TROPICAL MYELOPATHIES AND MYELONEUROPATHIES[1]

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INTRODUCTION

Diseases of the nervous system are a frequent cause of disability and death in the tropics. Nevertheless, the number of neurologists in Third World countries is still quite limited; and this fact (along with other geographic, economic, and political factors) has hampered the gathering of statistics for accurately determining the epidemiologic magnitude of the main tropical neurology problems *(1)*. (It should be noted that the World Health Organization recently began studies that are now yielding valuable information on the prevalence of neurologic problems in the Third World—*2–4*).

For the aforementioned reasons, the high prevalence of neuropathies and myelopathies in some tropical regions has passed all but unnoticed. During World War II a large number of war prisoners in the Far East developed these neurologic complications while in captivity—much more frequently, in fact, than similar prisoners in cold regions where nutritional and caloric deficiencies were possibly more severe. This indicated that environmental, nutritional, and possibly neurotoxic factors conspire in the tropics to produce a higher incidence of myelopathies and myeloneuropathies, even though the etiologies of most of these are still unknown. This article briefly reviews the main foci of tropical myelopathies, underscores some of the advances in the physiopathology of the tropical malabsorption syndrome and its neurologic effects, describes the neurotoxic effects of cassava, and provides recent evidence indicative of the possible role of the human T-lymphotropic virus type I (HTLV-I) in cases of tropical spastic paraparesis.

DEFINITIONS

The word "myelopathy" is a general term used to define any pathology involving the spinal cord. When a peripheral nervous system lesion affects not only the distal nerve endings but also the neuronal bodies (either in the ganglia of the dorsal roots or in the anterior horns of the spinal cord) and the central prolongations of the sensory

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neurons in the posterior columns of the spinal cord, the term used is "myeloneuropathy." The best known example of myeloneuropathy is the so-called "subacute combined degeneration" produced by vitamin B_{12} deficiency—a condition characterized by demyelinization of the posterior and lateral columns of the spinal cord that is associated with bilateral and symmetrical sensory polyneuropathy.

Tropical myelopathies and myeloneuropathies are divided into two basic groups *(5)*: (1) *tropical ataxic neuropathy* (TAN), characterized clinically by profound sensory ataxia, loss of proprioceptive function, and posterior funiculus damage; and (2) *tropical spastic paraparesis* (TSP), which presents as a predominantly spastic lower-limb palsy that progresses slowly and is accompanied by minimal sensory deficit. Of course, there are various intermediate forms with differing degrees of spasticity and ataxia, as well as cases complicated by optic neuritis, nerve deafness, or episodes of confusion. Table 1 summarizes the principal clinical characteristics commonly found among patients with TAN and TSP.

Etiology

It should be noted at the outset that both of these conditions may arise from many causes. Even in cases like those produced by excessive cassava consumption, a deficiency acts as a predisposing factor, setting the stage for the development of neurologic complications. The following are some forms

TABLE 1. Signs and symptoms associated with tropical ataxic neuropathy (TAN) and tropical spastic paraparesis (TSP).

Clinical characteristics of patients with TAN and TSP	Frequency with which indicated characteristic is found among patients with:	
	Tropical ataxic neuropathy (TAN)	Tropical spastic paraparesis (TSP)
"Burning feet" and other paresthesias and dysesthesias of the legs	>75%	<25%
Difficulty walking	50–75%	>75%
Weakness of the legs	<25%	>75%
Loss of proprioception and vibratory sensation in the feet	>75%	<25%
Loss of perception of pain and temperature in the feet	<25%	<25%
Muscular atrophy (perceneal muscles)	<25%	<25%
Absence of patellar and Achilles tendon reflex	>75%	Usually not found
Patellar and Achilles hyperreflexia	Usually not found	>75%
Babinski's sign	<25%	>75%
Sphincter disorders	<25%	50–75%
Backache	<25%	50–75%
Spasticity	<25%	>75%

of TAN and TSP whose etiology has been most closely studied. Their possible causes are summarized in Table 2.

Tropical Ataxic Neuropathies

Nutritionally induced tropical ataxic neuropathy. A syndrome characterized by orogenital dermatitis, amblyopia, and painful peripheral neuropathy ("burning feet") was recognized early in this century. It has since been found rather frequently among malnourished populations in the tropics. The lesions described in these cases—such as angular chelitis, stomatitis, glossitis, geographic tongue, dermatitis, scrotal and vulvar eczema, periorificial lesions of the nose and eyelids, and neovascularization of the cornea—result mainly from a riboflavin deficiency. This deficiency is combined in many cases with other vitamin deficiencies such as hypovitaminosis A (causing xerophthalmia and keratomalacia), lack of niacin (leading to scarlet tongue and pellagroid dermatitis), folate and vitamin B_{12} deficiencies (causing megaloblastic anemia), and iron deficiency (leading to hypochromic anemia). Conditions that increase nutritional requirements (such as pregnancy and lactation) and intercurrent infections (such as malaria) often precipitate the neurologic syndrome.

Hundreds of patients with problems involving painful neuropathy and ataxia have been described over the years in such places as Ceylon, Egypt, Ghana, India, Kenya, Liberia, Malaysia, Nigeria, Rhodesia, Senegal, Sierra Leone, Somalia, and Uganda *(5)*. For instance, Collomb et al. *(6)* studied a group of 47 patients with tropical ataxic neuropathy in Dakar, Senegal; 18.6% had some degree of visual impairment and 13.4% had nerve deafness. The highest incidence of the disease was found to occur among women in their thirties, one-third of whom experienced the problem in association with breastfeeding and pregnancy. In another third, chronic diarrhea was the triggering factor. Vitamin B complex injections produced improvement in 65% of the patients.

Tropical ataxic neuropathy in prisoners of war. Symptoms similar to those described in nutritionally-induced TAN cases have been found among prisoners of war in tropical and subtropical regions. The first symptom is burning pain in the feet, followed by dysesthesia of the hands and feet, sensory ataxia, difficulty walking, Romberg's sign, and hyporeflexia or complete loss of reflexes. Loss of eyesight was frequent, and in some internment camps up to two-thirds of the prisoners lost visual acuity. Symptoms associated with other neurologic syndromes included deafness, vertigo, spastic paraplegia, and acute ophthalmoplegia *(7)*.

Malnutrition caused by dietary deficiency was further aggravated by the presence of diarrhea—possibly as a result of tropical malabsorption—with stomatitis, glossitis, pellagroid erythema, scrotal eczema, tachycardia, and arterial hypertension. The neuropathologic lesions observed in these patients *(8)* were a systematic loss of axons on the posterior columns of the spinal cord, especially in the fasciculus gracilis, and a similar lesion of the maculopapillary bundle of the optic nerve, possibly owing to damage to the bipolar neurons of the macula lutea.

Similar cases were also seen during the Spanish Civil War and in the

TABLE 2. Possible causes of tropical myelopathies and myeloneuropathies.

Type of lesion or problem	Observations
1) Injury (fracture, cervical disk herniation, spondylosis, hematomyelia, others)	Usually acute onset. History of trauma. Radiology (+). Cervical spondylosis rare in tropics.
2) Tumor (extra- or intradural; bony or epidural metastasis.)	Symptoms of hemisection or central spinal cord lesion, radiculopathy. There is myelopathy due to paraneoplastic effect of carcinoma.
3) Vascular problems (thrombosis of anterior spinal artery, arteriovenous malformations, vasculitis—lupus, etc.)	Acute onset, transverse myelitis.
4) Multiple sclerosis (MS)	Generally fluctuating course with relapses. Several neurologic lesions. The association of myelopathy and optic neuritis is called Devic's syndrome.
5) Nutritional problems (subacute combined degeneration from vitamin B_{12} deficiency; pellagra; deficiency of pantothenic acid, folates, and vitamin E)	Associated with anemia, dermatitis, malabsorption, dietary deficiency, vegetarian diets, diarrhea.
6) Infections:	
Viral	Motoneuronal lesion in diseases caused by the polio and coxsackie viruses, as well as by some echo and arboviruses. Also in acute hemorrhagic conjunctivitis. Transverse myelitis from herpes simplex II (genital), combined degeneration in AIDS patients with antibodies to human T-lymphotropic virus Type III (HTLV-III), also called human immunodeficiency virus (HIV). Recent reports of HTLV-I antibodies in TSP and MS.
Bacterial	Tuberculosis (Pott's disease), epidural abscesses, arachnoiditis, syphilis, yaws, brucellosis, mycoplasma, leptospirosis, borrelia (Lyme disease).
Fungal	Rarely cause myelopathies.
Parasitic	Schistosomiasis (*S. haematobium, S. mansoni*), filariasis (*Dracunculus medinensis*), eosinophilic meningitis (angiostrongyliasis), neurocysticercosis, hydatidosis.
7) Neurotoxicity:	
Lathyrism	Most common cause of tropical spastic paraparesis in India.
Cyanide	Consumption of cassava alone. Common in Nigeria and Tanzania; causes tropical ataxic neuropathy.
Clioquinol (Entero-Vioform)	Has caused subacute myelo-optic neuropathy in Japan.
Organophosphates	Commonly used as pesticides.
8) Other problems	Triorthocresylphosphate causes tropical ataxic neuropathy. Familial paraplegia, syringomyelia, etc.

prisons of Assam, Ceylon, Johore, Singapore, and Tanganyika *(5)*—most of them being caused by a very poor diet and chronic diarrhea. Treatment of these conditions centered on the parenteral administration of high doses of B complex vitamins. Injections of thiamine, riboflavin, pantothenic acid, nicotinic acid, cyanocobalamin, and folic acid, given individually, produced only partial improvement.

Recently, vitamin E deficiency has been recognized as the cause of problems involving retinal degeneration, sensory ataxia, and spinocerebellar degeneration in patients with severe fat malabsorption. Treatment with vitamin E, administered parenterally, improves the neurologic symptoms *(9)*. Nonetheless, as Pallis and Lewis have pointed out *(10)*, it is futile to seek the factor responsible for neurologic complications in a patient whose condition is characterized by generalized malabsorption and malnutrition.

Tropical malabsorption. The term "tropical sprue" has been used exclusively to designate cases of severe malabsorption with steatorrhea and severe diarrhea. Hence, there is a tendency to forget that chronic intermittent diarrhea—only slightly symptomatic and without steatorrhea—is much more common in the tropics. All these diverse manifestations have been brought together under the inclusive term "tropical enteropathy" *(11)*.

In fact, the intestinal mucosa of people living in the tropics commonly presents alterations similar to those found in patients with malabsorption, such as flattening of the intestinal villi. These changes may result from repeated viral, parasitic, and most particularly bacterial infections. The vast majority of cases—including cases of traveler's diarrhea—are caused by intestinal colonization with enterotoxigenic strains of coliform bacteria. For these reasons, Cook *(11)* has called the condition "postinfectious tropical malabsorption."

Because of this, asymptomatic inhabitants of the tropics usually have abnormally low intestinal absorption of D-xylose, glucose, folate, and cyanocobalamin *(11)*. In turn, the folic acid deficiency tends to perpetuate the damage to the intestinal mucosa and worsen the malabsorption. Vitamin, mineral, calorie, and protein deficiencies become clinically apparent and symptomatic during pregnancy, childbirth, and lactation, and also during bouts of intestinal infections, malaria, or famine.

The neurologic manifestations found in prisoners of war in the tropics during World War II probably resulted from a combination of dietary deficiency and tropical malabsorption. Postinfectious tropical malabsorption responds well to treatment with tetracycline, which helps to explain the absence of these neurologic complications during the Vietnam War, during which all cases of diarrhea were treated routinely with antibiotics. This association of tropical malabsorption and malnutrition could explain the relatively high prevalence of tropical ataxic neuropathy in populations subjected to drought and famine, and the existence of cases of tropical amblyopia *(5)* and sensory polyneuropathies in those groups.

Tropical ataxic neuropathy caused by excessive cassava consumption. Cassava, also known as the mandioca or tapioca plant (*Manihot esculenta* Crantz, *M. utilissima;* French *manioc;* Spanish *yuca*) is one of the most important sources of calories in tropical countries. Some 300 million people depend on it for their subsistence, especially in the tropical regions of the Americas and in Africa. (It is the basic staple in Mozambique, Nigeria, Tanzania, Uganda, and Zaire.)

Unfortunately, even the varieties of "sweet" cassava contain cyanide in the form of a cyanogenic glycoside, linamarin, which releases cyanide by the enzymatic action of linamarinase or by hydrolysis. Chronic cyanide intoxication has been confirmed as the cause of the tropical ataxic neuropathy described in Nigeria and Tanzania *(12-14)*. Likewise, eating cassava during pregnancy can cause endemic cretinism, the cyanide ingested by the mother being converted into thiocyanate, a goitrogen *(15)*. Other cyanogenetic plants are yams (*Dioscorea sativa, D. alata*), beans, maize, millet, and sugarcane.

According to Osuntokun *(12)*, in some Nigerian hamlets where the only food is a kind of cassava cake called "gari," the prevalence of tropical ataxic neuropathy is 18 to 26 cases per thousand inhabitants. The clinical symptoms of these patients are summarized in Table 3. Just how the neurotoxic mechanism in cassava operates is not clearly understood. Treatment with high doses of cyanocobalamin, riboflavin, and other B complex vitamins has not been satisfactory, suggesting that vitamin deficiencies may play a secondary role in the condition's pathogenesis.

In 1981 two new epidemic outbreaks of cassava myeloneuropathy in Africa were described. The most severe, called "mantakassa" locally *(16, 17)*, took place during a drought in Mozambique's Nampula Province. More than a thousand cases of spastic paraparesis were reported, affecting women and children in particular. The prevalence of the disorder was 29 to 34 cases per thousand inhabitants. The sec-

TABLE 3. Clinical characteristics of cassava myeloneuropathy observed among 375 patients studied by Osuntokun *(12)* in Nigeria.

Signs and symptoms	Patients affected (%)
"Burning" feet	85
Visual changes	81
Deafness	36
Weakness of legs	35
Sphincter disorders	4
Mucocutaneous lesions	40
Psychiatric symptoms	9
Loss of posterior column sensibility	83
Hypotonia of lower limbs	53
Hypertonia of lower limbs	17
Ataxic (sensory or "tabetic") gait	60
Proximal weakness of lower limbs	13
Proximal and distal weakness of lower limbs	17
Muscular atrophy	12
"Gloves and socks" loss of sensation	16

ond outbreak, known for many years by the names of "konzo" and "kitondji," occurred in the Bandundu region of Zaire during the drought months, from May to December. More than 200 cases were reported, the highest percentages again occurring among women and children. Vitamin and nutritional treatment produced little improvement *(18)*.

Although regional procedures for cassava flour processing remove almost all the cyanide, during the famines that follow droughts these procedures tend to be shortened or ignored, and many people, especially women and children, eat the cassava raw or merely sun-dried. When one considers that the cyanide content of cassava increases during drought, it is not surprising that severe intoxication should occur. The thiocyanate level in patients with myeloneuropathy ranged between 29.8 and 33.6 moles per decaliter (normal: 1–4), and the estimated daily intake of HCN ranged from 15 to 31.5 mg.

Tropical Spastic Paraparesis (TSP)

Unlike TAN, tropical spastic paraparesis produces generally minimal sensory involvement. The main lesion is typically in the pyramidal tract, especially in the lumbar region. The clinical characteristics are difficulty in walking, spasticity, hyperreflexia of the lower limbs, spastic bladder, and bilateral Babinski's sign. It can occur in cases of chronic cassava intoxication, as already noted, although only 17% of the patients studied by Osuntokun *(12)* in Nigeria had spasticity and signs of pyramidal involvement.

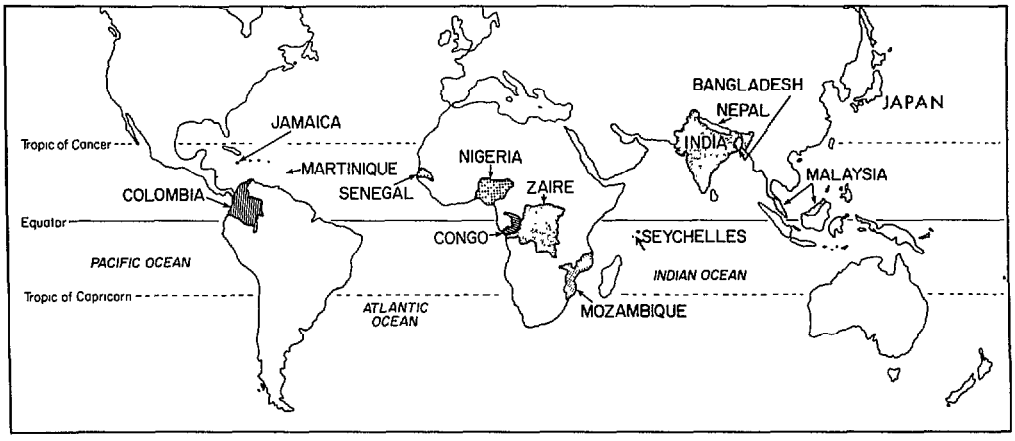
Tropical spastic paraparesis can also be associated with tropical malabsorption-malnutrition. This association was found by Collomb et al. *(6)* in 21% of the cases studied in Senegal and in some prisoner-of-war camps *(7)*. The best known and most frequent cause of paraplegia in the tropics is lathyrism.

Lathyrism. It has been known from time immemorial that eating vetch flour made from the seeds of plants of the *Lathyrus* family, especially *Lathyrus sativus, L. clymenum,* and *L. cicera* causes chronic intoxication. A neurotoxic amino acid, beta-oxalyl-aminoalanine (BOAA), appears to be responsible for the spastic paralysis of lathyrism. This condition is still an endemic problem in some regions of Bangladesh, Ethiopia, and India, where workers are customarily paid in vetch flour. These plants are very drought-resistant, and their consumption in times of war and famine produces epidemics of spastic paraplegia such as those observed in Europe *(19, 20)*, Spain *(21)*, northern Africa, and Asia. The neuropathologic damage done by lathyrism consists of bilateral axonal depopulation of the pyramidal fasciculi, with minimal loss of axons in the fasciculus gracilis in the lumbar region of the spinal cord.

Other TSP patterns. Even excluding the cases of lathyrism and tropical spastic paraparesis associated with tropical malabsorption malnutrition—such as those described in southern Africa *(22)* and Senegal *(23)*—there are still a number of geographic foci of tropical spastic paraparesis (Figure 1) in which the prevalence of paraparesis is greater than that of multiple sclerosis in some Scandinavian countries, including the following:

- *Paraplegia in southern India.* Since 1940, cases of spastic paraparesis have been described in regions of

FIGURE 1. Worldwide distribution of clusters of endemic tropical myeloneuropathies.



southern India where there is no lathyrism. Mani et al. *(24)* studied 45 cases of TSP over a five-year period. These patients had varying socioeconomic backgrounds and showed no evidence of malnutrition. The authors assumed an infectious etiology, but the cause of the syndrome is unknown.

• *Paraplegia in South Africa.* Cosnett *(25, 26)* studied a total of 74 patients with spastic paraparesis among the Bantu of South Africa. Most of the patients were from rural areas, and the usual causes of paraplegia could be ruled out. The condition occurs predominantly among males, and its cause is unknown.

• *Paraplegia in the Indian Ocean.* In 1982, Kelly and DeMol *(27)* reported 83 cases of TSP on the Seychelles Islands in the Indian Ocean. Román et al. *(28)* have recently confirmed the existence of this condition there. The clinical picture is characterized by slowly progressive paraparesis with difficulty walking, lumbar pain, lower-limb spasticity, spastic bladder, impotence in males, severe constipation, and pyramidal signs. Decubitus ulcers occur in advanced cases. There is a predominance of black patients. The prevalence fluctuates between 30.8 and 120 cases per 100,000 inhabitants.

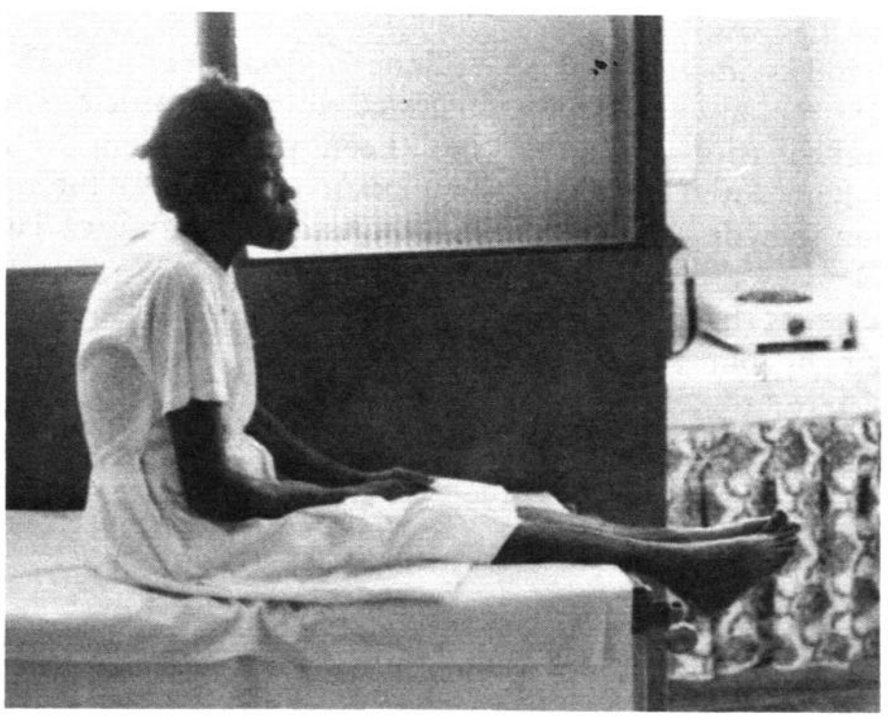
• *Myeloneuropathy on Jamaica.* In 1956 Cruickshank *(29)* described a hundred cases of TSP observed in Jamaica over a three-year period. Half of the patients also presented evidence of posterior column lesions, 26% had optic neuropathy, and 12% had nerve deafness. All the cases occurred in black patients between the ages of 35 and 40. In a later study of a group of 206 patients *(30)*, TAN was found in 25, of which seven had also suffered pyramidal damage. The remaining 181 patients had TSP, and some of these also exhibited slight signs of posterior funiculi lesion (50%), optic atrophy (15%), deafness (7%), and slight peripheral neuropathy (13%). Sixty percent of these patients tested positive serologically for syphilis in the blood and 6% tested positive for syphilis in the cerebrospinal fluid. More than 40% of the patients had pleocytosis, increased pro-

teins, and gamma globulins in the cerebrospinal fluid. Despite treatment with penicillin and vitamins, the disease continued its chronic and progressive course *(31)*.

A neuropathologic study of 15 fatal cases revealed chronic leptomeningitis with a lymphocyte-predominant inflammatory reaction *(32)*. Fibrous thickening of the meninges and a vascular reaction with hyaline changes and proliferation of the intima were found. Myelin staining revealed severe demyelination, especially in the pyramidal fascicles, and to a lesser extent in the posterior cords and the spinothalamic and spinocerebellar tracts. The optic and auditory nerves presented similar lesions. Some authors believe that the myeloneuropathy of Jamaica could be a late neurologic complication of yaws or an atypical form of tertiary syphilis *(30–33)*.

• *Spastic paraparesis in Colombia.* In 1981 Zaninovic et al. *(34)* described an outbreak of TSP along the southern Pacific coast of Colombia. These authors found 69 cases of TSP among black patients from the coastal region. Román et al. *(35, 36)* confirmed the high frequency of this condition in the port of Tumaco, finding a prevalence of 98 cases per 100,000 inhabitants. The condition progresses slowly and is characterized by lumbar pain, difficulty walking, and pyramidal signs. There is also a slight decrease in distal vibratory sensation in the feet.

This region of Colombia was hyperendemic for yaws until the mid-fifties, when an eradication campaign was launched *(37)*. In Tumaco, 74% of the patients with TSP had a history of yaws. In contrast, only three of the 29 males in the group studied had had syphilitic chancres, and none of the 21 women in the study group had a history of recurrent abortions or infertility—common complications of syphilis. Treponemal serology (using the fluorescent treponemal antibody-absorbtion test) was positive in more than 90% of the patients, and cerebrospinal fluid



A patient from Tumaco, Colombia, with TSP. Note the disuse atrophy of the legs and the spontaneous extensor plantar response.

specimens from 26 patients yielded positive results in five cases (19%). These findings suggest that the TSP in Colombia's Pacific coastal region, like the tropical myeloneuropathy in Jamaica, could be considered a late lesion of yaws *(1, 38)*.

• *Paraparesis in the French Antilles.* The existence of TSP among the black population of Martinique has been known for many years *(39)*. However, in 1985 Gessain et al. *(40)*, in a serologic study of patients with TSP from Fort-de-France, reported the presence of positive antibodies to human T-lymphotropic virus Type I (HTLV-I) in 66% of the patients with spastic paraparesis. This virus, which causes adult T-cell leukemia and non-Hodgkin's lymphoma, belongs to the same family as the virus causing the acquired immune deficiency syndrome (AIDS). These findings, which have recently been confirmed, open up interesting possibilities for study and research.

Concluding Remarks

Tropical myelopathies and myeloneuropathies are common conditions in some equatorial regions. Though first described around the turn of the century, they have only recently begun to receive the attention they deserve. In a vast majority of cases the cause is unknown, but it is evident that several processes are involved. In some regions of Africa it has been shown that TAN is generally due to chronic cyanide intoxication caused by an exclusive diet of cassava. In India, lathyrism is the most common etiology of TSP. In some African countries, and in some provinces of India, these myeloneuropathies may result from a vegetarian diet combined with tropical postinfectious malabsorption. This combination of malnutrition plus malabsorption leads to protein-calorie and multiple vitamin deficiencies (especially of folates, cyanocobalamin, pantothenic acid, and vitamin E), each of which can cause neurologic damage. The presence of TSP in Jamaica and Colombia, in areas where yaws was previously hyperendemic, together with the treponemal serology and autopsy results indicating a possible infectious etiology, suggest that TSP in these regions of the Americas could be a late or tertiary form of yaws. However, antibodies to the human T-lymphotropic virus type I (HTLV-I) have been detected in more than half of the patients with spastic paraparesis in Martinique, Colombia, Jamaica, and the Seychelles *(41)*, as well as in patients with aspastic myelopathy in Japan. These findings indicate possible involvement of a retrovirus in the pathogenesis of these disorders *(42)* and clearly merit further investigation.

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Summary

Until recently, the high incidence of myelopathies in some tropical regions of the Americas and elsewhere passed all but unnoticed—partly because the statistical data on these problems were limited. This article reviews the information available on known tropical myelopathies and describes their principal forms and features.

The two main forms of tropical myelopathy are tropical ataxic neuropathy (TAN), a myeloneuropathy with prominent sensory ataxia, and tropical spastic paraparesis (TSP), a myelopathy with predominantly spastic paraplegia and minimal sensory deficit. These conditions arise from many causes associated with malnutrition, postinfectious tropical malabsorption, chronic cyanide intoxication from excessive cassava consumption, and lathyrism.

Geographic foci of these conditions occur in several developing countries, the prevalences in these foci being far higher than those of multiple sclerosis in temperate regions. Clusters of unknown etiology occur in Jamaica, several other Caribbean islands, the Pacific lowlands of Colombia, southern India, South Africa, and the Seychelles. Treponemal infection (late yaws) could be an etiologic factor in the Caribbean islands and Colombia. Recent reports from Martinique, Jamaica, Colombia, and the Seychelles, have found antibodies against human T-lymphotropic virus type I (HTLV-I) in more than half of the TSP patients. Obviously, further research is needed on this matter as well as on other important questions relating to the tropical myelopathies.

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