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The Myeloneuropathies of Jamaica

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Abstract

This article summarizes the present state of knowledge of TSP/HAM as it is seen in Jamaica. It reviews the historical and clinical aspects of the disease, and shows how the discovery of HTLV-I has generated research in several countries and contributed to a better understanding of the disease. It highlights the need for continued collaboration between basic scientists and clinical neurologists in order that the dilemmas relating to therapy and pathogenicity may be successfully addressed.

Index Entries: Human T-lymphotropic virus type 1 (HTLV-I); HTLV-I-associated myelopathy; tropical spastic paraparesis.

Introduction

In 1956, Cruickshank described the first 100 cases of "A neuropathic syndrome of uncertain origin" *(1)*, which he called "Jamaica neuropathy." The clinical, laboratory and pathological findings as well as the etiology of 206 cases were later studied *(2)*. Patients were separated into two groups—ataxic, with posterior column signs, deafness, and retrobulbar neuropathy; and spastic, with upper motor neuron signs.

Jamaican neuropathy is one of the tropical myeloneuropathies—a descriptive term applied to several neurological syndromes of varying etiology occurring in tropical countries *(3)*. The earliest reports originated from Jamaica *(4,5)*, but later similar reports emerged from Africa *(3)* and the Far East among prisoners of war *(6,7)*. The tropical myeloneuropathies were also divided into two groups, tropical ataxic neuropathy (TAN) and tropical spastic paraparesis (TSP), and correspond to the ataxic and spastic groups of Montgomery et al. *(2)*. The term will from here on be used to refer to that spastic form of Jamaican neuropathy that is commonly seen today. Its etiology remained in doubt until the human T-cell lymphotropic virus type-1 (HTLV-I) was associated with TSP. This significant observation stimulated intense debate and research. This article reviews the current status of the disease and discusses the significance of new developments in this rapidly evolving field.

Epidemiology

Tropical spastic paraparesis is common in HTLV-I endemic regions, such as the Caribbean, equatorial Africa, Seychelles, Southern Japan, and South America *(8–11)*. It has also been reported from non-

endemic areas, such as Europe and the United States, in both immigrant and indigenous people. The prevalence of the disease ranges from 8.6/100,000 inhabitants in Kyushu, Japan, to 128/100,000 *(12,13)*. The incidence is more difficult to estimate because of the insidious nature of the disease and limitations in case finding. The disease mainly affects females (female to male ratio—3:1) in the third or fourth decades but may occur at any age.

Clinical Features

Tropical Ataxic Neuropathy (TAN)

Tropical ataxic neuropathy (TAN) is an indolent myeloneuropathy characterized by burning feet, and severe loss of position and vibration sense. Sensory loss is pronounced more distally, and is accompanied by loss of knee and ankle jerks. In Nigeria, Osuntokun has shown that TAN is related to the high concentrations of cyanide in subjects who consume cassava and whose diet is deficient in the sulfur-containing amino acids necessary for detoxification of cyanide *(4)*.

The incidence of TAN has declined in Jamaica. We have encountered only one new case in the last 5 yr, and have not been able to incriminate either cyanide or retroviruses in the etiology of our remaining cases. One ataxic patient from Cruickshank's original series, who was studied electrophysiologically, had the features of a chronic axonal peripheral neuropathy *(15)*.

Tropical Spastic Paraparesis (TSP)

Two epidemiological forms of TSP exist: acute (epidemic) nutritional and chronic (endemic) of infectious origin.

Epidemic (Acute) TSP

Epidemic TSP does not occur in Jamaica; large outbreaks resulting from cassava toxicity have been reported in Mozambique, Tanzania, and Zaire *(16,17)*. Onset of the paraplegia is acute, and accompanied by visual disturbances and dysarthria. Few patients recovered useful neurological function.

Endemic (Chronic) TSP

This form of TSP is common in Jamaica and is associated with HTLV-I infection. The seropositive and seronegative forms of the disease are clinically indistinguishable. Similar syndromes with identical clinical features have been described from different geographic regions *(18–22)*. Criteria for diagnosis based on clinical features have been established by the WHO working party, Kagoshima, 1988 *(23)*. The onset is insidious; occasionally, it is abrupt. Initial symptoms include leg stiffness and weakness. Both legs may not be affected simultaneously or to the same extent. Lumbar pain and sensory symptoms, such as numbness, burning, and pins and needles in the legs, are often associated. Urinary frequency, urgency, and incontinence as well as constipation and penile impotence are common.

Difficulty in walking develops within 3–6 mo of these early symptoms, and remains the major disability because of degeneration of the corticospinal tracts, paraparesis, or spastic paraplegia. In contrast to the prominent sensory symptoms, less significant signs of the posterior column and spinothalamic tracts are evident in the legs. Brisk reflexes may be the only abnormality in the upper limbs. Cranial nerve abnormalities may include optic neuropathy, facial palsy, and nerve deafness *(24,25)*.

Outside the nervous system, uveitis, arthropathy, ichthyosis, nephropathy, pulmonary alveolitis, Sjogren's syndrome, and vasculitis have been described. Rarely, other HTLV-I associated diseases, such as polymositis, adult T-cell lymphoma/leukemia, and TSP coexist *(9,26,27)*.

TSP must be differentiated from other progressive myelopathies. Spinal tumor, meningovascular syphilis, multiple sclerosis, spinal arachnoiditis, and vitamin B_{12} deficiency may be distinguished by appropriate clinical and laboratory findings.

Course and Prognosis

Many patients deteriorate lowly over a period of months before stabilizing; others become rapidly disabled before reaching a plateau. Few have a fluctuating course. About 60% of our patients walk unaided, 20% require support, and 20% are totally incapacitated. In our cases, intercurrent urinary tract infection and pulmonary emboli are the major factors that adversely influence life expectancy.

Investigations

Hemoglobin, peripheral white cells, and platelets are within the normal range. Large bizarre lymphocytes with convoluted nuclei—ATL-like cells—may be seen in the smears of blood and CSF. Immunofluorescent and cytofluorographic studies on peripheral blood lymphocytes show that most of the T-cells are CD_4 with a slight decrease of CD_8 and increase of CD_4/CD_8 ratio. The percentage of B cells (CD_{19}, CD_{20}) is normal or low. The subpopulation of CD_{25} cells (interleukin-2 receptors) is usually

increased. Peripheral blood lymphocytes cultured in vivo undergo spontaneous lymphocytic proliferation, which is also observed in asymptomatic HTLV-I-infected persons *(28)*. The binding of interleukin-2 to its receptor seems to mediate this phenomenon *(29)*.

Specific IgG antibodies to HTLV-I are present in over 90% of sera and CSF by ELISA and confirmatory Western immunoblot. A mild pleocytosis and elevation of protein concentration is common in the CSF, and immunoglobulin levels are increased because of local synthesis. There is oligoclonal banding pattern of IgG on electrophoresis. Both IgA and IgM antibodies to HTLV-I appear in the CSF. Tumor necrosis factor, α-interferon, and interleukin 1_B transcripts are upregulated in patients with TSP and seropositive carriers indicating immune dysfunction (30).

Unlike HTLV-I asymptomatic seropositive individuals, patients with TSP have high levels of circulating HTLV-I specific cytotoxic T-lymphocytes *(31,32)*. Polyclonal integration of HTLV-I in most patients with TSP has been demonstrated by Southern blot analyses worldwide. The correlation between a high viral load and the number of abnormal lymphoid cells suggests that the morphologically abnormal cell may carry the HTLV-I provirus integrated in their DNA *(13)*. In the presence of exogenous IL-1, long-term T-cell lines producing HTLV-I have been established from cultured peripheral blood mononuclear cells and lymphocytes from bronchoalveolar lavage lymphocytes and CSF of TSP patients. These viral isolates are similar to those from ATL and seropositive carrier-derived cell lines *(33–35)*. Molecular studies have not revealed any major difference between the viruses of TSP and ATL, and therefore, do not support the existence of a neurotropic strain *(36,37)*. Contrast myelography is useful to exclude compressive lesions of the spinal cord; swelling or atrophy may be shown by computerized tomography and magnetic resonance imaging (MRI). In some cases, MRI of the brain demonstrates small isolated paraventricular lesions. Electrophysiological studies sometimes provide evidence of subclinical lesions, since visual evoked, brain stem auditory, and somatosensory-evoked potentials may be abnormal *(13,38)*. We have found the conduction times in the central pathways to be consistently prolonged in all 21 patients studied by magnetic stimulation of the cortex. No specific EEG abnormalities occur, but disorganization of background activity, diffuse slow waves, and spikes without localizing value may be found. Nerve conduction studies, F-waves latencies, and needle electrode examination reveal no consistent abnormalities *(15)*. An overactive detrusor with incoordinate detrusor-urethral spincter activity characterizes the bladder dysfunction *(39)*.

Pathological Findings

The histopathological findings are similar to those reported by Robertson and Cruickshank *(40)*. The brain is grossly normal, but the basal leptomeninges are uniformly thickened. Similar, but even more extensive changes are observed in the spinal cord, which shows moderate to severe atrophy, especially in its middle and lower thoracic segments. Characteristically, the neuropathological changes are those of a chronic progressive inflammatory process, preferentially involving the gray and white matter of the spinal cord. The inflammatory cell collection around small parenchymal vessels is usually accompanied by cellular exudation into adjacent parenchymal tissues. Unlike the anterior columns, which are only marginally affected, the lateral columns are severely and symmetrically involved in this process. There is a paucity of cells in the subarachnoid spaces. Severity of the inflammation is determined by the duration of the disease process—lymphocytic and monocytic cell infiltration being intense in more recent disease. The main constituents of the parenchymal cell exudates are lymphocytes, which are readily labeled with a monoclonal antibody (MAb) for T-cells with a marker for monocyte–macrophage lineage *(41)*. Fibrous thickening of the adventitia of small cells is common, but the endothelium shows no appreciable changes and there is no obliteration of vessels *(2,42)*. In myelin preparations, symmetrical pallor of the lateral funiculi, especially of the lateral pyramidal tract, is prominent. Demyelination is less marked in the posterior columns and in the spinothalamic and spinocerebellar tracts *(41)*. Outside the spinal cord, perivascular lymphocytic infiltration is mild in the medulla, pons, midbrain, cerebral, and cerebellar white matter *(41,43)*. The spinal nerve roots and peripheral nerves are spared in most cases, with loss of some myelinated fibers; neurons are preserved.

Cause and Pathogenesis

The chronic inflammatory changes observed and reactive serological tests for syphilis suggested chronic infection *(1,44,45)*. Recent studies from our

laboratories have shown that the prevalence of reactive STS in sera and CSF in TSP patients had fallen to 28 and 3%, respectively, making a syphilitic etiology unlikely. We found that the high reactive serological rates previously reported could have been the result of childhood yaws, a high incidence of biological false positives, and concurrent syphilis *(46)*.

Evidence implicating HTLV-I was provided by Gessain et al. *(8)*. This was confirmed in Jamaica, Colombia, Trinidad and Tobago, the Seychelles Islands, and Japan *(9,22,47)*. The association was supported by the demonstration of intrathecal synthesis of antibody against HTLV-I oligoclonal immunoglobulin bands in the CSF reacting with viral antigens, identification of HTLV-I nucleic acid sequences in blood, CSF and CNS tissue detection of viral antigens in CSF, and culture of the virus *(48)*.

HTLV-I has several known modes of transmission. Mother-to-child transmission, sexual intercourse, blood transfusion, and reuse of contaminated needles are the main routes by which the virus is spread. Nevertheless, the pathogenesis of central nervous system lesions remains unclear. It is possible that the disease process is initiated by chronic restricted infection of the nervous system with virus, but that tissue injury develops as a consequence of host responses. An autoimmune phenomenon via cytotoxic T-lymphocyte against HTLV-I-infected cell and direct HTLV-I neurotoxicity, as shown in HIV, have also been suggested *(30,31,49,50)*. In addition, immunogenetic factors linked to HLA haplotypes may determine the genetic and immunological background against which ATL and HAM/TSP develop *(51)*.

Treatment

Early referral to physiotherapists for graded exercises while patients are still ambulant will prevent contractures. In more advanced cases, spasticity may be relieved by drugs, such as lioresal, diazepam, or dantrolene. Danazol, an attenuated androgen, reduces spasticity, and also improves urinary incontinence *(52)*. The measures employed in the care of the skin, bladder, and rectum in paraplegic patients apply.

The use of immunomodulators and antiviral agents are therapeutic strategies based on the presumed autoimmune nature of the disease. Corticosteroids, plasmaphoresis, and α-interferon therapy seem to exert only a marginal short-term benefit.

The rationale for the use of antiretroviral therapy is based on its ability to block the replication of HTLV-I, but the results of therapy with zidovudine have not been encouraging *(53,54)*. Therapeutic trials using antibodies against the α-chain of the interleukin-2 receptor (anti-TAC) are being evaluated *(29)*.

Concluding Remarks

Immunological and molecular biological procedures now in use have enhanced the study of this HTLV-I-associated disease. As the mechanisms whereby HTLV-I causes TSP are slowly resolved, it is likely that new insights into the pathogenesis of other similar diseases will be acquired.

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