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Possible etiologies for tropical spastic paraparesis and human T lymphotropic virus I-associated myelopathy

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Abstract

The epidemiology of tropical spastic paraparesis/human T lymphotropic virus I (HTLV-I)-associated myelopathy (TSP/HAM) is frequently inconsistent and suggests environmental factors in the etiology of these syndromes. The neuropathology corresponds to a toxometabolic or autoimmune process and possibly not to a viral disease. Some logical hypotheses about the etiology and physiopathology of TSP and HAM are proposed. Glutamate-mediated excitotoxicity, central distal axonopathies, cassava, lathyrism and cycad toxicity may explain most cases of TSP. The damage caused to astrocytes and to the blood-brain barrier by HTLV-I plus xenobiotics may explain most cases of HAM. Analysis of the HTLV-I/xenobiotic ratio clarifies most of the paradoxical epidemiology of TSP and HAM. Modern neurotoxicology, neuroimmunology and molecular biology may explain the neuropathology of TSP and HAM. It is quite possible that there are other xenobiotics implicated in the etiology of some TSP/HAMs. The prevention of these syndromes appears to be possible today.

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- Cassava

Human T lymphotropic virus I (HTLV-I), the first human retrovirus, was discovered in the USA in 1980 by Poiesz et al. (1), who detected it in a patient with cutaneous T-cell lymphoma. So far, 61 different syndromes and diseases have been associated with this retrovirus (2). Tropical spastic paraparesis (TSP) and HTLV-I-associated myelopathy (HAM) have also been associated with the dual infection of HTLV-I and HIV-2 (3), with HIV-2 only (4), and with the combination of HTLV-I and HTLV-II (5). In 1993, HTLV-II was isolated in the absence of any other detectable human retroviruses from a 52-year-old black man with TSP/HAM from Baltimore (6). In the same year a 54-year-old black Bahamian woman with spastic ataxia (a syndrome similar to TSP/HAM) was found to have only HTLV-II as determined serologically, by the polymerase chain reaction (PCR) and by viral culture (7). In 1995, several patients with ataxic myelopathy (another TSP/HAM-like syndrome) associated only with HTLV-II were confirmed in Southeastern Brazil (8). These recent publications implicated different retroviruses in the pathogenesis of TSP/HAM.

Preliminary hypotheses about the causes of TSP and HAM

Spastic myelopathies without HTLV-I or

any other retroviruses are well-known clinical syndromes associated with toxic environmental factors (see below). The epidemiology of TSP/HAM is inconsistent and sometimes paradoxical.

The first stage of HAM begins at birth with perinatal HTLV-I infection, or during adult life by sexual or transfusion transmission, but HAM apparently develops when there is damage to astrocytes and as a consequence of the noxious actions of xenobiotics. The neuropathology of TSP and HAM indicates the occurrence of a toxic or autoimmune process.

There are well-known types of retroviral seronegative spastic paraparesis, mainly tropical, with specific and proven causes: subacute myelo-optic neuropathy (SMON), lathyrism and Konzo. Glutamate and aspartate excitotoxicity mediated by ionotrophic D,L-ß-amino-3-hydroxy-5-methylisoxasole-4-propionic acid (AMPA) receptors may explain the physiopathology of some TSPs without the presence of retroviruses. The central distal axonopathy caused by clioquinol and similar iodine compounds also explains some HTLV-I-seronegative TSPs like SMON.

The damage caused by HTLV-I and other retroviruses to astrocytes may produce HAM and other syndromes by disturbing the blood-brain barrier and the oligodendroglia.

Review of the epidemiology, neuropathology and toxicology of TSP and HAM

The epidemiology of TSP/HAM is inconsistent and paradoxical. In Japan, Ainus from Hokkaido (9,10) have one of the highest rates of HTLV-I seroprevalence in the world (45%), but there are no confirmed published cases of HAM among members of the Ainu people (11). HTLV-I seroprevalence in Ryukyus from Okinawa is higher (32.6%) than in Ryukyus from South Kagoshima (11.7%). The relative number of HAM cases is higher in Ryukyus from South Kagoshima than in Ryukyus from Okinawa (11).

While on Tsuchima Island (Northwest Kyushu, Sea of Japan) with 22.7% HTLV-I seroprevalence HAM cases are very rare (12), in South Kyushu (Pacific Ocean) with a lower seroprevalence (11.7%), HAM cases are very frequent (13). Curiously, in Fukuoka, a city located a few hundred miles North of Kagoshima on the same HTLV-I endemic Kyushu Island, with a similar HTLV-I seroprevalence and with an equal genetic background, only 50% of spastic spinal paraparesis patients were found to be HTLV-I seropositive (14). The cited report demonstrated that HTLV-I-seronegative spastic spinal paraparesis, a TSP-like syndrome, does exist in Kyushu, South Japan.

In Inongo (Zaire, Democratic Republic of Congo), no TSP cases were found in the ethnic group Bolia with an HTLV-I seroprevalence of 6.5%, while in the racial group Ntomba, with a seroprevalence of 2.2%, 6 TSP cases were found (15).

In sub-Saharan Africa, a well-known reservoir of HTLV-I, with at least 5 million infected people (16), most cases of TSP are not associated with HTLV-I infection (17).

In Tumaco (South Pacific coast of Colombia), among blacks of African origin with a 3.0 to 3.5% HTLV-I seroprevalence there is one of the highest prevalence rates of TSP in the world (98 x 100,000) (18), while on the North Pacific coast, Waunama-Embera, Chamie and Cuna Indians with HTLV-I seroprevalences of 1, 2 and 15%, respectively, have not developed TSP (19).

The West Pacific Islands show very high prevalence rates of HTLV-I in isolated populations: Banks and Torres Islands, 21 to 48%; New Guinea, 26 to 50% (the world highest reported rate); Solomon Islands, 9 to 21% (20). Most (83%) cases of idiopathic spastic paraparesis were not associated with HTLV-I on these islands. Curiously, these HTLV-I carriers had not had any previous contact with Japanese or African individuals (21).

Japanese immigrants (Okinawans-Ryukyuans) living in Campo Grande, Mato Grosso do Sul, Brazil, had a 13% HTLV-I seroprevalence in 1986 (22). So far, there are no published cases of TSP/HAM among these "supposedly genetically susceptible" Japanese descendants living in Campo Grande and showing such a high HTLV-I seroprevalence.

The most disturbing data against the causal relationship between HTLV-I and TSP/HAM are shown in Table 1.

Neuropathology of TSP/HAM

Iwasaki from Japan (23), Liberski from the USA (24), and Cartier from Chile (25,26) published the best neuropathological papers about TSP/HAM findings between 1989 and 1997. The most important findings were: 1) retrograde (dying back) axomyelinic degeneration of the corticospinal tracts and, to a lesser extent, of the posterior columns; 2) perivascular cuffing of the small vessels of the spinal cord, brain stem, thalamus and brain, without "vasculitis" or obstruction of the vessels; 3) chronic inflammatory reaction of the spinal cord; 4) variable changes in the small interneurons and in some neurons of the anterior horns.

Unfortunately, of the 6 autopsies described by Cartier et al. (26) only 2 corresponded to typical TSP, whereas the other 4 corresponded to different syndromes and diseases associated with HTLV-I.

The neuropathology of TSP/HAM apparently does not correspond to any viral disease of the central nervous system (CNS).

Epidemiological comparison of TSP with and without HTLV-I

The main worldwide publications from 1985 to 1996 on the epidemiology of TSP have been reviewed (27). Special emphasis was placed on the ratio and percentage between HTLV-I-seropositive and -seronegative TSPs. Japanese HAM could not be compared because HAM, by definition, includes only cases of neurological syndromes and diseases with seropositivity for HTLV-I.

Countries with more than 50% association of TSP with HTLV-I were: Martinique (reports of 59 and 78%), Jamaica (67%, 83%) Colombia (73%, 87%), Trinidad-Tobago (100%), Seychelles Islands (85%), Dominican Republic (85%), Northeastern Brazil (71%), Ecuador (100%), Zaire (96%), and Panama (56%). Blacks from the Caribbean living in New York also showed a high percentage (77%) of HTLV-I-seropositive TSPs.

The proportion of HTLV-I-seronegative TSPs was surprisingly high (more than 50%) among other tropical and non-tropical countries or regions like 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, 96 patients with spastic spinal paraparesis of unknown etiology were all (100%) found to be HTLV-I seronegative (personal written communication from Dr. J. Sotelo, Instituto Nacional de Neurología, Mexico City, 1994). Until the end of 1996, of 2,811 cases of TSP/HAM reported throughout the world, only 1,261 (45%) were associated with HTLV-I, whereas 1,550 (55%) were not (28). In

Table 1. Paradoxical epidemiology of tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM).

Region	HTLV-I seroprevalence (%)	Prevalence (number of cases x 100,000)	Attack rate
Okinawa	18-33	2.8	1:8000 (very low)
Kagoshima	12	8.6	1:1464
Jamaica	5	12.0	1:400
Martinique	1-2	22.0	1:90-250
Tumaco (Col)	3	98.0	1:300 (very high)

HTLV-I = human T lymphotropic virus I.

Fukuoka (Kyushu island, South Japan) only 50% (13/26) of the cases of idiopathic spastic spinal paraparesis, a TSP-like syndrome named HAM, were associated with HTLV-I (14).

It is well known that some seronegative cases of TSP/HAM are HTLV-I seropositive by PCR. The tax gene was amplified from peripheral blood mononuclear cells of 5 of 10 HTLV-I-seronegative TSP/HAM patients from Chile but long terminal repeat (LTR) was not detected in any of them (29). Twelve seronegative TSP patients who underwent PCR in Northeastern Brazil (30) persisted negative. PCR performed in 13 of our 25 HTLV-I-seronegative TSP patients revealed that 4 (31%) were PCR positive. In our cases from Colombia, most HTLV-I-seropositive cases of TSP were black women from the Pacific coast but most HTLV-I-seronegative cases of TSP were male Mulattos from the Andes region.

Toxic and toxoviral etiologies for TSP and HAM

TSP is a well-defined clinical pyramidal syndrome with a neuropathology that reflects an ascending axomyelinic degeneration of the corticospinal tracts and a descending axomyelinic degeneration of the posterior columns. In TSP there is no evidence of direct retroviral lesions in CNS neurons.

There are 3 TSP-like syndromes associated with toxins and toxic agents and not associated with HTLV-I or any other retroviruses: 1) SMON associated with oral and topic clioquinol (31), reported to occur in tropical and subtropical regions including Southern Japan (see below); 2) lathyrism (32), an acute and epidemic spastic paraparesis possibly caused by the excitatory amino acid ß-N-oxalylamino-L-alanine (ßOAA) or its metabolites, associated with massive consumption of the grass pea *Lathyrus sativus* and mainly occurring in Ethiopia, India and Bangladesh; 3) konzo, associated with bitter cassava cyanide consumption (33).

Industrially the largest use of cassava starch is in the production of monosodium glutamate lysine, high fructose syrup, liquid glucose, dextrose monohydrate, anhydrous dextrose, sorbitol, etc. Cassava derivatives are good candidates for producing not only HTLV-I-seronegative TSP but also HAM, especially in Brazil, most of South America, the Caribbean and Southern USA.

ß-N-methylamine-L-alanine (ßMAA) has been isolated from the seeds of some Cycadaceae such as the false sago palm (*Cycas circinalis*, L) (34) and from the seeds of *Cycas revoluta*. These seeds are widely consumed as food and or medicine, e.g., oral tonics and poultices, by the Western Pacific population of Southern Japan, the Chamorros of Guam, the inhabitants of the Kii peninsula of Southern Japan, and the Auyu people of Iran Jaya (New Guinea), Australia and western Pacific Islands. The seeds and stems of another Cycadaceae species, *Zamia roezlii* (Figure 1) called "pepa de chigua", are also consumed by the natives of the Pacific coast of Colombia as a staple of the local diet.

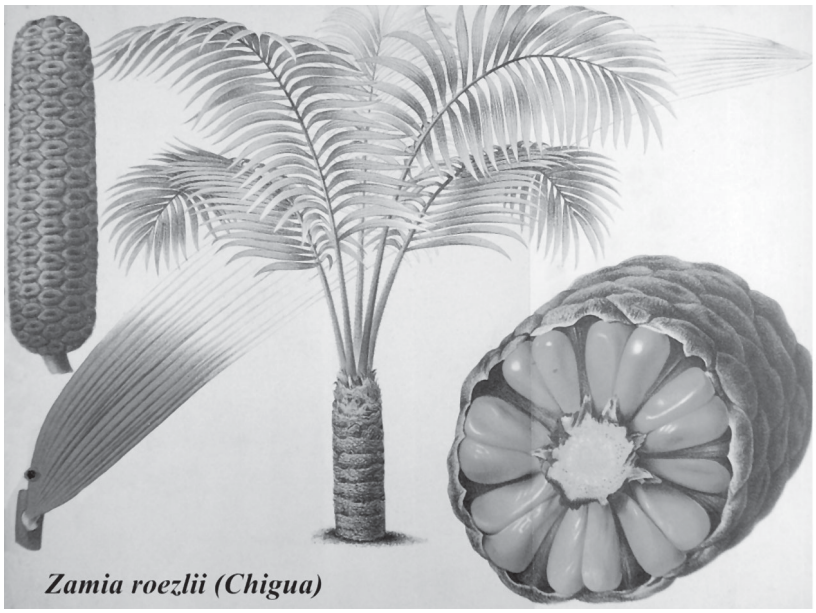
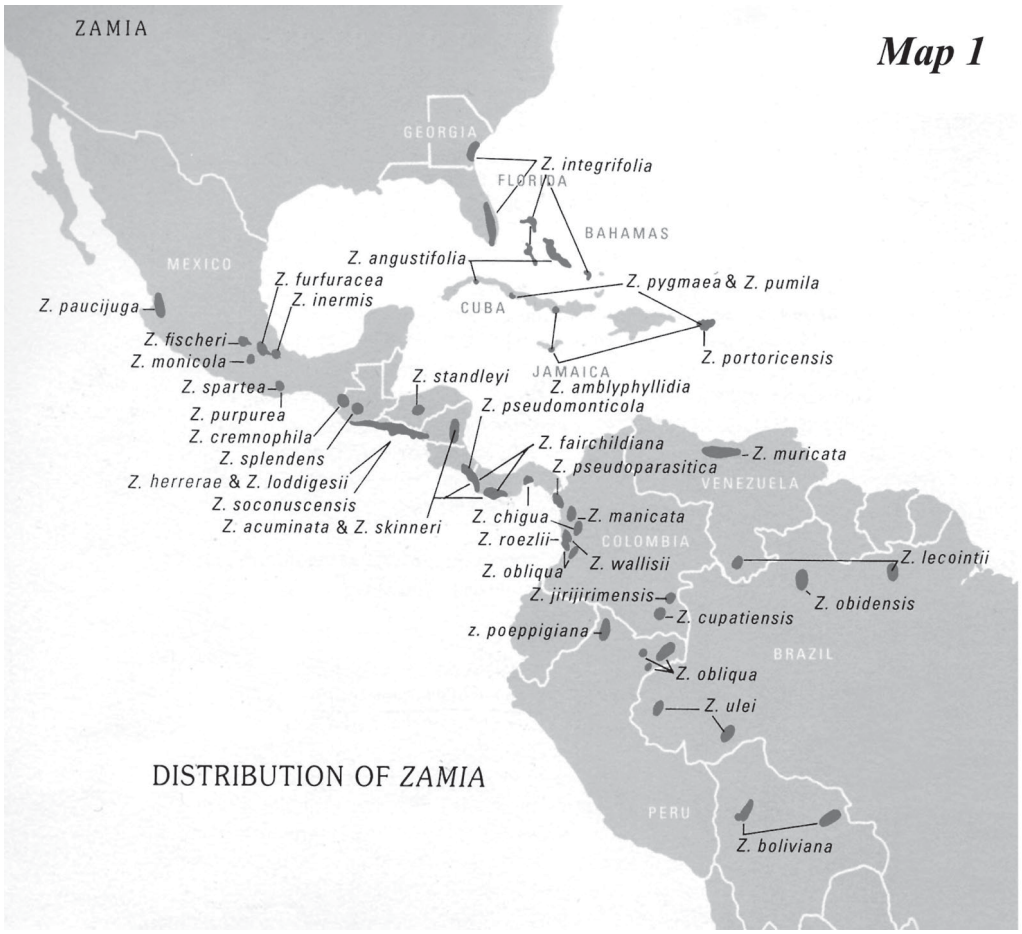


Figure 1. *Zamia roezlii* from the Pacific coast of Colombia and Ecuador. Reproduced from Ref. 36, with permission from Royal Botanic Gardens, Sydney, Australia.

Neurotoxic compounds like ßMAA, that resembles the neurotoxin ßOAA associated with lathyrism, and methyl asoxymethanol (MAM), an alkylating substance with hepatotoxic teratogenic, carcinogenic and mutagenic properties, are good candidates for causing TSP. The cytotoxic mechanisms of MAM appear to include DNA alkylation, nitric oxide generation, and perturbed DNA repair. MAM increases glutamate-stimulated neuronal tau mRNA expression and cell loss in neuronal cultures, possibly indicating that it produces long-term perturbation of the neuronal responses to physiological levels of glutamate (35).

Some TSPs from the Pacific coast of Colombia may be due to chronic exposure to neurotoxins from derivatives of the seeds and stems of *Zamia* plants (order Cycadales, family Cicadaceae) like *Z. roezlii* (chigua), endemic on the Colombian Pacific coast (36) (Map 1). *Cycads* derivatives are traditionally consumed as food and are utilized as natural medicine by the black and Amerindian populations of this region. Most Colombian TSP patients are blacks from the Pacific coast. The exposure to cycad derivatives and animals such as birds, rodents (pacas, "guatín" and wild rats ("ratón de monte")), squirrels, peccaries ("zaínos"), monkeys and marsupials such as opossums ("chucha", "zarigüeya") and to other animals that feed on cycads such as bats and porcupines appears to play an important role in the etiology of TSP on the Colombian Pacific coast, and in other tropical and subtropical regions of the world. Furthermore, some liquors, like some types of sake made



Map 1. Distribution of Zamias in Latin America, the Caribbean and Southeast USA. Reproduced from Ref. 36, with permission from Reed New Holland, Sydney, Australia.

from cycads, have also been consumed in Southern Japan, the endemic region of HAM.

By 1993, 185 species and 11 genera of living *Cycads* had been identified. After carefully looking at Map 1 it is surprising to find that the endemic TSP foci in Latin America are mainly found in the regions where there are cycads of the species *Zamia roezlii*, *Dioon*, *Cycads circinalis* (personal observation in Fortaleza, Ceará, Brasil), *Z. intergrifolia* and *C. ceratozamia* (36).

It was in Jamaica where the first cases of TSP were reported by H. Strachan in 1888 and where the first epidemic outbreak of TSP was published in 1918 by H.H. Scott. In Martinique TSP was associated with HTLV-I for the first time in 1985 by Gessain et al. (37). In Cuba most TSP patients were HTLV-I seronegative (see above). TSP also exists in Trinidad-Tobago and Puerto Rico. Even more interesting is the fact that the Southern part of Florida is the most endemic TSP region in the USA (38). Because *Zamia integrifolia* produced more starch (65%) in Florida than in other regions, massive export to Jamaican markets occurred between 1800 and 1925 (36).

There are other cycad varieties on the Caribbean islands and on the Atlantic coast of South America including Colombia, Venezuela, French Guyana and Northeast Brazil (36).

The genera *Zamia* and *Dioon* with different varieties also exist in Central America and Mexico (Pacific coast and Gulf of Mexico) and in Honduras where they are utilized as foods and as "natural" medicines. These countries have also HTLV-I-seronegative TSP endemic regions and the derivatives of *Dioon edule* and *D. mejiae* are utilized for consumption in some foods like "tortillas". Indeed cycad seeds contain neurotoxin, which must be neutralized or destroyed prior to consumption. In the mountains of Mexico and Guatemala there are also some species of the genus *Ceratozamia* (36). All *Dioon* species have an edible kernel but only three species (*D. edule*, *D. spinulosum* and *D. mejiae*) are eaten regularly after roasting, boiling or being ground to a meal and converted into tortillas. In fact, *D. edule* was so named (edule = edible) because of the fondness of local Mexicans for making tortillas from a meal obtained from its seeds. The seeds of *D. mejiae* are so popular with local people that the plants are protected by the Honduran government (36).

In sub-Saharan Africa most TSPs are not associated with HTLV-I, and *Cycads encephalartos* ("breadhead"; Figure 2) and *C. stangeria* abound among other varieties (Map 2) and have been consumed. Nigeria, Zaire, Central African Republic, Democratic Republic of Congo, Ivory Coast and South Africa are well-recognized countries where TSP without HTLV-I occurs (17).

In Cuba, a well-known country with HTLV-I-seronegative TSP, there are *Zamia angustifolia*, *Z. pigmaea*, *Z. pumila* and *Z. portoricensis* (Map 1). Cuba has one of the lowest HTLV-I seroprevalences in Latin America, which explains why most TSPs are HTLV-I seronegative.

Oral and topical clioquinol intoxication produces a spastic paraparesis associated with optic atrophy named SMON. About 10,000 cases were diagnosed in Japan in the 1956-1972 outbreak when even the "SMON virus" was isolated (31). The SMON syndrome almost disappeared after the identification of its cause and neurotoxicological

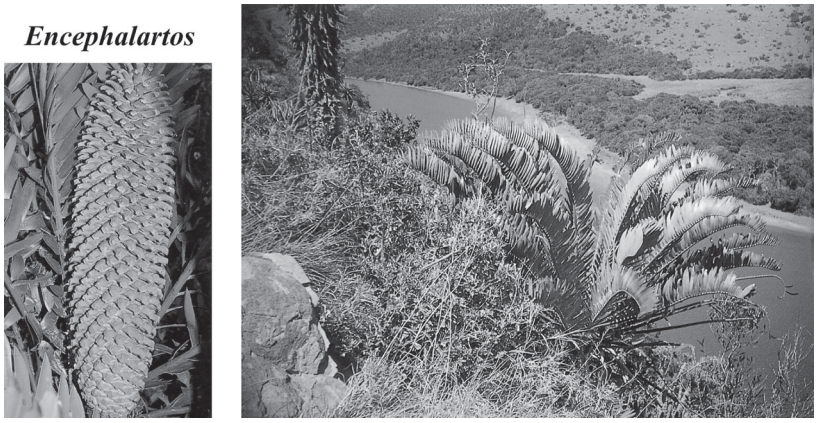


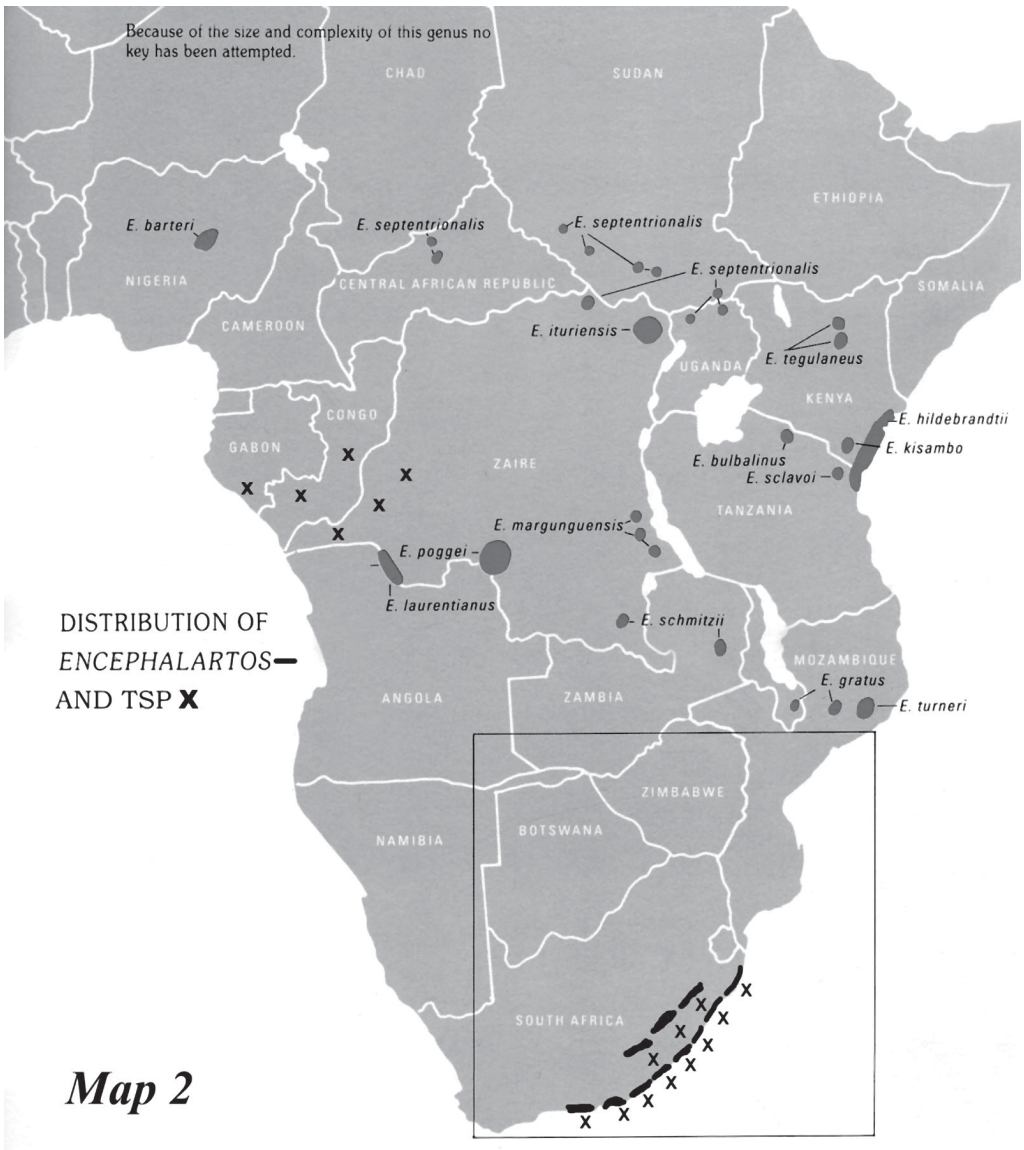
Figure 2. *Cycads encephalartos* from Africa. Reproduced from Ref. 36, with permission.

mechanism: clioquinol induces in humans and animals a retrograde degeneration of the central and distal axonal process of the dorsal root ganglion cell but leaves the cell and its peripheral processes intact. This pathophysiological mechanism is known as central distal axonopathy (39) and may explain the descending axomyelinic degeneration of the longest fibers in the posterior columns.

Glutamate, aspartate and astrocytes

Glutamate and aspartate (two non-essential diamino acids) are believed to mediate most of the excitatory synaptic traffic in the CNS. Thus, agents that directly or indirectly increase the excitatory drive or the postsynaptic effects may cause degeneration of neurons bearing excitatory amino acid (glutamate) receptors. Glutamate released from nerve terminals is taken up by glial cells, converted to glutamine and probably recycled back to the neurons. Under normal conditions, circulating amino acids are excluded from the CNS by the blood-brain barrier.

Human illness associated with glutamate-



Map 2. Distribution of *Cycas encephalartos* and tropical spastic paraparesis (TSP) in Africa. Reproduced from Ref. 36, with permission from Reed New Holland, Sydney, Australia.

and aspartate-containing substances is a matter of debate. Concern about the possibility of amino acid excitant neurotoxicity is particularly high for infants and those who may have impaired blood-neural regulatory interfaces due to illness, malnutrition, or other causes. Patients with HTLV-I-seropositive TSP and HAM could be exposed to excess glutamate or aspartate because HTLV-I disturbs the astrocytes responsible for maintaining part of the blood-brain barrier. It was recently demonstrated that HTLV-I-infected T lymphocytes impair the catabolism and uptake of glutamate by astrocytes via tax gene and tumor necrosis factor alpha (40). Tax 1 and cytokines produced by HTLV-I-infected T cells impair the ability to manage the steady-state level of glutamate, which in turn may affect neuronal and oligodendrocytic functions and survival. There is evidence that cell-cell fusion occurs between HTLV-I-infected lymphocytes and brain endothelial cells, with the latter being susceptible to transient HTLV-I infection (41). The interactions between HTLV-I-infected lymphocytes and brain endothelial cells may be one of the mechanisms of viral damage to the CNS that may also lead to lesions of the blood-brain barrier. These facts may be important steps in determining the progression to neurological diseases like HAM and may explain the axomyelinic degeneration of the longest fibers of the corticospinal tracts and posterior columns that are glutamatergic.

Final general considerations

Considering the above information as a whole, three different situations may be proposed to be involved in the etiology of TSP and HAM: 1) patients with TSP caused only by toxins or toxic agents without HTLV-I-II, HIV, HIV-2 or HBV; 2) patients infected with retroviruses, mainly HTLV-I, acquired since birth or during adulthood by sexual transmission of by transfusions who are later exposed to toxic agents or toxins. These patients may develop a polymorphic syndrome named HAM, usually with multiple clinical and pathological variations. These cases could be due to the damage caused to the astrocytes by the retroviruses which disrupts the blood-brain barrier and enhances the glutamate excitotoxicity to the corticospinal system. Depending on immunological, virological, metabolic, toxicological or genetic factors, parasitic infestations and/or nutritional status, these patients may develop any of the 61 diseases or syndromes associated with HTLV-I, including cancers, lymphomas and even amyotrophic lateral sclerosis. The reverse situation is also possible: patients that are exposed to low levels of toxins or toxic agents could develop TSP/HAM and many other syndromes after being infected by retroviruses which disturb the protective action of astrocytes in the blood-brain barrier. 3) Patients infected with HTLV-I and/or another retrovirus but without exposure to toxic agents or toxins, and without metabolic dysfunctions, malnutrition, immunological or genetic defects would act as carriers of retroviruses.

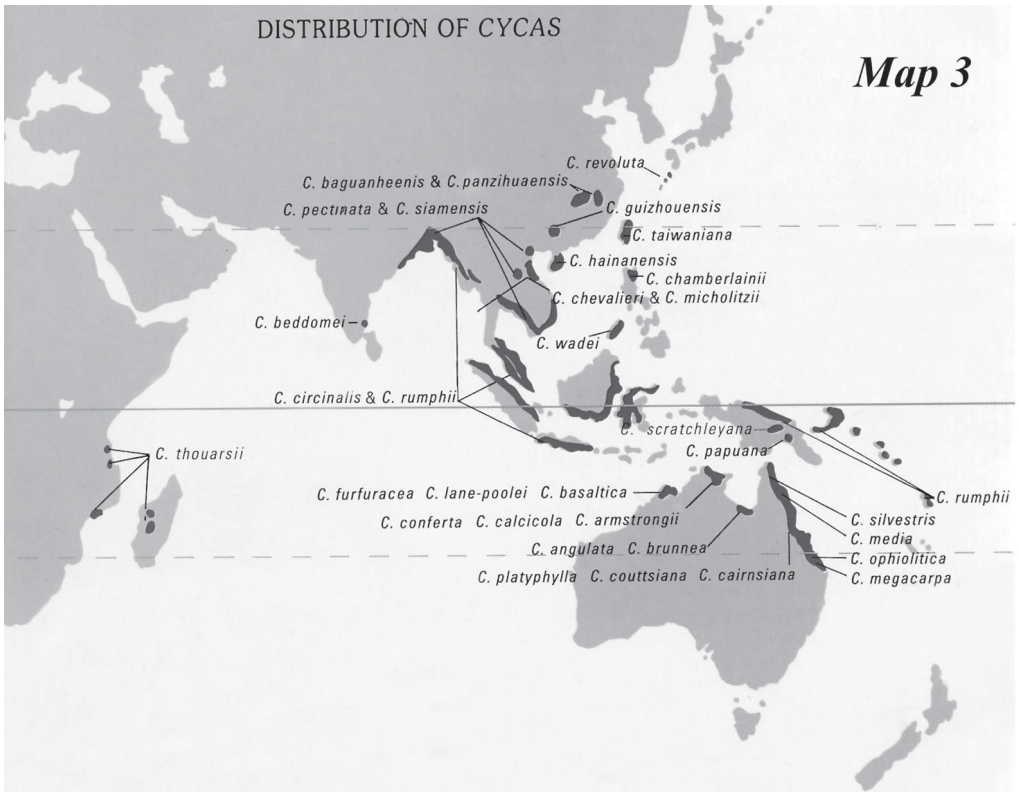
At this time it is opportune to analyze the epidemiologic inconsistencies of HTLV-I and TSP/HAM on the West Pacific islands: 83% of TSP patients were HTLV-I seronegative despite the high HTLV-I seroprevalence ranging from 12 to 50%. On these islands as well as in New Guinea, Australia, Burma, Java, Sumatra, Thailand, Cambodia, Indonesia, Southeast China and Philippines, cycads exist and are consumed directly or indirectly, the same occurring on Southern Japan islands, Riukyuans, Kyushu and Shikoku (Map 3), the most endemic TSP/HAM regions in Japan. In Southern Japan *Cycads revoluta*'s seeds and stems (Figure 3) have been consumed for many years as a traditional food named "sotetsu". *Cycads revoluta* is the most commonly cultivated cycad in the world and its seeds are used by animals and humans as a food source. This species is commonly known as "sago palm" which is really a false

sago palm and is also frequently used as an ornamental plant and as an expensive bonsai. *Cycads* toxins could also be consumed by eating animals that eat the fruits, roots or leaves of these plants. *Cycads revoluta* is suited to temperate and subtropical regions but is also commonly planted in the tropics. *Cycads circinalis* is found in India, Burma, Thailand, Sri Lanka, Malaysia, Indonesia, most islands of the Southern Pacific regions (36) and especially in Northeast Brazil where TSP, HAM and amyotrophic lateral sclerosis are endemic.

A wide range of animals is attracted to the seeds, stem leaves and roots of *Cycads*, on which they actively feed. Several rodents, squirrels, bears, peccaries, pigs, baboons, monkeys, elephants, marsupials such as opossums, kangaroos and wallabies, large birds such as parrots, cockatoos, crows, emus, cassowaries, mockingbirds, hornbills, porcupines and fruit bats feed on *Cycads* (36).

On the Pacific coast of Colombia (one of the most endemic TSP/HAM regions in the world), natives of African origin and Amer-

Figure 3. *Cycas revoluta* from Southeast Asia and Southern Japan. Reproduced from Ref. 36, with permission.



Map 3. Distribution of *Cycas* in Southeast Asia, Australia, Western Pacific Island and Southern Japan. Reproduced from Ref. 36, with permission from Reed New Holland, Sydney, Australia.

indians eat not only *Cycads* by-products but also wild animals. They eat large rodents, peccaries, monkeys, opossums, parrots and different varieties of large colorful birds that feed on *Zamia* seeds, stems and leaves. They also eat domestic fowl, pigs, and cattle fed with *Zamia roezlii* derivatives and waste.

Map 4 shows the world distribution of *Cycads* and of TSP/HAM. This interesting coincidence, apparently real, between world *Cycads* distribution and the presence of TSP/HAM in the tropical and subtropical regions of the world should be further investigated.

It should be remembered that the physiopathology of adult T-cell leukemia lymphoma (ATL) has not been clarified. *Cycads* also produce cycasin that is transformed to MAM, a well-known hepatotoxic, mutagenic, teratogenic and carcinogenic substance in rodents. Some ATL cases have been produced by blood contaminated with HTLV-I and that there are proven cases of ATL without HTLV-I. As is the case for TSP/HAM, the epidemiology of ATL is sometimes also inconsistent and "paradoxical". It appears possible that some cases of ATL could also be associated with cycad utilization with and without HTLV-I.

Conclusions

The incidence of TSP and HAM appears to depend on the HTLV-I/toxic or toxin (xenobiotic) ratio. The analysis of this ratio shows 5 possibilities: 1) Regions with high HTLV-I seroprevalence but with low levels of toxins or toxic agents: many HTLV-I carriers, very few TSP and few HAM cases (Ainus

Map 4

Map 4. This composed map shows the coincidence of world distribution of *Cycads* (–) (reproduced from Ref. 36, with permission from Reed New Holland, Sydney, Australia) and of TSP/HAM (x) according to the author.

from Hokkaido North Japan, natives from the Western Pacific islands). 2) Regions with high HTLV-I seroprevalences and high levels of toxic agents or toxins: many TSP and many HAM cases (South Japan, blacks on the Pacific coast of Colombia and Ecuador, Caribbean Islands, and Northeast Brazil). 3) Regions with a low HTLV-I seroprevalence and low levels of toxins or toxic agents: almost no TSP/HAM and few HTLV-I carriers (Europe, North China and Russia). 4) Regions with low HTLV-I seroprevalence but with high levels of toxins or toxic agents: there are many TSP and very few HAM cases (sub-Saharan Africa, India, Cuba, Thailand and Mexico). 5) Regions with very low HTLV-I and without toxins or toxic agents: there are no TSPs and no HAMs (Arctic and Antarctic regions).

The gradual variations of the HTLV-I/toxic agent-toxin ratio could explain most of the paradoxical epidemiology of TSP and HAM around the world.

Many HTLV-I-seronegative TSPs in India, Bangladesh and Ethiopia and possibly some cases from Chile may be caused by lathyrism.

Cassava derivatives, glutamate, clioquinol and similar iodine compounds, and *Cycads* may cause most cases of TSP in Brazil, Latin America, the Caribbean and Africa.

Cycads derivatives associated or not with HTLV-I may account for some TSP/HAM on the Pacific coast of Colombia and Ecuador, in Australia, in the Western Pacific Islands and in Southern Japan.

HAM appears to be one of the virotoxic and autoimmune retrovirus-associated encephalomyelopathies associated mainly with HTLV-I, but also associated with HTLV-II, HIV-2 and HBV that damage the astrocytes and the blood-brain barrier.

It is reasonable to assume that there are more toxins and toxic agents associated with TSP and with HAM and that TSP/HAM is a multifactorial syndrome.

If the arguments and reasoning presented in this manuscript are at least partially correct the prevention of most TSPs and HAMs appears to be possible today.

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