On the Etiology of Tropical Spastic Paraparesis and Human T-cell Lymphotropic Virus-I–Associated Myelopathy

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ABSTRACT

The purpose of this review is to present some concepts on the etiology of tropical spastic paraparesis or human T-cell lymphotropic virus-I (HTLV-I)-associated myelopathy (TSP/HAM). The large number of syndromes that have been associated with HTLV-I (60 to date), the existence of TSP/HAM cases associated with other retroviruses (human immunodeficiency virus-2 [HIV-2]; HTLV-II), the existence of many TSPs without HTLV-I, and the evidence of clear epidemiologic contradictions in TSP/HAM indicate that the etiopathogenesis of TSP/HAM is not yet clear. Tropical spastic paraparesis/HAM affects patients of all human ethnic groups, but usually in well localized and relatively isolated geographic regions where HTLV-I has been endemic for a long time. Environmental factors and geographic locations appear to be critical factors. Because the neuropathology of TSP/HAM suggests a toxometabolic, rather than a viral cause, it is proposed that an intoxication similar to neurolathyrism could account for some TSP/HAM cases, mainly in tropical and subtropical countries. If this were the case, HTLV-I could be a cofactor or act as a bystander. It is possible that co-infection with another agent is necessary to produce TSP/HAM and most of the syndromes associated with HTLV-I.

Key words: cofactors, environmental, HIV-1, HTLV-I, HTLV-I–associated myelopathy, HTLV-II, myelopathy, tropical spastic paraparesis


In 1969, the term tropical spastic paraparesis (TSP) was introduced.1 These authors discussed the strong possibility that a slow virus was involved in this perplexing disorder found in India and Jamaica. Most cases used to come from predominantly rural areas, which raised the possibility of a viral reservoir in mammals or fowl. In 1981, the first endemic focus of TSP in continental America in the South Pacific coast of Colombia was reported.2 At that time the relation of human T-cell lymphotropic virus-I (HTLV-I) with this syndrome was unknown. Four years later, the association of TSP with HTLV-I in patients from Martinique was reported.3 The HTLV-I, a retrovirus, had been discovered in 1980 at the National Cancer Institute of America.4 Three months after the pioneering publication from Martinique, a group consisting of North American, Jamaican, and Colombian investigators confirmed the French findings in serum and in cerebrospinal fluid (CSF) of patients with TSP from the south Pacific coast of Colombia and from Jamaica.5 Four months after that publication, Japanese investigators described the association of HTLV-I with spinal spastic paraparesis (SSP), a syndrome with characteristics similar to those of TSP.6 This group, from Kagoshima, a city located on the island of Kyushu (southern Japan), named the syndrome HAM (HTLV-I-associated myelopathy). The author proposed the term RAMs (retroviruses-associated myelo-neuropathies) for both syndromes, TSP and HAM.7 The World Health Organization Health Committee recommended the use of the conciliatory term TSP/HAM.8 Since 1985, many cases of TSP associated with HTLV-I have been reported around the world: Martinique, Jamaica, the south Pacific coast of Colombia, Ecuador, Trinidad and Tobago, Dominican Republic, Seychelles, Brazil, Zaire (DRC), and Florida (southern USA) are, so far, the most endemic tropical and subtropical regions of TSP in the world. Japan, a nontropical country, is, after Brazil, the country with the highest incidence of TSP/HAM. In Japan most TSP/HAM patients live or have lived in the southern islands (Kyushu, Shikoku) and in subtropical Okinawa.9 By definition, all HAM cases (100%) are associated with HTLV-I.

CLINICAL SPECTRUM OF HTLV-I

Human T-cell lymphotropic virus-I has been considered the cause of adult T-cell leukemia-lymphoma (ATLL),10 and also has been associated with polymyositis,11,12 arthritis,13,14 uveitis,15-17 idiopathic thrombocytopenic purpura,18 Sjögren syndrome,19 infective dermatitis,20,21 chronic prostatitis and interstitial cystitis,22 lymphocytic alveolitis,23,24 hypereosinophilic syndromes,25 pseudo-amyotrophic lateral sclerosis,26,27 lymphocytic meningitis,28 Hashimoto thyroiditis,29 xerosis and erythema,30

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increased malignancy of cervix and vaginal cancer, inflammatory peripheral neuropathies, demyelinating neuropathies, atypical lumbosacral plexopathies, and Guillain-Barre\textsuperscript{55} facial nerve palsy, persistent lymphadenopathy, retinal vasculitis, pigmentary retinal degeneration, chronic polyradiculoneuropathies, necrotizing vasculitis of the skin, crusted (Norwegian) scabies, olivopontocerebellar atrophy, a variant of multiple-sclerosis,\textsuperscript{37} malignant fibrous histiocytoma,\textsuperscript{43} multiple sclerosis, Behcet disease,\textsuperscript{45} multiple system atrophy,\textsuperscript{46} pseudohypoparathyroidism,\textsuperscript{47} monoclonal gammopathy and chronic renal failure,\textsuperscript{48} strongyloidiasis,\textsuperscript{49} dermatopolymyositis,\textsuperscript{50} chronic dacryosialadenitis,\textsuperscript{51} hyperthyroidism, hypothyroidism, M proteinemia multiple myeloma and mild subcortical dementia,\textsuperscript{9} cranial polineuritis, bulbar palsy, and basal ganglia syndromes,\textsuperscript{48} primary biliary cirrhosis,\textsuperscript{52} familial or hereditary spastic paraparesis,\textsuperscript{53,54} rhombencephalitis,\textsuperscript{55,56} dementia,\textsuperscript{57} neuropsychological disorders,\textsuperscript{58} primary sclerosing cholangitis,\textsuperscript{59} folliculitis decalvans,\textsuperscript{60} cranial pachy-neuromeningitis,\textsuperscript{61} myasthenia gravis,\textsuperscript{62} progressive flaccid myelopathy,\textsuperscript{63} cerebellar syndrome,\textsuperscript{64} systemic lupus erythematosus, and most recently, in Canada, with peripheral neuropathy associated with cerebral white matter lesions in the absence of spastic paraparesis.\textsuperscript{65} Fortunately, schizophrenia was not conclusively associated with HTLV-I.\textsuperscript{67} These numerous and heterogeneous associations cast some doubt on the causal association of HTLV-I with all these syndromes and diseases.

OTHER RETROVIRUSES ASSOCIATED WITH TSP/HAM

In 1987, a 32-year-old man from Ivory Coast with TSP was found to have both, HTLV-I and HTLV-IV (HIV-2). This was the first reported case of tropical spastic paraparesis associated with dual exposure to retroviruses. The authors emphasized that retroviral polyinfections also could result in an increase of neurologic complications in Africa and that concomitant infections with two types of retrovirus may lead to new forms of neoplastic transformation. In 1988, a second patient, a 31-year-old man (also from Ivory Coast), was found to have TSP associated with HIV-2 only.\textsuperscript{69}

In 1991, in Fukuoka, Japan, located on HTLV-I-endemic Kyushu island, 12 of 18 (67%) TSP/HAM patients were co-infected with HTLV-I and HTLV-II.\textsuperscript{70} This report has been controverted by other Japanese investigators. One year later, two HTLV-II seropositive Amerindian sisters from New Mexico with a TSP/HAM-like syndrome (olivopontocerebellar atrophy), a variant of multiple-system atrophy, were reported.\textsuperscript{71}

In 1993, HTLV-II was isolated in the absence of any other detectable human retrovirus in a 52-year-old black man with TSP/HAM from Baltimore.\textsuperscript{75} In the same year, a 54-year-old black Bahamian woman with spastic ataxia, a similar illness to TSP/HAM was found to have HTLV-II, serologically, by polymerase chain reaction (PCR) and by viral culture.\textsuperscript{73} In 1995, several patients with ataxic myelopathies (another TSP/HAM-like syndrome) associated with HTLV-II from Porto Alegre (southeast Brazil) were described.\textsuperscript{74} These publications implicated different retroviruses in the pathogenesis of TSP/HAM and similar myelopathies.

TSP/HAM AFTER TRANSFUSION

The rapid development of myelopathy after blood transfusions to a cardiac transplant patient in France, apparently demonstrated the causal relation among HTLV-I and TSP/HAM.\textsuperscript{75} It must be considered that this patient received blood components from 59 donors and that only HIV-1, herpes simplex virus types 1 and 2, cytomegalovirus, Epstein-Barr virus, and hepatitis B virus were investigated. The HTLV-I-seropositive donor was a healthy woman from the French West Indies in the Caribbean, a well-known HTLV-I-endemic area. At that time it was believed that such a case represented indisputable proof that HTLV-I was the only cause of TSP/HAM, because HTLV-I was found in the blood used for the cardiac transplant and because the patient was HTLV-I seronegative before the heart transplant. Unfortunately, no molecular biology or immunology were performed in this case.\textsuperscript{76} It needs to be remembered that blood transfusions can transmit not only germs but also toxins and antibodies.

HTLV-I–SEROPOSITIVE TSP/HAM VERSUS HTLV-I–SERONEGATIVE TSP

The major international publications from 1985 to 1996 on epidemiology of TSP were reviewed. Spectral emphasis was given to the ratio of HTLV-I-seropositive and seronegative TSPs.\textsuperscript{77} The HTLV-I-associated myelopathy found in Japanese patients could not be compared to most of the world's cases of TSPs because HAM, by definition, includes only cases of neurologic syndromes and diseases with seropositivity to HTLV-I.

Countries with more than a 50% association of TSP with HTLV-I are: Martinique (59%, 78%), Jamaica (67%, 83%), Colombia (73%, 87%), Trinidad and Tobago (100%), Seychelles (85%), Dominican Republic (85%), northeastern Brazil (71%), Ecuador (100%), Zaire (96%), and Panama (56%). Foreign blacks (Caribbean's) living in New York also showed a high percentage (77%) of HTLV-I-seropositive TSPs. In the countries and regions with the larger proportion of seropositive TSPs, most patients lived in or came from rural areas of tropical countries, which suggests that environmental factors may be involved in the etiology of this syndrome.

The percentage of HTLV-I seronegative TSPs was surprisingly high (more than 50%) among other tropical and
nontropical countries or regions: Chile (56%), northeastern Brazil (63%), eastern Brazil (64%), West Africa (74%), North American blacks living in New York (75%), Ivory Coast (85%, 89%), Solomon Islands (83%), Thailand (100%), Indian Ocean islands (100%), Ethiopia (91%), Cuba (100%), Venezuela (56%), India (92%), and Egypt (86%). In Mexico, from 96 patients with spastic paraparesis of unknown cause, 96 (100%) were found to be HTLV-I seronegative (Sotelo J. Personal communication). Until the end of 1996, of the 2811 cases of TSP/HAM reported throughout the world, only 1261 (45%) were associated with HTLV-I.9

It is well known that some seronegative TSP/HAMs are HTLV-I seropositive by PCR. From 10 HTLV-I-seronegative TSP/HAM cases from Chile, the tax gene was amplified from PBMN of five patients but Ztr was not detected in any patient.79 Twelve seronegative TSPs tested by PCR in northeastern Brazil,80 were persistently negative. In 13 of 25 HTLV-I-seronegative TSPs, 4 patients (31%) were PCR positive. In cases from Colombia, most HTLV-I-seropositive TSPs were black women from the Pacific coast, but most HTLV-I-seronegative TSPs were male mestizoes from the Andes region.

The epidemiology of HTLV-I and TSP/HAM has been inconsistent, and the fact that HTLV-II has accounted for some HTLV-I-false-seropositive results in the past complicates the critical analysis of many of the initial epidemiologic reports on TSP/HAM.

CONTRADICTORY EPIDEMIOLOGY OF TSP/HAM

Japan

The Ainu population from Hokkaido have one of the highest HTLV-I-seroprevalence rates in the world (45%).81,82 However, there are no confirmed published cases of HAM among the Ainu.83

In the Ryukyuans from Okinawa, HTLV-I seroprevalence is higher (32.6%) than in Ryukyuans from south Kagoshima (11.7%). The prevalence of HAM is higher in Ryukyuans from south Kagoshima than in Ryukyuans from Okinawa.84

Whereas in Tsushima Island (northwest of Kyushu) with 22.7% HTLV-I seroprevalence HAM cases are rare,85 in south Kyushu, with a lower seroprevalence (11.7%), HAM cases frequently occur.85

Curiously, in Fukuoka, a city located a few hundred miles north of Kagoshima city, in the same HTLV-I-endemic Kyushu island, with a similar HTLV-I seroprevalence and with equal genetic background, only 50% of SSP patients were HTLV-I seropositive.86

Brazil

Japanese immigrants (Okinawans, Ryukyuans), living in Campo Grande (Matto Grosso do Sul) had 13% HTLV-I seroprevalence in 1986.84 Eleven years later there are no published cases of TSP/HAM among these "supposed genetically susceptible" Japanese descendants.

EPIDEMIOLOGIC DATA SUGGESTING ENVIRONMENTAL COFACTORS IN TSP/HAM

Caribbean

The incidence in Martinique of TSP associated with HTLV-I ranges from 12 per 100,000 on the drier side of the island to 50 per 100,000 on the wetter side.25

In TSP cases from Trinidad there appeared to be a relation to the proximity of watercourses, poor housing, and absence of a piped water supply.26

United States of America

Most TSP cases in Florida and in New York (77%) are among immigrants of African descent from Haiti, Dominican Republic, and Jamaica, working on small farms or as domestic servants.77,78
From 25 TSP/HAM cases found in the United States, 92% (23/25) had become symptomatic while living in the United States.99

NEUROPATHOLOGY OF TSP/HAM

Iwasaki from Sendai published an excellent book that included most autopsy cases of HAM in Japan.100 In 1989, Liberski et al, from the United States, reviewed the neuropathology of TSP in one woman from Jamaica and in one Caucasian man.101 This publication included the electron microscopy findings of these two cases. In the same year, Cartier, from Chile, compared the histopathology of three Chilean cases.102 In 1997, the same author published the clinical and neuropathologic findings of six patients with spastic paraparesis associated with HTLV-I.103 In 1989, another book discussed most known autopsy cases of HAM, including the cases published by Iwasaki in 1988.104

Here, the main neuropathologic findings of Iwasaki, Liberski, and Cartier and colleagues are summarized.100-103 According to Iwasaki, the cardinal neuropathologic findings of HAM/TSP are histopathologic observations of the spinal cord, the distribution of white matter degeneration in the spinal cord, and lesions outside the spinal cord.

Histopathologic Observations of the Spinal Cord

The main feature of the neuropathologic changes in HAM/TSP was a chronic progressive inflammatory process preferentially involving the white and gray matter of the spinal cord.

Inflammatory Reactions

The chronic inflammatory process of the white and gray matter of the spinal cord mainly affected the lateral funiculus. There were various degrees of glialmesenchymal tissue reactions. The inflammatory cell collection around small parenchymal vessels was almost always accompanied by a cellular exudation into the adjacent parenchymal tissues. Perivascular cuffs had formed mostly around small veins or venules, and the walls of these small vessels often were obscured by the overlying cellular exudates. However, perivascular cuffing of small arteries was not rare. Although cellular exudation occurred randomly in both the gray and white matter, it was more frequently seen in the deeper portion of the cord than in the surface areas.

The lateral column was most extensively, and usually symmetrically involved in the inflammation, whereas the anterior column was affected irregularly and less severely. Inflammatory cell infiltration in the posterior column usually was mild, and was confined mostly to the ventromedial portion. Although the inflammatory process could be seen throughout the entire length of the spinal cord, the extent and severity of the inflammation were most severe in the lower thoracic cord, and it tended to taper off gradually in both upward and downward directions. The paucity of inflammatory cells in the subarachnoidal space could be consistent with the clinical finding of mild or no pleocytosis in the CSF.

The severity of inflammation in each lesion also appeared to depend on the duration of the disease process. Lymphocytic and monocytic cell infiltration was usually more intense in areas with better preservation of normal tissue architecture than in areas with pronounced glial and mesenchymal reactions, and in such areas a relatively small number of lymphocytes was intermingled with a mass of foamy cells. Lymphocytes were confined mostly to the perivascular spaces and were often intermingled with macrophages.

Parenchymal Tissue Damage

The inflammation involved both the white and gray matter, but the white matter was preferentially degenerated at the sites of inflammation. In long-standing lesions, both the myelin and the axon were equally degenerated and lost, and the tissue was largely replaced by glial scars seeded with numerous foamy cells, microglial cells, and a small number of lymphocytes.

In inflammatory lesions, neurons were relatively well preserved and the number of large neurons did not seem to be reduced, although increased lipopigment content and various degrees of shrinkage of cell bodies commonly were seen in both the anterior and posterior horns. The neurons in the intermediolateral and Onuf's nuclei also were in various states of degeneration, but the severity of neuronal degeneration in these nuclei did not exceed that in the anterior and posterior horns.

Alteration of vascular walls also was conspicuous. Fibrous thickening of adventitia was most consistent, and a hyalinized change in small vessels often was common. Such changes in the vessel walls were not confined to the white matter; small vessels in the gray matter were equally affected, often accompanied by marked gliosis in the surrounding tissues. The endothelium, however, showed no appreciable changes, and no obstructive change was found in the parenchymal vessels. Frank tissue necrosis or cavity formation was found in none of these cases.

Distribution of White Matter Degeneration in the Spinal Cord

The lower thoracic cord, Th7-12, was most severely and possibly initially involved in the disease process. Old lesions always were found in the lower thoracic cord, and the lesions in the upper thoracic and cervical segments always appeared to be relatively new.

In myelin stain preparations, symmetrical pallor of the lateral funiculi, particularly of the lateral pyramidal
tract was found. The entire length of the lateral pyramidal tract was involved, but it was most severely degenerated in the lower thoracic and upper lumbar segments.

Involvement of the posterior funiculi was suspected in all cases. The severity and extent of myelin pallor in the posterior funiculus usually were mild and more variable than in the pyramidal tract.

**Lesions Outside the Spinal Cord**

Perivascular mononuclear cell infiltration in the brain was not uncommon, but usually it was not accompanied by any appreciable parenchymal tissue damage. Similar mild perivascular cell infiltration was seen in the medulla oblongata in the cerebellum and the thalamus. Although the spinal nerve roots and peripheral nerves appeared to be spared in most cases, marked loss of the myelinated fibers was reported in the sural nerve, the sciatic nerve, and the cauda equina.

Iwasaki concluded stating

HAM/TSP is a rare CNS manifestation of an autoimmune process associated with the persistent HTLV-I infection of T-lymphocytes rather than a direct consequence of virus infection into CNS tissue. Because of the unusual chronicity of the disease process, the classical histopathological features of acute parainfectious encephalomyelitis are obviously modified, but perivenous inflammatory degeneration of the white matter, a characteristic of parainfectious diseases, is still retained in HAM/TSP. 'Chronic progressive parainfectious myelopathy', therefore appears to be the most appropriate term to describe this unusual situation.

In the publication of Liberski and colleagues, the ultrastructural electron microscopy findings of TSP autopsies were similar to those observed in human motor neuron diseases, especially amyotrophic lateral sclerosis and Werdnig-Hoffmann disease. These authors remarked on the accumulation of lipofuscin, the dystrophic neurites, the spheroids, and the chromatolitic neurons that are present in both diseases. It was interesting to note the phenomenon of glial bundles found in one of their cases.

In the publication by Cartier et al, the macroscopic examination showed marked atrophy of the thoracic spin in two cases, mild atrophy in two cases, and no atrophy in the other two. The histology showed glial thickening with lymphocytic infiltrates. Demyelination of the lateral funiculus with frequent vacuolization of the myelin and degeneration of the corticospinal tracts was evident.

The lower motor neurons depicted some degree of chromatolysis and pyknosis especially in the thoracic and lumbar regions. There was some loss of the smaller neurons (interneurons) and fibrillar gliosis.

In most cases, the thalamus seemed to show a slight reduction of neurons, and some of them were overloaded with lipofuscin. In the thalamic area and internal capsule there were vessels with lymphocytic cuffing. The basal ganglia and hypothalamus showed no structural changes. In two cases, some neurofibrillary changes were seen in the motor cortex.

The sacral and lumbar dorsal ganglia showed proliferation of satellite cells of the neurons in four cases and slight lymphocytic infiltration in two cases. The neurons appeared to be preserved, but some of them showed chromatolysis, pyknosis, or a pale cytoplasm. The histologic study of the median, sural, and sciatic nerves and nerve roots and muscles showed no abnormalities.

Following is most of the 'Discussion' from this excellent publication.

This clinicopathological study shows that TSP/HAM has a clearly defined pathological pattern. The clinical differences in these 6 TSP/HAM patients are related to the extension and severity of this pattern. The cases showed a close clinicopathological correlation. All of them had lesions in the axons and myelin of the pyramidal tract of the spinal cord, which followed an ascendant pattern similar to some degenerative diseases, as in familiar spastic paraparesis, with marked abnormalities in the lumbar and thoracic segments of the spinal cord that became less severe as the tract reached the cervical segments. Four cases had lesions in the Goll's tract distributed in a descendant pattern, with maximal involvement in the cervical region and becoming negligible towards the caudal regions.

The spinal cord lesions of patients with TSP/HAM, ascendant in the pyramidal tract and descendant in the posterior columns, have been interpreted elsewhere as demyelinating, either as a primary cytotoxic disorder or secondary to inflammatory or immunological disorders. However, primary demyelinating diseases, either viral or inflammatory in origin, damage myelin in several areas, usually confluently and in a transverse fashion. Disorders that damage the myelin affect different systems simultaneously, such as in multiple sclerosis or multifocal leukoencephalopathy. Central nervous system demyelinating diseases involve groups of oligodendrocytes, and each oligodendrocyte myelates several axons independent of their functions. However, in TSP/HAM lesions, the myelin follows the axons in a dying-back fashion (axial) that especially affects the longest axons. The lesions in the posterior columns also support the idea of an axonmyelinic degeneration. The lesions of Goll's tract in the cervical spinal cord are selective, affecting the longest axon from the legs.

It seems unlikely that these parenchymal changes are secondary to vascular changes. Abnormal vessels with gross thickening of the adventitia were seen in
all patients, many of them with lymphocytic cuffs, especially in the spinal cord, brain stem, midbrain, thalamus, and meninges, but were unrelated to the location or severity of the parenchymal damage. Furthermore, vascular changes are restricted to a proliferation on the adventitia, and we did not find vasculitic changes such as necrosis of the vascular wall, endothelial proliferation, or ischemic lesions in the surrounding tissue in any of our cases.

This study contributes to the idea that cerebral involvement is part of the TSP/HAM picture. In two cases that presented with intellectual impairment, demyelination of the subcortical and parahippocampal areas without U fiber involvement was observed.

All cases showed histological sialoadenitis. These findings seem to be part of the same disease and do not seem to be secondary to an immunological phenomenon.

DISCUSSION

It is well known that HTLV-I infection is an old phenomenon in most TSP/HAM endemic regions and that the high prevalence of TSP in such geographically similar foci as Tumaco, Colombia,105 Mâhe in the Seychelles,106 Lisala and Inongo,87,107 in Zaire (DRC), suggests the presence of environmental factors. These regions are located near the equator. The initial TSP outbreak described in Jamaica was epidemic, and most patients were sugar cane workers.108

Experimental TSP/HAM in Rats

An argument that appears to favor the causal relation between HTLV-I and TSP/HAM is the development of TSP/HAM-like syndromes in rats after inoculation with HTLV-I.109-113 After a peer review of this impressive experimental work, some crucial observations cast doubt on these conclusions:

1. The anatomopathologic findings of the TSP/HAM-like syndrome in WKA rats are quite different from those of human TSP/HAM and are unlikely to cause spasticity in the animals.
2. The pathologic findings of those HTLV-I-infected rats correspond more to the ones found in the polio encephalomyelopathy (PEM) of wild mice of lake Casitas (southern California) caused by an exogenous MuLV,114 and it is accepted that mice, rats, and humans carry endogenous retroviral sequences.
3. Only 37 to 63% of the WKA rats and none of the F344 rats developed signs of human TSP/HAM.110,111
4. One Wistar rat whose mother received blood from a PCR HTLV-I-seronegative TSP patient developed paraparesis, and this rat also was HTLV-I seronegative.115

Recently in Japan, some cases of slowly progressive spastic paraparesis associated with hepatitis B virus (HBV) without HTLV-I were seen. This new and interesting syndrome was named hepatitis B virus-associated myelopathy (HBVAM).115

Neurolathyrism

Neurolathyrism is a neurologic disorder caused by excessive ingestion of Lathyrus, or chick pea species. Lathyrism has been known since ancient times; epidemics have occurred in some regions, including Russia, southern Europe, the Mideast, and India, particularly during times of famine, when chick pea consumption increased. Lathyrus sativus, L. cicera, and Vicia sativa are the species implicated. Horses, cattle, swine, and birds have been affected.

Clinically, lathyrism often presents relatively rapidly after a prolonged period (months) of ingesting large amounts of the chick peas, often in the context of general malnutrition. Disease often commences with complaints of pain or cramps in the legs or in the region of the lumbar spine. Lower extremity weakness and spastic dysfunction then develop, soon evolving into permanent spastic paraparesis. The cramping pains and the sphincter dysfunction usually subside when the intoxication ceases and spasticity develops.116

There are a few pathologic studies of lathyrism, but a report by Hirano et al confirms earlier descriptions of bilateral atrophy in the distal pyramidal tract in the lumbar cord.117 Additionally, there have been morphologic descriptions of degenerative changes in the spinocerebellar tracts and dorsal columns. In concert, these data suggest a central nervous system (CNS) disease expressed most pronouncedly in the distribution of the longest CNS fibers.

Konzo or Buka-Buka is an acute or chronic form of spastic paraparesis more common in tropical countries than in temperate climates. Deficiencies or toxicities due to primitive diets as well as infectious agents have been implicated.118 Konzo is similar to lathyrism but differs from TSP/HAM and from lathyrism in its abrupt onset, nonprogressive course. Normal magnetic resonance imaging scans of brain and spinal cord in severely affected patients provide evidence of selective damage of the upper motor neurons. All Konzo patients were seronegative to retroviruses.119

The possibility that the pathogenesis of TSP/HAM is secondary to an autoimmune process produced via molecular mimicry recently has been postulated by F Garcia, a biologist at Valle University in Cali, Colombia, working with Max Essex of Harvard School of Public Health, Boston. Currently, this theory appears to be one of the best possible explanations for TSP/HAM and most HTLV-I-associated syndromes.120,121 This theory also could explain some of the "contradictory" epidemiology of
TSP/HAM, and further, it would indicate the prevention and possible treatments of TSP/HAM.

CONCLUSIONS
1. The etiopathogeneses of TSP/HAM are not yet clear.
2. The etiology of HTLV-I-seronegative TSP is unknown.
3. The neuropathology of TSP/HAM does not correspond to that seen in other viral diseases.
4. The epidemiology of TSP/HAM suggests critical environmental unknown cofactors, and some cases could be neuroathlyrism or Konzo.
5. Some TSP/HAM cases may be due to unknown "lathyrergic" toxometabolic processes secondary to immunologic reactions. HTLV I/II could cause bystander damage, or act as cofactors.
6. The name HAM should be changed because in TSP/HAM there are anatomopathologic changes in the brain, cerebellum, and brain stem.
7. The disease is present outside the tropics.

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