic Paraparesis / HTLV-I Associated Myelopathy (TSP/HAM) is clinically characterized by chronic insidious spastic paraparesis associated with variable sensory impairment and sphincter symptoms. Neuropathological studies of this condition are based on a few autopsied cases, and on experimental animal models. However, divergent aspects exist between human and experimental animal neuropathology of TSP/HAM, namely, the site of lesions in the spinal cord, the involvement of peripheral nerves and roots, the nature of histological abnormalities, and the cellular reactions. Moreover, unanswered questions as to the preferential site of spinal affection, the temporal inflammatory picture, the selective damage of the corticospinal tract, the sparing of lower motor neurons, the inconsistent affection of sensory tracts, and the involvement of the brain, are outlined. A long-term, chronological, correlated clinical and neuropathological study in HAM experimental animals is suggested.

Key words : TSP/HAM ; human myelopathy ; experimental animal ; neuropathology ; HTLV-I/II.

Introduction

Tropical Spastic Paraparesis (TSP) is a myelopathy described in several countries of tropical and temperate regions, that was originally denominated tropical spastic paraplegia by Mani *et al.* (1969) in India (Spillane, 1973).

In these previous studies, this condition was etiologically undefined and of unknown origin, although some considered that different causes such as malnutrition, toxins, syphilis and yaws might be implicated. From 1985 on, an association of TSP with the retrovirus HTLV-I was found firstly by Gessain *et al.* (1985) and Osame *et al.* (1986) in around half of their cases, and afterwards by several other investigators (Zaninovic', 1999). Osame *et al.* (1986) denominated it as HTLV-I associated myelopathy (HAM). Later on, TSP associated with HTLV-I and HAM was considered to be the same entity (Román & Osame, 1988).

The incubation period from HTLV-I infection to clinical manifestation ranges from months to decades and the major modes of transmission include blood transfusion, parenteral drugs, sexual contact and breast feeding (Edlich *et al.*, 2000).

In the endemic area, besides HTLV-I seropositive TSP patients, seronegative TSP cases have also been described (De Castro-Costa *et al.*, 1994, 2001 ; León *et al.*, 1997). They are clinically similar since they present insidious and progressive paraparesis with sphincter and sensory impairment in some of the cases. Most of them are partially incapacitated, requiring some support for walking such as crutches and other people. A slight trend to more incapacitating states seems occur in the seropositive patients (De Castro-Costa, 1996a).

Demographically, the HTLV-I seropositive TSP cases are mainly women, while there is a slight predominance of men in the seronegative ones. Both have a mean age of around 40-45 years. Racially, they are distributed in the Caucasoid, Negroid and Mongoloid populations (De Castro-Costa *et al.*, 1995a ; De Castro-Costa, 1996a).

Clinically, TSP/HAM is characterized by an insidious (rarely acute) onset of motor dysfunction, which leads to progressive gait disturbance associated with variable sphincter and sensory impairment. The patients present symmetrical or asymmetrical spastic paraparesis with hyperreflexia, clonus and Babinski signs in the lower limbs as well as hyperreflexia and Hoffmann signs in the upper limbs. Paresis of the upper limbs is uncommon and rare. The TSP/HAM patients become relatively stable a few years after onset and most of them die of concurrent interrelated diseases.

The laboratorial diagnosis of TSP/HAM includes the presence of anti-HTLV-I/II antibodies (EIA) in serum and CSF and the presence of genomic proteins (GD21 and rgp46-I, p19 and/or p24) shown by confirmatory tests such as Western blot and Inno-Lia. Molecular tests such as polymerase chain reaction (PCR) and real time PCR, may define this infective condition by amplifying

the viral nucleic acids (Compton, 1991 ; Wolcott, 1992). Besides this specific viral-related diagnosis, CSF studies also show mild lymphocytic pleocytosis and milder elevation of proteins. Immunological studies of CSF reveal an inflammatory reaction with oligoclonal bands, indicative of intrathecal synthesis of IgG (Puccioni-Sohler *et al.*, 1995). Spinal cord MRI may indicate atrophy of the lower thoracic region and nonspecific changes in the white matter, suggestive of possible cerebral demyelination. Electrophysiological studies may show impairment of peripheral nerves and sensory ascending tracts (Moritoyo *et al.*, 1996). Moreover, the impairment of corticospinal tracts in TSP/HAM is shown by studies of motor evoked potentials (Foster *et al.*, 1993).

At present there is no definite treatment for TSP/HAM, although oral prednisone, i.v. methylprednisolone, plasmapheresis, interferon, oral azathioprine and vitamin C have been tried and have shown transient effects (Edlich *et al.*, 2000).

Experimentally, animal models have been developed to study clinical and histopathological expression of TSP/HAM, with the aim of understanding underlying pathogenetic mechanisms.

These experimental studies have shown clinically the presence of pyramidal signs in 1 out of 6 rabbits after six weeks of HTLV-I inoculation (Minagawa *et al.*, 1991), and spastic paraparesis in 3 out of 16 seronegative Wistar-King-Aptekman (WKA) rats 16 months after MT2 cell inoculation (Ishiguro *et al.*, 1992), in 1 out of 2 seropositive WKA rats 27 months after Ra-1 cell inoculation and 1 out of 8 seropositive WKA rats 20 months after MT2 cell inoculation (Kushida *et al.*, 1993), and in 6 out of 8 seropositive WKA rats 29 months after MT2 cell inoculation and 1 out of 2 seropositive WKA rats 30 months after Ra-1 cell inoculation (Kushida *et al.*, 1994). No F344 rats showed neurological changes in these studies (Table 1). Beside these results, minor (reduced motor capacity and behavior) and major (paralysis) changes have been shown in parents and sibling rats inoculated with the whole blood of TSP/HAM patients (De Castro-Costa, 1996b ; De Castro-Costa, 1998 ; De Castro-Costa *et al.*, 1998). Correia *et al.* (2001) established an experimental model of HTLV-I infection in rats (F344) and mice (C3H/Hej and BALB/c), in which they observed that none of the inoculated mice exhibited antibodies whereas 91.6% presented provirus in at least one of the analyzed tissues. Eighty percent of the inoculated adult rats exhibited a persistent antibody immune response whereas provirus was found in only 5 out of 15 (33%) rats. The histopathological analysis showed only minor findings in liver and muscles, whereas the spinal cord and brain were normal. No animal, however, showed any motor disability.

Experimental studies with transgenic rats have also been carried out. However, none of these rats

showed neurological symptoms or lesions, excluding their consideration as HAM models. Nevertheless, they are very suited as models for HTLV-I associated arthropathy (Grossman & Ratner, 1996).

In brief, most of the animals inoculated with HTLV-I exhibited tardive major neurological signs (15 to 30 months after inoculation) in seropositive and seronegative WKA rats. These are in fact old animals since rats have an average life span of 24 months (Adams *et al.*, 1997), and this obviously differs from human clinical findings.

This work reviews critically the different neuropathological aspects shown in the studies of human and experimental animal TSP/HAM.

Human and Animal Neuropathology of TSP/HAM

HUMAN NEUROPATHOLOGY

To-date there have been around 25 autopsied cases of TSP/HAM (Akizuki *et al.*, 1987, 1989 ; Furuzono *et al.*, 1989 ; Izumo *et al.*, 1989 ; Kobayashi *et al.*, 1989 ; Picardo *et al.*, 1988 ; Iwasaki, 1990 ; Bhigjee *et al.*, 1991 ; Ogata *et al.*, 1993 ; Wu *et al.*, 1993 ; Yoshioka *et al.*, 1993 ; De Castro-Costa *et al.*, 1995b ; Cartier *et al.*, 1997 ; Leite *et al.*, 1997).

All cases presented thoracic spinal cord atrophy (Fig. 1) with less prominent cervical or lumbar atrophy. Demyelination of the corticospinal tracts was predominant in all cases, in addition to impairment of the posterior and, less frequently, anterior funiculi as shown in one of our cases (De Castro-Costa *et al.*, 1995b) (Fig. 2). Lower motor neurons were spared and perivascular and parenchymal inflammatory infiltration with lymphocytes and macrophages was mostly present in the short evolutive cases (Yoshioka *et al.*, 1993) and absent (Iwasaki, 1990), or slight, in the long evolutive ones (Figs. 3 and 4) (De Castro-Costa *et al.*, 1995b ; Cartier *et al.*, 1997 ; Wu *et al.*, 1993). Hyaline degeneration of the vessel walls (adventitia and media) (Fig. 4) and astrocytic proliferation were found in all cases in different stages of the condition. However, viral particles or viral antigens were not found in these studies. Moreover, vacuolation was not described in most of the cases, except for that of Yoshioka *et al.* (1993) (Table 2). Brain involvement in TSP/HAM has also been suggested (Cartier *et al.*, 1997 ; Aye *et al.*, 2000). However, this inflammatory involvement occurs mainly in cases where there is active chronic-inflammation (i.e., with marked perivascular inflammatory infiltration) and in none where there is inactive-chronic inflammation (i.e., without inflammatory change, but with marked fibrotic change of blood vessels), thus suggesting an encephalo-myelitic process in the early stage of this condition.

Table 1
Experimental animal models of HTLV-I infection and myelopathy (HAM) : clinico-neuropathological findings

Author	Number and Kind of Animal and Cell Line	Clinical	Results		Presence of Viral Particle or Provirus	Post-Inoculation Time
			Clinical	Neuropathological		
MINAGAWA <i>et al.</i> , 1990	Rabbits (n = 6)	6 seropositive	–	–	–	6 weeks
	HTLV-I strains	1 with pyramidal signs	Slight spinal thoracic atrophy	–	Provirus in 8/9	16 months
ISHIGURO <i>et al.</i> , 1992	WKA rats (n = 9)	3 out 8 seronegative	Slight spinal thoracic atrophy	Macrophage infiltration	No viral particle	
	MT2 cells	Spastic paraparesis	Demyelination of lateral-anterior funiculi	Vacuolation		
KUSHIDA <i>et al.</i> , 1993	WKA rats (n = 10)	18 seropositive	Absence of lymphocytic infiltration	Demyelination of anterior-posterior roots	Provirus in 1/3 WKA	27 months
	MT2 cells	3 out 8 WKA (MT2)	Myelin degeneration and Macrophage infiltration		MT2	20 months
KUSHIDA <i>et al.</i> , 1994	Ra-1 cells	1 out 2 WKA (Ra-1)	No lymphocytic infiltration	Cervical / Thoracic spinal cord	No viral particle	
	F344 rats (n= 8)	0 out 8 F344 (MT2)	Degeneration of nerve roots and peripheral nerves			
KUSHIDA <i>et al.</i> , 1994	WKA rats (n = 10)	18 seropositive	White matter degeneration	Macrophage infiltration	Provirus in 18/18 in PBMC	29 months
	MT2 cells	3 out 8 WKA (MT2)	Cervical / Thoracic spinal cord		Provirus in 2/8 WKA	30 months
KUSHIDA <i>et al.</i> , 1994	Ra-1 cells	1 out 2 WKA (Ra-1)	Vacuolation / Gliosis	Posterior-anterior-lateral funiculi	MT2	
	F344 rats (n= 8)	0 out 8 F344 (MT2)	Macrophage infiltration	No lymphocytic infiltration	Spinal cord	
	MT2 cells	Spastic paraparesis	Peripheral nerve degeneration and macrophage infiltration		No viral particle in spinal cord and peripheral nerve	



FIG. 1. — Spinal cord atrophy

ANIMAL NEUROPATHOLOGY

Neuropathological studies of the HAM model have been carried out by Ishiguro *et al.* (1992) and Kushida *et al.* (1993, 1994). These studies have been reviewed by Iwasaki (1993), Mizusawa *et al.* (1994) and Yoshiki (1995).

The main findings included demyelination of the lateral and anterior funiculi of the cervical and thoracic spinal cord, of the nerve roots and peripheral nerves, as well as vacuolation and gliosis of the posterior, anterior and lateral funiculi. In all rats there was macrophage infiltration and absence of lymphocytes. This macrophage infiltration was also present in peripheral nerves and roots. Mizusawa *et al.* (1994), however, pointed out similar but milder lesions in old control WKA normal rats. Despite detecting viral provirus in polymorphic mononuclear blood cells, and occasionally in the spinal cord, they did not detect any viral particles in the spinal cord and peripheral nerves of the paretic rats (Yoshiki, 1995) (Table 1). Brain involvement was only shown in a transgenic model carrying the LTR-env-pX gene of HTLV-I, where

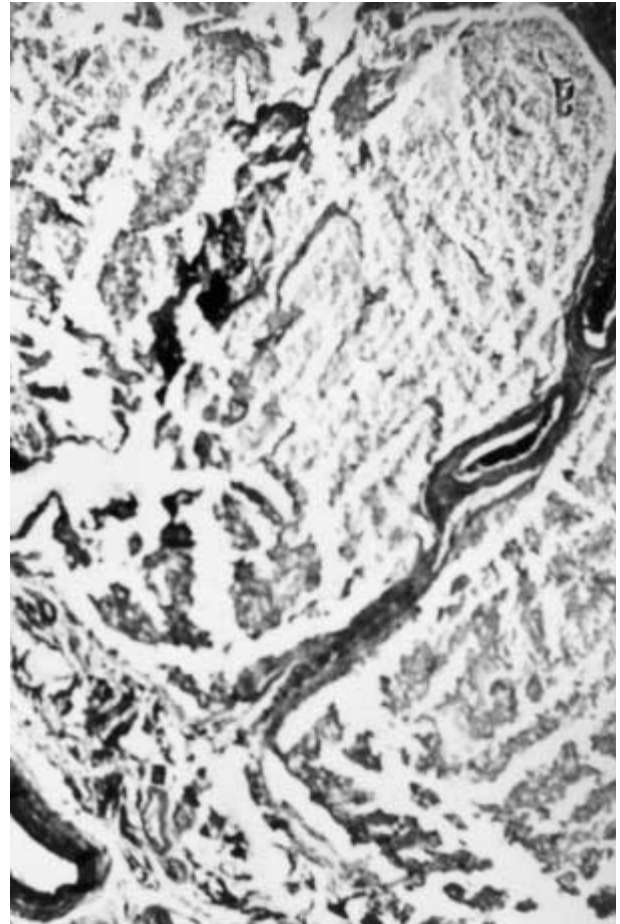


FIG. 2. — Demyelination of the anterior corticospinal tract at thoracic level (upper right). Normal anterior spinal artery (lower left) (Kluver-Barrera $\times 200$).

infiltration of activated microglia/macrophages intermingled with many apoptotic cells was evident (Yoshiki, 2001).

Discussion

The Montgomery *et al.* (1964) anatomopathological reports on the “Jamaican Neuropathy” (later defined as TSP) were similar to the presently described cases. However, at that time, an etiology of these cases had not yet been defined.

The neuropathological lesions described in the TSP/HAM autopsied cases still have many unanswered questions such as : the preferential affection of the lower thoracic spinal cord ; the lack of temporal correlation of clinical and histopathological (inflammatory) expression ; the sparing of the lower motor neurons ; the inconsistent affection of sensory tracts ; the main and selective damage of corticospinal tracts and partially of the posterior funiculi (De Castro-Costa *et al.*, 1999). The demyelination of the pyramidal tract is predominant, and this is corroborated by electrophysiological studies with evoked motor potentials (Castillo

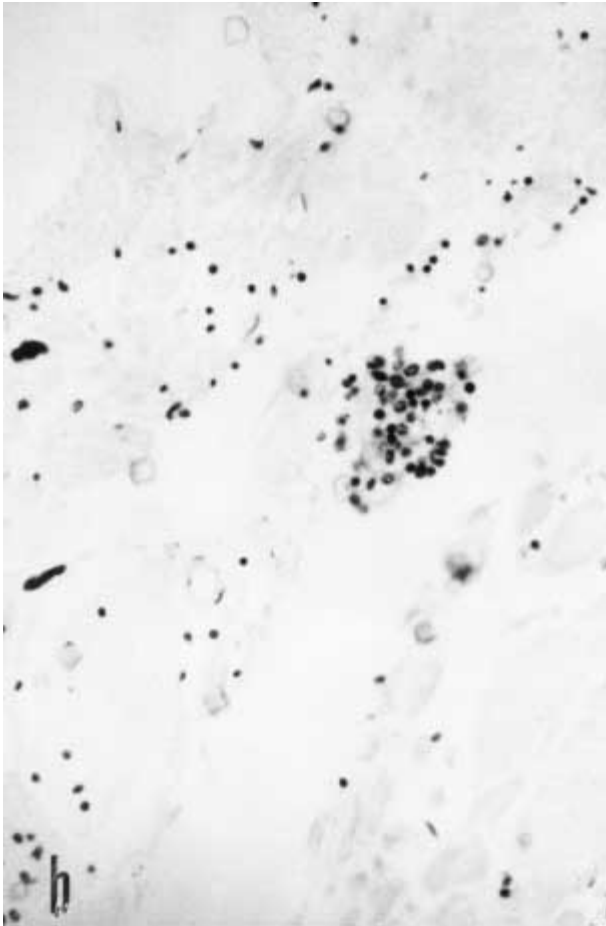


FIG. 3. — Small focus of inflammatory cells in the gray matter at thoracic level (HE \times 200).

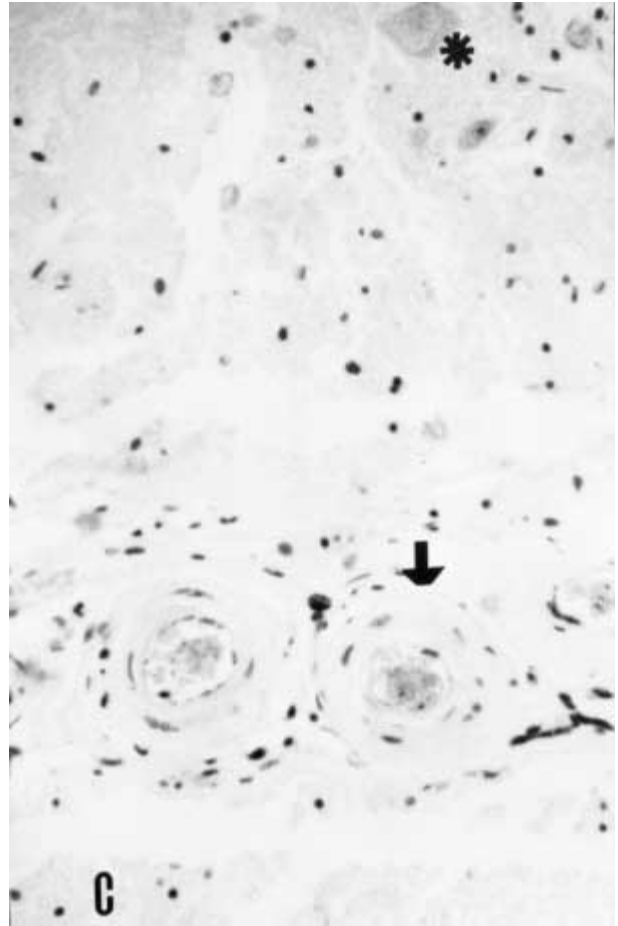


FIG. 4. — Preservation of some anterior horn cells (*), thickening of vascular walls (↓) and slight lymphocytic perivascular infiltration (HE \times 200).

et al., 1996). However, a correlation between slight to absent cervical demyelination of corticospinal tracts (Iwasaki, 1990) and the presence of hyperreflexia of the upper limbs with normal force in most of the patients is still lacking.

When human and animal TSP/HAM cases are neuropathologically compared, striking differences emerge (De Castro-Costa, 1998 ; De Castro-Costa *et al.*, 1998). The main sites involved in the animals are the cervico-thoracic-lumbar levels with clinical expression limited to the lower limbs. Demyelination is shown in the lateral and anterior tracts as well as in the peripheral nerves and roots in a most expressive manner. Comparatively, in the human TSP/HAM cases, peripheral nerve impairment is less frequent. The presence of both lesions in animals makes it difficult to accept the term "spastic" paraparesis since the peripheral impairment should lead to flaccid paralysis. Indeed, in addition to this paralysis, atrophy of the lower limbs of these animals has been described (Kushida *et al.*, 1994). Vacuolation is a characteristic lesion in AIDS myelopathy, which does not exist in human TSP/HAM. It is thus surprising to observe its presence in HAM animals, and possibly this may be the expression of an age-related phenomenon since

control old rats show similar, but milder, lesions (Mizusawa *et al.*, 1994). The absence of lymphocytes and presence of macrophage infiltration in animal models is another of the divergent points from human TSP/HAM. Possibly different mechanisms are involved in these phenomena, and the macrophage infiltration may be correlated with the severity of myelin loss and vacuolation (Yoshiki, 1995) ; it may also represent a scavenger reaction for myelin debris, and so does not mean an active immune process as seen with lymphocytic proliferation. Moreover, vacuolation is a non-specific response to a variety of stimuli such as nutritional deficiencies, cytokine-mediated injuries, metabolic and neurotoxic disorders (Jacobs *et al.*, 1979 ; Lampert *et al.*, 1973 ; Louis *et al.*, 1993). On the other hand, it is remarkable that spinal cord lesions in seropositive HAM rats were the same as in the seronegative rats, as shown in Table 1 (Yoshiki, 1995), and this finding may foretell possible lesions to be found in human seronegative TSP. Evidence of apoptosis of myelin-producing cells, oligodendrocytes and Schwann cells, and the participation of TNF- α (and other cytokines) in the seropositive animals, may represent an important finding to clarify the pathogenesis of this HTLV-I

Table 2
Neuropathological findings in human HAM/TSP

Author	Spinal Cord Atrophy	Demyelination	Inflammatory Infiltration	Vascular Changes	Astrocytic Reaction	Viral Particle or Provirus	Evolution	Vacuolation	Number of Cases
AKIZUKI <i>et al.</i> , 1988	Lower Thoracic	Lateral Anterior Posterior	Lymphocytes Plasmocytes Macrophages Perivasc. / Parench.	Proliferation Capillary Hyaline Thickness	Yes	None	2 years	-	1
PICARDO <i>et al.</i> , 1988	None	Lateral Posterior Anterior Nerve Root	-	Capillary Proliferation	Yes	?	1 year 5 years	No	2
IWASAKI 1990	Middle Lower Thoracic	Lateral Posterior Nerve (less)	Lymphocytes Mononuclear Gray/White Perivascular (0-3>4-6 years)	Hyaline Thickness	Yes	-	0-3 years 4-6 years 9-28 years	No	10
BHIGJEE <i>et al.</i> , 1991	Thoracic	Lateral Posterior	Lymphocytes Parenchyma Perivascular	-	NR	No Proviral DNA	1 year	No	1
OGATA <i>et al.</i> , 1993	Thoracic	Lateral Posterior Anterior	None	Hyaline Thickness	Yes	-	36 years	No	1
YOSHIOKA <i>et al.</i> , 1993	Thoracic	Lateral Posterior	Lymphocytes Perivascular	-	NR	No antigen	9 months	Yes	1
WU <i>et al.</i> , 1993	Cervical Thoracic Lumbar Sacral + Brainstem	Lateral Posterior	Lymphocytes Parenchyma Perivascular	Adventitia Giltosis	Yes	-	25 years	No	1
DE CASTRO-COSTA <i>et al.</i> , 1995	Cervical Thoracic Lumbar	-	Macrophages Lymphocytes (T) Perivasc. / Menin.	Hyaline Thickness	Yes	-	13-40 years	-	2
CARTIER <i>et al.</i> , 1997	Lumbar Thoracic	Lateral (L/T) Posterior (C) Spinocerebellar	Lymphocytes Perivascular Parenchyma	Hyaline Thickness	NR	-	3-17 years	-	6

NR : not reported

Total : 25

associated condition (Yoshiki, 1995). Moreover, chronological examination showed that a high provirus load and pX expression were evident just before the appearance of apoptosis. Additionally, marked suppression of bcl-2 was observed in the isolated oligodendrocytes *in vitro*. Both elements may be related to the pathogenesis of HAM rat disease (Yoshiki, 2001).

Only few papers describe long-term observations of human, clinical and neuropathological evolution of TSP/HAM (De Castro-Costa, 1996a; Araújo *et al.*, 1995). However, there is now an increased interest in detecting minimal neurological signs in asymptomatic HTLV-I positive blood donors, and this will allow an accurate follow-up of them, which may be representative of a contribution to pathogenetic and therapeutic purposes (Leite *et al.*, 2001). In this context, it is our intention to carry out further long-term neuropathological studies in inoculated rats in order to detect, by histopathological and molecular methods, the evolutive characteristics of the lesions, correlating each phase with clinical expression. Moreover, the seronegative TSP patients have not yet been studied neuropathologically and comparative analysis of both seronegative TSP and TSP/HAM will be of interest and importance for understanding of the pathogenesis of both conditions.

Acknowledgements

We thank Dr. David Neil Criddle for the review of the English style and Sílvia A. Costa for the accurate electronic typewriting of this manuscript.

REFERENCES

- ADAMS R. D., VICTOR M., ROPPER A. H. The neurology of aging. In: *Principles of Neurology*. New York, McGraw-Hill, 1997, 608-620.
- AKIZUKI S., NAKAZATO O., HIGUCHI K., TANABE K., SETOGUCHI M. *et al.* Necropsy findings in HTLV-I associated myelopathy. *Lancet*, 1987, **1**: 156-157.
- AKIZUKI S., YOSHIDA S., SETOGUCHI M., HIGUCHI S., YAMAMOTO S. *et al.* The neuropathology of human T-lymphotropic virus type I associated myelopathy. In: *HTLV-I and the Nervous System*. ROMÁN G. C., VERNANT J. C., OSAME M. (eds.). New York, Alan R. Liss Inc., 1989, 253-260.
- ARAÚJO A. Q. C., LEITE A. C. C. B., DULTRA S. V., ANDRADA-SERPA M. J. Progression of neurological disability in HTLV-I associated myelopathy / tropical spastic paraparesis (HAM/TSP). *J. Neurol. Sci.*, 1995, **129**: 147-151.
- AYE M. M., MATSUOKA E., MORITOYO T., UMEHARA F., SUEHARA M. *et al.* Histopathological analysis of four autopsy cases of HTLV-I-associated myelopathy / tropical spastic paraparesis: inflammatory changes occur simultaneously in the entire central nervous system. *Acta Neuropathol.*, 2000, **100**: 245-252.
- BHIGJEE A. I., WILEY C. A., WACHMAN W., AMENONIORTI T., PIRIE D. *et al.* HTLV-I associated myelopathy: clinicopathologic correlation with localization of provirus to spinal cord. *Neurology*, 1991, **41**: 1990-1992.
- CARTIER L. M., CEA G., VERGARA C., ARAYA F., BORN P. Clinical and neuropathological study of six patients with spastic paraparesis associated with HTLV-I: an axomyelinic degeneration of the central nervous system. *J. Neuropathol. Exp. Neurol.*, 1997, **56** (4): 403-413.
- CASTILLO J. L., VERDUGO R. J., CEA J. G. Clinical neurophysiology of HAM/TSP. In: *HTLV - Truths and Questions*. ZANINOVIC' V. (ed.). Cali, Feriva, 1996, 187-193.
- COMPTON J. Nucleic acid sequence-based amplification. *Nature*, 1991, **350**: 91-92.
- CORREIA T. G., DE PAULA E. F., ANDRADA-SERPA M. J. HTLV-I infection in mice and rats. *AIDS Res. Hum. Retroviruses*, 2001, **17** (Suppl. 1): S-45.
- DE CASTRO-COSTA C. M. A preliminary analysis of an experimental long-term study of motor behavior and clinical aspects of Wistar rats inoculated with blood from HTLV-I positive TSP patients from Ceará (Northeastern Brazil). In: *HTLV - Truths and Questions*. ZANINOVIC' V. (ed.). Cali, Feriva, 1996b, 89-95.
- DE CASTRO-COSTA C. M. A review of tropical spastic paraparesis in Ceará (Northeastern Brazil). In: *HTLV - Truths and Questions*. ZANINOVIC' V. (ed.). Cali, Feriva, 1996a, pp. 105-130.
- DE CASTRO-COSTA C. M. Análisis comparativo entre la Paraparesia Espástica Tropical humana y la experimental. In: *La PET/HAM - La Paraparesia Espástica Tropical o Mielopatía Asociada con el HTLV-I*. ZANINOVIC' V., DE CASTRO-COSTA C. M. (eds.). Cali, Colciencias-Feriva, 1998, 124-130.
- DE CASTRO-COSTA C. M., CARTON H., GOUBAU P., DE FIGUEIREDO E. G., GIFFONI S. D. A. Paraparesia Espástica Tropical nos Trópicos e Brasil: Análise Histórica. *Arq. Neuropsiquiatr.*, 1994, **52** (1): 106-109.
- DE CASTRO-COSTA C. M., CARTON H., SANTOS T. J. T. HTLV-I Negative Tropical Spastic Paraparesis: A Scientific Challenge. *Arq. Neuropsiquiatr.*, 2001, **59** (2-A): 289-294;
- DE CASTRO-COSTA C. M., DOM R., CARTON H., GOUBAU P., FERREIRA M. V. P., NETO F. U. S. A pathological analysis of two first Brazilian autopsied cases of HAM/TSP (abstract). *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, 1995b, **10**: 229.
- DE CASTRO-COSTA C. M., FIGUEIREDO E. G., SANTOS T. J. T., FROTA C. H., LOBO C. C. G. *et al.* Experimental HTLV-I infection and associated myelopathy. *Arq. Neuropsiquiatr.*, 1998, **56** (3-A): 44-497.
- DE CASTRO-COSTA C. M., GOUBAU P., LIU H. F., VANDAMME A. M., DA CUNHA F. M. B. *et al.* HTLV-Negative and HTLV Type I-Positive Tropical Spastic Paraparesis in Northeastern Brazil. *AIDS Res. Hum. Retroviruses*, 1995a, **11** (2): 315-318.
- DE CASTRO-COSTA C. M., SCIOT R., CARTON H. Are specific HTLV-I antibodies involved in the selective degeneration of the lateral columns of the thoracic spinal cord in HAM/TSP? *Acta Neurol. Colomb.*, 1999, **15** (Suppl. 2): 9-10.

- EDLICH R. F., ARNETTE J. A., WILLIAMS F. M. Global epidemic of human T-cell lymphotropic virus type-I (HTLV-I). *J. Emerg. Med.*, 2000, **18** (1) : 109-119.
- FOSTER A., MORGAN O., YOUNG R., McKECHNIE R., RODGERS-JOHNSON P. Central motor conduction time in tropical spastic paraparesis – a magnetic stimulation study. *Electroencephal. Clin. Neurophysiol.*, 1993, **86** : 10P.
- FURUZONO H., NAKAZATO O., GOTO K., AKIZUKI S., OKAJIMA T. An autopsy case of HTLV-I associated myelopathy (HAM). *Clin. Neurol. (Japan)*, 1989, **29** : 349-354.
- GESSAIN A., BARIN F., VERNANT J. C., GOUT O., MAURS L. *et al.* Antibodies to human T-lymphotropic virus type I in patients with tropical spastic paraparesis. *Lancet*, 1985, **2** : 407-409.
- GROSSMAN W. J., RATNER L. Transgenic mouse models for HTLV-I infection. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, 1996, **13** (suppl. 1) : S162-S169.
- ISHIGURO H., ABE M., SETO K., SAKURAI H., IKEDA H. *et al.* A rat model of human T-lymphocyte virus type I (HTLV-I) infection. 1. Humoral antibody response, provirus integration, and HTLV-I associated myelopathy / tropical spastic paraparesis-like myelopathy in seronegative HTLV-I carrier rats. *J. Exp. Med.*, 1992, **176** : 981-989.
- IWASAKI Y. Pathology of chronic myelopathy associated with HTLV-I infection (HAM/TSP). *J. Neurol. Sci.*, 1990, **96** : 103-123.
- IZUMO S., USUKU K., OSAME M., MACHIGASHIRA K., JOHNOSONO J., NAKAGAWA M. The neuropathology of HTLV-I associated myelopathy in Japan : report of an autopsy case and review of the literature. In : *HTLV-I and the Nervous System*. ROMÁN G. C., VERNANT J. C., OSAME M. (eds.). New York, Alan R. Liss Inc., 1989, 261-267.
- JACOBS J. M., MILLER R. H., WHITTLE A., CAVANAH J. B. Studies on the early changes in acute isoniazid neuropathy in the rat. *Acta Neuropathol. (Berl.)*, 1979, **47** : 85-92.
- KOBAYASHI I., OTA K., YAMAMOTO K., MURAKAMI H., MARUYAMA S. An autopsy case of HTLV-I associated myelopathy. *Neurol. Med.*, 1989, **30** : 409-412.
- KUSHIDA S., MATSUMURA M., TANAKA H., AMI Y., HORI M. *et al.* HTLV-I associated myelopathy / tropical spastic paraparesis-like rats by intravenous infection of HTLV-I producing rabbit or human T-cell line into adult WKA rats. *Jpn. J. Cancer Res. (Gann)*, 1993, **84** : 831-833.
- KUSHIDA S., MIZUSAWA H., MATSUMURA M., TANAKA H., AMI Y. *et al.* High incidence of HAM/TSP-like symptoms in WKA rats after administration of human T-cell leukemia virus type I producing cells. *J. Virol.*, 1994, **68** (11) : 7221-7226.
- LAMPERT P., O'BRIEN J., GARRET R. Hexachlorophene encephalopathy. *Acta Neuropathol. (Berl.)*, 1973, **23** : 326-333.
- LEITE A. C., ALAMY A. H., OLIVEIRA A. L. A., VEZZANI R., GUIMARÃES P. A. P. *et al.* Other neurological abnormalities associated to HTLV-1. *AIDS Res. Hum. Retroviruses*, 2001, **17** (Suppl. 1) : S-19.
- LEITE A. C., SERAPIÃO M. J., NEVES E. S., LENZI M. E. R., NASCIMENTO D. J., ARAÚJO A. Q. C. Autopsy findings in two cases of HTLV-I myelopathy (HAM/TSP). In : *VIIIth International Conference on Human Retrovirology : HTLV*. Rio de Janeiro, Brazil, Jun., 1997, CS 15.
- LEÓN-S F. E., DE CASTRO-COSTA C. M., GAFFGA M. Discrepancy, coincidence or evidence in chronic idiopathic spastic paraparesis throughout the world : a meta-analysis of 2811 patients. *Arq. Neuropsiquiatr.*, 1997, **55** (3-B) : 530-535.
- LOUIS J. C., MAGAL E., TAKAYAMA S., VARON S. CNTF protection of oligodendrocytes against natural and tumor necrosis factor-induced death. *Science*, 1993, **259** : 689-692.
- MANI K. S., MANI A. J., MONTGOMERY R. D. A spastic paraplegic syndrome in South India. *J. Neurol. Sci.*, 1969, **9** : 179-199.
- MINAGAWA H., MORA C. A., ASHER D. M., STONE G. A., LIBERSKI P. P., GIBBS C. J. Transmission of human T-cell leukemia virus type I from a patient with HTLV-I associated myelopathy / tropical spastic paraparesis and a asymptomatic carrier to rabbits. *Arch. Virol.*, 1991, **118** : 235-245.
- MIZUSAWA H., KUSHIDA S., MATSUMURA M., TANAKA H., AMI Y. *et al.* A neuropathological study of paraparetic rats infected with HTLV-I producing T-cells. *J. Neurol. Sci.*, 1994, **126** : 101-108.
- MONTGOMERY R. D., CRUICKSHANK E. K., ROBERTSON W. E., MACMENEMEY W. H. Clinical and pathological observation on Jamaican neuropathy : a report of 206 cases. *Brain*, 1964, **87** : 425-462.
- MORITOYO H., ARIMURA K., ARIMURA Y., TOKIMURA Y., ROSALES R., OSAME M. Study of lower limb somatosensory evoked potentials in 96 cases of HTLV-I associated myelopathy / tropical spastic paraparesis. *J. Neurol. Sci.*, 1996, **138** : 78-81.
- OGATA A., NAGASHIMA K., TASHIRO K., MIYAKAWA A., MIKUNI C. H. MRI-pathological correlate of brain lesions in a necropsy case of HTLV-I associated myelopathy. *J. Neurol. Neurosurg. Psychiatry*, 1993, **56** : 194-196.
- OSAME M., USUKU K., IZUMO S., IJICHI N., AMITANI H. *et al.* HTLV-I associated myelopathy : a new clinical entity. *Lancet*, 1985, **1** : 1031-1032.
- PICARDO P., CERONI M., RODGERS-JOHNSON P., MORA C., ASHER D. M. *et al.* Pathological and immunological observations on tropical spastic paraparesis in patients from Jamaica. *Ann. Neurol.*, 1988, **23** (Suppl.) : S156-S160.
- PUCCIONI-SOHLER M., KITZE B., FELGENHAUER K. HTLV-I associated myelopathy in patients from Brazil and Iran : neurological manifestations and cerebrospinal fluid findings. *Arq. Neuropsiquiatr.*, 1995, **53** : 213-217.
- ROMÁN G. C., OSAME M. Identity of HTLV-I associated tropical spastic paraparesis and HTLV-I associated myelopathy (Letter). *Lancet*, 1988, **1** : 651.
- SPILLANE J. D. Tropical neurology. Oxford Univ. Press., 1973.
- WOLCOTT M. J. Advances in nucleic acid-based detection methods. *Clin. Microbiol. Rev.*, 1992, **5** (4) : 370-386.
- WU E., DICKSON D. W., JACOBSON S., RAINE C. S. Neuroaxonal dystrophy in HTLV-I associated myelopathy / tropical spastic paraparesis : neuropathologic and neuroimmunologic correlations. *Acta Neuropathol.*, 1993, **86** : 224-235.

- YOSHIKI T. Chronic progressive myeloneuropathy in WKA rats induced by HTLV-I infection as an animal model for HAM/TSP in humans. *Inter-virology*, 1995, **38** : 229-237.
- YOSHIKI T. Rat models for HTLV-I infection. *AIDS Res. Hum. Retroviruses*, 2001, **17** (Suppl.) : S14.
- YOSHIOKA A., HIROSE G., VEDA Y., NISHIMURA Y., SAKAI K. Neuropathological studies of the spinal cord in early stage HTLV-I associated myelopathy (HAM). *J. Neurol. Neurosurg. Psychiatry*, 1993, **56** : 1004-1007.
- ZANINOVIC' V. On the etiology of tropical spastic paraparesis and human T-cell lymphotropic virus-I-associated myelopathy. *Intern. J. Infect. Dis.*, 1999, **3** (3) : 168-177.

C. M. DE CASTRO COSTA,
Lab. de Neurologia
Experimental e Neurofisiologia,
Depto. de Fisiologia e Farmacologia,
Universidade Federal do Ceará,
Rua Cel. Nunes de Melo, 1127,
Rodolfo Teófilo, Fortaleza-CE – 60.430-270.
E-mail : pst016@sec.secel.com.br