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

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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. methyl-prednisolone, 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; Piccardo et al., 1988; Iwasaki, 1990; Bhigee 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>
<thead>
<tr>
<th>Author</th>
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<th>Clinical</th>
<th>Neuropathological Results</th>
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<th>Post-Inoculation Time</th>
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<tr>
<td><strong>MINAGAWA et al., 1990</strong></td>
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<td>–</td>
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<tr>
<td></td>
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<td>Slight spinal thoracic atrophy</td>
<td>Provirus in 8/9</td>
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<tr>
<td></td>
<td></td>
<td>3 out 8 seronegative</td>
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<td>16 months</td>
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<td>Macrophage infiltration</td>
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<td>Vacuolation</td>
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<td>Absence of lymphocytic infiltration</td>
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<td>Demyelination of anterior-posterior roots</td>
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<td>–</td>
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<td>Absence of lymphocytic infiltration</td>
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<td>Demyelination of anterior-posterior roots</td>
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<tr>
<td><strong>KUSHIDA et al., 1993</strong></td>
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<td>Myelin degeneration and Macrophage infiltration</td>
<td>Provirus in 1/3 WKA</td>
<td>27 months</td>
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<td>Provirus in 1/3 WKA</td>
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<td>MT2</td>
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<td></td>
<td></td>
<td></td>
<td>No viral particle</td>
<td>27 months</td>
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</tr>
<tr>
<td><strong>KUSHIDA et al., 1994</strong></td>
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<td>White matter degeneration</td>
<td>Provirus in 18/18 in PBMC</td>
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<td>WKA rats (n = 10) MT2 cells</td>
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<tr>
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<td>MT2 cells</td>
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<td>Macrophage infiltration</td>
<td>No viral particle in spinal cord and peripheral nerve</td>
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<td></td>
<td>No lymphocytic infiltration</td>
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<td>Peripheral nerve degeneration and macrophage infiltration</td>
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</table>
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 infiltration of activated microgli/a/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...
et al., 1996). However, a correlation between slight to absent cervical demyelination of corticospinal tracts (Iwasaki, 1990) and the presence of hyper-reflexia 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>
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<tr>
<th>Author</th>
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<th>Demyelination</th>
<th>Inflammatory Infiltration</th>
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<th>Astrocytic Reaction</th>
<th>Viral Particle or Provirus</th>
<th>Evolution</th>
<th>Vacuolation</th>
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<td>?</td>
<td>1 year</td>
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<td>IWASAKI 1990</td>
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<td>–</td>
<td>0-3 years</td>
<td>No</td>
<td>10</td>
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<td>BHIGEE et al., 1991</td>
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<td>Lateral</td>
<td>Lymphocytes Perivascular</td>
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<td>25 years</td>
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<td>DE CASTRO-COSTA et al., 1995</td>
<td>Cervical Thoracic Lumbar Sacral + Brainstem</td>
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<td>Macrophages Lymphocytes (T)</td>
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<td>–</td>
<td>13-40 years</td>
<td>–</td>
<td>2</td>
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<td>CARTIER et al., 1997</td>
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<td>Lateral (L/T)</td>
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<td>3-17 years</td>
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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.

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