Tropical spastic paraparesis

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Human T-cell lymphotropic virus type I (HTLV-I) is the cause of endemic tropical spastic paraparesis (TSP) or HTLV-I-associated myelopathy (HAM). Because TSP/HAM is not a fatal disease, the neuropathology of this disease, albeit relatively well understood, is based on the examination of just a few incidental cases. We summarise our experience with the neuropathology of tropical spastic paraparesis/HTLV-I associated myelopathy (TSP/HAM). We studied three cases of TSP/HAM from different parts of the world. We demonstrated peculiar lamellated structures, called "multilamellar bodies" (MLB). It is tempting to suggest that MLB may represent specific ultrastructural markers of TSP/HAM. The pathology of the anterior and posterior horns was similar and comprised axonal degeneration, accompanied by extensive astrocytic gliosis. Lymphocytic infiltration, particularly observed as "cuffs" around blood vessels, was scattered among other cellular elements. Ultrastructurally, myelin sheaths were relatively well preserved, and some demyelinated but not remyelinated fibres were observed. Moreover, axons with abnormal accumulations of neurofilaments, suggestive of axonal degeneration, were detected. Several axons contained Hirano bodies. In many samples glial processes replaced most of the remaining neuropil.

key words: HTLV-I, neuroinfection, paraparesis

INTRODUCTION

In neurological practice, progressive paraparesis of unknown origin in tropical regions of the world presents a difficult diagnostic challenge. The discovery of HTLV-I during the last decade as a causative agent of this disease has brought understanding to the problem [4, 6, 11, 12].

Spastic paraparesis is a common disease in certain parts of the world, especially the Caribbean basin and south Japan. However, because the disease is not fatal and diagnostic facilities are not readily available in some regions, a cause was not found for many years. A correlation between disease prevalence and the geographical epidemiology of HTLV-I was discovered since patients with tropical spastic paraparesis showed seropositivity for HTLV-I in the majority of cases. Following careful exclusion of other etiological factors such as: multiple sclerosis, lathyrisn, nutritional deficiency and other viral or bacterial infections, the conclusion that this retroviral infection is responsible for tropical cases of spastic paraparesis was inevitable. Thus the term “tropical spastic paraparesis” (TSP) was coined. At the same time, Japanese researchers named paraparesis with a seropositivity for HTLV-I: “HTLV-I associated myelopathy (HAM)”. Further studies showed that it is the same disease and the consensus for TSP/HAM as a term for it
was achieved [8, 20, 22]. Many studies showed the presence of HTLV-I in the blood of TSP/HAM patients, and antibodies against HTLV-I both in blood and cerebrospinal fluid were readily detected. Then, because of the AIDS pandemic, all human retroviral infections became the object of speedy interest and it appeared that HTLV-I, like HIV, has the same predilection to invade the central nervous system (CNS).

Indeed we demonstrated HTLV-I-like particles in the spinal cord [15] but the report has still to be confirmed by others.

Although there is no doubt that HTLV-I infection is a cause of TSP/HAM, the pathology and pathogenesis of this disease are still poorly understood. As the knowledge of this disease is rather limited among Polish readers, we decided to summarise our experiences with the neuropathology and ultrastructure of TSP/HAM. Some data on these cases have already been published elsewhere [13–15].

**Geographical appearance and epidemiology**

TSP/HAM has a geographical distribution ex definitione coincident with that of HTLV-I. Therefore, it is most frequent in countries and regions where the infection is endemic, like: the Caribbean basin, southern Japan, the Seychelles, Columbia, Chile and parts of Papua New Guinea [5, 24]. Like other retroviral infections, HTLV-I is transmitted by blood to blood contact, sexual intercourse, in which the receptive partner is more susceptible than the insertive one, and in families, where the virus is transmitted both vertically and horizontally. Some studies showed a familial clustering of the disease. Females are more commonly infected than males and age-dependent prevalence increases linearly until the age 60–80 years, after which it declines.

Because of a high migration ratio in the world, HTLV-I infection is also found outside the tropics, in temperate regions. In these places, a high prevalence of HTLV-I infection occurs in the first and second generation of emigrants from HTLV-I infection endemic regions.

The epidemiology of HTLV-I has been changing vastly since development in understanding of TSP/HAM was made. In Japan for example the HTLV-I blood test was introduced for blood donors and has significantly reduced the spread of the virus in this country.

**Neurological appearance**

TSP/HAM has an insidious onset and gradual progression in the majority of (~60%) cases. It usually reaches a plateau after several years.

**Neuropathological appearance**

Despite the fact that post mortem examination of the CNS of patients with TSP/HAM is quite rare, the data on neuropathology of TSP/HAM are consistent [1, 10].

The essential feature is chronic meningiomyelitis, predominantly at the thoracic level with involvement of long tracts, meninges, nerve roots, grey and white matter. The evidence of inflammation is robust and it consists of perivascular cuffing with lymphocytes, plasma cells, histiocytes and abundant reactive astrogliosis. Small parenchymal vessel proliferation and fibroblastic thickening also appear. In the posterior columns and pyramidal tracts loss of myelin, cuffs and degeneration are observed. Sometimes changes are so intense that status spongiosus is seen.

**MATERIAL AND METHODS**

We studied three cases of TSP/HAM from different parts of the world [13–15]. The CNS specimens were routinely prepared for evaluation by light microscopy.

For electron microscopy, approximately 1-mm³ specimens, dissected from the anterior and posterior horns of the spinal cord, frontal cortex, dorsal root ganglia and skeletal muscles, were fixed in 2.5% glutaraldehyde prepared in cacodylate buffer, then postfixed in 4% osmium tetroxide for 2 hours, dehydrated through graded ethanol and propylene oxide and embedded in Epon 812. Semithin sections were stained with toluidine blue, and ultrathin sections, stained with lead citrate and uranyl acetate, were examined with a Zeiss EM 109 transmission electron microscope at 80 kV.
RESULTS

Light microscope neuropathology was virtually the same in all cases and consistent with the findings of other researchers. The hallmark of the disease was an inflammatory reaction in the thoracic spinal cord. Inflammation was presented as perivascular cuffing by lymphocytes. Demyelination was present mostly in the lateral columns but no remyelinated fibres were seen. Anterior horns seemed to be unchanged except for robust lipofuscin accumulation. Reactive astrocytes were scattered across all samples. Numerous axons with accumulations of neurofilaments (Fig. 1), suggestive of axonal degeneration, were also detected. Others contained intraaxonal Hirano bodies (Fig. 2). Electron microscopy revealed disrupted cells, spherical and vesicular structures were readily observed. Numerous activated microglia containing electro-lucent empty vacuoles, suggestive of high lipid content, were also seen. In a few specimens of the anterior and posterior horns of the spinal cord, crystalline structures, previously labelled “Hirano-like bodies” or multilamellar bodies, were observed (Fig. 3). These structures consisted of stacks of 30 to 40 electron-dense lamellae, which were interrupted by narrow electron-lucent spaces. All of the lamellae were immersed within an amorphous substance of intermediate electron density.

Neurones of the dorsal root ganglia were basically normal except for increased lipofuscin accumulation. As in the spinal cord, myelinated axons were well preserved, but a few were demyelinated and surrounded by concentric arrays of Schwann cell membranes. Also, axons of the dorsal roots accumulated an increased number of neurofilaments. Mast cells (Fig. 4) and Schwann cells were increased in number, the latter containing abundant \( \pi \) granules.

Skeletal muscles were characterised by myofibrillar degeneration with glycogen accumulation within electron-lucent vacuoles. Furthermore, scanty lymphocytic infiltration was observed.

Figure 1. Large myelinated axon with abundant accumulation of neurofilaments. Original magnification, \( \times 7000 \).

Figure 2. Low (A) and high (B) magnification of intraaxonal Hirano bodies (arrows). Original magnifications; A \( \times 12 \) 000, B \( \times 30 \) 000.

Figure 3. Low (A) and high (B) magnification of multilamellar bodies. Original magnifications; A \( \times 30 \) 000, B \( \times 140 \) 000.

Figure 4. A typical mast cell. Original magnification, \( \times 12 \) 000.
DISCUSSION

Since TSP/HAM was first described, huge progress in understanding its epidemiology and origin has been achieved. A plethora of epidemiological and virological studies substantiated the infectious nature of TSP/HAM. They showed the presence of anti-HTLV-I antibodies both in serum [2, 3, 17, 21] and CSF [3, 17, 18], the detection of HTLV-I antigens in peripheral blood cells [2, 19, 14, 16] and in CSF [12, 14, 16], the integration of proviral DNA in peripheral blood mononuclear cells [19], and the demonstration of HTLV-I RNA within the CNS in cells which phenotypically are characterised as astrocytes [17]. Thus, the causal role of HTLV-I in TSP/HAM is now unequivocal. At the moment, TSP/HAM is a useful designation for this disease.

We must remember, however, that neuropathological studies of TSP/HAM are quite unique, because TSP/HAM is not a fatal disease and it is underdiagnosed. Most of our findings are consistent with other studies. A unique and consistent finding in our studies is the presence of multimembranous bodies (MLB), previously described as “Hirano-like bodies”. Firstly, we suggested that MLB are intracellular structures, but better preservation discovered, on the contrary, that they are rather extracellular. We thus suggested that they could be at least a characteristic structure for TSP/HAM. This hypothesis requires further tests, but to date these structures have not been reported in any other condition.

Unfortunately, the ultrastructural findings presented here do not provide a definitive clarification about the sequence of events in the pathogenesis of TSP/HAM as only specimens from terminal stages of TSP/HAM were available. Having said that, it is not altogether clear if TSP/HAM is a direct or indirect result of HTLV-I infection. To what extent activation of inflammatory cytokines is largely responsible for the CNS degeneration in TSP/HAM is still unsettled. Immune-mediated destruction of the CNS, activated by HTLV-I infection, is a hypothesis that has generated considerable investigative inquiry. Molecular mimicry with myelin serving as an antigenic target, leading to profound demyelination, warrants further study. Recent studies have focused on an autoimmune-molecular theory. In this regard, CD4+ T cells infiltrating lesions in the spinal cord of TSP/HAM patients seem to be the target of inflammatory process [7, 9].

Increased adherence of T lymphocytes from TSP/HAM patients to human endothelial cells [24], as well as simultaneous up-regulation of mRNA expression of inflammatory cytokines, including TNFα, IFNγ and IL-1β, have been frequently found in perivascular mononuclear cells in lesions in spinal cords of patients with TSP/HAM [15]. All these findings suggest that the expression of adhesion molecules on PBMC and endothelial cells and the up-regulation of inflammatory cytokines play crucial roles in the pathogenesis of TSP/HAM [23].

REFERENCES


