Human T-cell Leukaemia/Lymphoma Virus Type-1 Associated Myeloneuropathies – A Caribbean Perspective

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ABSTRACT

This review follows the contributions of researchers from the Caribbean in improving the understanding of the disease mechanisms, clinical features and aetiology of neurological syndromes manifesting as diseases of the spinal cord and peripheral nerves. The evolution from the initial descriptions of neuropathies of presumed nutritional aetiology and later the recognition of two distinct subgroups, an ataxic neuropathy and a spastic myelopathy, are highlighted. The link between the natural history of human T-cell leukaemia/lymphoma virus type-1 (HTLV-1) infection and the immunopathogenesis of tropical spastic paraparesis is explored.

Keywords: HTLV-1, myelopathy, neuropathy

Mieloneuropatías Asociadas con el Virus Humano de Células Tipo 1 de la Leucemia/Linfoma – una Perspectiva Caribeña

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RESUMEN

Este examen sigue las contribuciones de investigadores del Caribe encaminadas a mejorar la comprensión de los mecanismos de la enfermedad, rasgos clínicos y la etiología de los síndromes neurológicos que se manifiestan como enfermedades de la médula espinal y los nervios periféricos. El trabajo resalta la evolución de las descripciones iniciales de las neuropatías de etiología nutricional presuntiva y el posterior reconocimiento de dos subgrupos claramente distintos: la neuropatía atáxica, y la mielopatía espástica. Se explora el vínculo entre la historia natural de la infección por el virus humano de células tipo 1 (HTLV-1) en la leucemia/linfoma, y la inmunopatogénesis de la paraparesia espástica tropical.

Palabras claves: HTLV-1, mielopatía, neuropatía

INTRODUCTION

Neurological syndromes manifesting as acute and chronic disorders involving the spinal cord and peripheral nerves, classified as myeloneuropathies, have been reported from the West Indies since the turn of the 20th century. Since these original descriptions, many advances have been made in classifying these diseases according to disease mechanisms, clinical features and aetiology. This review highlights research linking human T-cell leukaemia/lymphoma virus type-1 (HTLV-1) infection to chronic neurological disorders commonly seen in the Caribbean and follows the evolution of understanding of these conditions from the earliest reports to recent contributions made by Caribbean researchers.

Human T-cell leukaemia/lymphoma virus type-1 was the first oncogenic human retrovirus to be identified and isolated (1, 2). Human T-cell leukaemia/lymphoma virus type-1 infection has a worldwide distribution and is endemic in the Caribbean, southwestern Japan, Melanesia, Australia, Sub-Saharan Africa, South America and North East Iran. Within endemic areas, HTLV-1 seroprevalence can vary between 1% and 20% in adults. The overall prevalence of severe HTLV-1-associated disease is 2 to 8% among the estimated 10–20 million HTLV-1-infected persons worldwide. Human T-cell leukaemia/lymphoma virus type-1 is now associated with numerous clinical conditions, including adult T-cell leukaemia (ATL), HTLV-1 associated myelopathy/tropical spastic

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paraparesis (HAM/TSP), paediatric infectious dermatitis, arthritis/arthropathy and polymyositis.

HTLV-1 associated myelopathy/tropical spastic paraparesis is a chronic myelopathy, usually slowly progressive or in some cases, static after initial progression. It is characterized by progressive lower-limb weakness more marked proximally, spasticity, hyperreflexia, clonus, extensor plantar responses and less prominent symptoms of paraesthesiae and loss of vibratory sensation. The initial symptoms are typically back pain, gait disturbance, increased urinary frequency (detrusor overactivity is an early feature), constipation and sexual dysfunction which are usually insidious over several weeks. The clinical features represent preferential thoracic cord involvement. Upper limb strength is typically normal with hyperreflexia being the only significant finding on upper limb examination. Less common features include cerebellar signs, depressed ankle reflexes and optic neuritis. Cognitive function is not affected. Magnetic resonance imaging of the spinal cord may reveal swelling or atrophy usually localized to the thoracic region, while imaging of the brain shows non-specific subcortical and periventricular white-matter lesions.

The Early Years
Long before HTLV-1 was discovered, neurologists had reported the frequent occurrence of myelopathies of unknown origin in tropical areas. Drs Henry Harold Scott and Henry Strachan gave the first descriptions of a chronic myeloneuropathy known to occur commonly in tropical areas (3–5). In 1888, Henry Strachan, then a senior medical officer in Jamaica, published findings of Jamaican sugar cane workers with "multiple peripheral neuritis" which he thought was due to malaria. He described patients with limb weakness, claw hands and an ataxic gait. Hyperpigmentation of the palms and soles were accompanied by sensory symptoms including severe burning pain of the hands and feet and impaired sensation to touch and temperature. Impaired vision and hearing was also found. Strachan, in commenting on the ataxic gait, noted that "it is only when the muscles of the lower limbs are much wasted that the patient cannot stand upright alone, with closed eyes or turn sharply in his walk" and that "coordination of his muscle actions appears to be good in proportion to the degree of perfection of muscle nutrition, the action of the muscles being short and jerky when wasting is present and the case an advanced one". He also noted desquamation of the edges of the eyelids and margins of the lips and nostrils in some patients as well as facial nerve palsies (3, 4). Miller Fisher would later describe an ataxic neuropathy with auditory or visual loss similar to Strachan's patients among malnourished Canadian prisoners of war in Japanese concentration camps during the Second World War and named the condition Strachan's disease (6).

In 1918, Sir Henry Harold Scott, a bacteriologist, described a "syndrome of central neuritis" in 21 Jamaican sugar cane workers from a sugarcane plantation near St Jago de la Vega or Santiago de la Vega, later called Spanish Town, the former capital of Jamaica (5). It was known locally as "Spanish Town disease". Scott divided his patients into those with "intestinal symptoms" (constipation followed by diarrhoea) and those with "nervous symptoms". The "nervous" cases had decreased vision, impaired hearing and a gait described as "variable, at times inclined to a spastic condition, the feet as it were sticking to the ground and shuffling; in many it was ataxic, the feet being thrown about wildly; in none was it really tabetic; in some again, it was a delicate half-shuffling, half stumbling gait, while in many it could not be tested owing to the patient being unable to stand, much less walk". Autopsy in two patients revealed demyelination of the optic and acoustic nerves, the posterior columns, posterior spinal nerve roots and the spinocerebellar tracts with sparing of the lateral corticospinal tracts. Scott considered a microbial origin "highly improbable" and believed the "central neuritis" was due to an "intoxication" rather than a nutritional deficiency.

Patients with similar clinical features were increasingly reported in Guyana, South Africa, Nigeria, Senegal, Singapore, India, and Trinidad and Tobago and Jamaica in the Caribbean (7–13). Eric Kennedy Cruickshank came to Jamaica in 1950 at age 35 years to be the foundation Professor of Medicine in the newly established University College of the West Indies (UCWI), and would eventually serve twenty-three years at what would be the Mona Campus of The University of the West Indies. In 1946, he had published an account of 500 cases of "painful feet" he observed while a Japanese prisoner-of-war (POW) in the Changi Camp, Singapore (12). Clinical features of stomatitis, impaired vision, painful feet and hyperreflexia (in 23%) were attributed to a peripheral neuropathy due to riboflavin and nicotinic acid deficiency. Interestingly, 23% of the patients demonstrated "exaggerated" reflexes mostly in severe cases, "not accompanied by any other signs" of corticospinal tract involvement. He noted that when the incidence of painful feet was at its height, there were cases of "frank spastic paraplegia and a few of quadriplegia of obscure aetiology".

In 1956, Cruickshank provided the first detailed description of a "neuropathic syndrome of uncertain origin" in 100 Jamaican adults investigated at the University College Hospital of the West Indies over a 3½-year period (13). Montgomery and Cruickshank, in 1964, gave a more detailed description of 206 Jamaican adults with what was then termed "Jamaican neuropathy" (15). They described patients in the second to sixth decade of life with leg weakness of usually gradual onset and progressive over weeks or months, significant lower limb but mild upper limb spasticity, exaggerated limb reflexes, vague limb and back pain, numbness or burning of the feet, and frequent bladder symptoms (hesitancy, urgency and incontinence). Posterior column involvement affected about half the cases, with pain and discriminative touch occurring much less frequently. There was "no mental impairment". The syndrome had five main

elements occurring in different combinations – damage to the corticospinal tracts and posterior columns of the spinal cord, selective lower motor neuron lesions, retrobulbar optic neuropathy and eighth nerve deafness.

Montgomery and Cruickshank were the first to divide the patients into two distinct clinical groups: (a) an ataxic group of 25 cases on a background of poor nutrition, presenting predominantly with sensory ataxia with a high incidence of optic atrophy and eighth nerve deafness, but only slight evidence of pyramidal tract damage and (b) 181 cases presenting predominantly as a spastic myelopathy but with a relatively low incidence of optic atrophy and eighth nerve deafness (15). The ataxic cases (tropical ataxic neuropathy – TAN) comprised only 12% of cases as compared to 33% in Cruickshank's earlier review of 100 cases in 1956, and are now practically non-existent in Jamaica (16). The aetiology of the spastic cases was the subject of considerable debate, with nutritional deficiency (8, 11), toxins (8), treponemal agents (17, 18), parasites or a "slow virus" being suggested as causes for similar cases in South India (19).

In a detailed description in 1964, Montgomery commented that the findings of 10 autopsy cases provided a "clear pathological explanation for the clinical syndromes encountered". The overall impression was of an inflammatory disease affecting principally the cord, and the brain to a considerably lesser extent. "In the more active cases of relatively short duration a striking feature is the cellular exudate . . . composed mostly of lymphocytes with a smattering of plasma cells and macrophages. In the cord, there is a distinct suggestion that the cellular response is greatest in the region of the pial vessels and that it spreads centripetally into the cord *via* the sheaths of the penetrating vessel. There appears to be a real increase in the smaller vessels of the cord substance . . . . The meningeal thickening and peripheral fibroglial adhesions account for the shrinkage and distortion of the cord . . . . Nerve roots, especially the posterior, are also involved in the inflammatory process. Endarteritis and thrombosis are not features of the disease. In more long-standing cases . . . the cellular response is less and may be virtually absent . . . myelin loss . . . has a peripheral distribution reminiscent of the so-called 'syphilitic halo'. The lateral pyramidal tracts and the posterior column of Goll are particularly and more severely affected. The spinocerebellar tracts are often, and the spinothalamic tracts occasionally . . . involved. . . . Nerve roots, especially the posterior roots, frequently show some loss of myelin, and there are similar findings in the optic and auditory nerves in those cases with relevant symptoms . . . . There is little clinical or histological evidence of damage to the unmyelinated peripherally placed fibres carrying pain and temperature sensation". The brain "was essentially normal in the gross" but revealed mild, patchy, mostly basal leptomeningeal thickening (15).

Cruickshank in his original description in 1956, noted that the syndrome is one in which the main brunt of the damage is borne by the corticospinal tracts. Noting that "nystagmus, dysarthria and intention tremor do not occur", he believed that the syndrome "seems most unlikely" to be multiple sclerosis "as it differs from classical multiple sclerosis in too many ways" (13, 14). In addition, he noted that though 30% of blood samples were VDRL positive, this fell "within the range of 12–44% positive tests in the different parishes in the island"; only three patients had dilution greater than 1:4 and all cerebrospinal fluid (CSF) samples of 93 patients were negative. He thought "it is extremely unlikely that syphilis or yaws is, if at all, more than a minor contributory factor".

With the background of his experiences with nutritional deficiencies associated with myeloneuropathies while himself a prisoner-of-war, Cruickshank commented in his "Neurological Retrospect of Jamaica" in 1975 that "it is highly likely that poor nutrition is a major contributing factor in the ataxic group". He noted, however, that most of the patients with the spastic syndrome were in good physical condition and "had no overt signs of any recognized deficiency syndrome". He believed that the pathological appearances were of "low-grade inflammation" with "some endarteritis" and "compatible with an autoimmune process" (20, 21).

HTLV-1 Link

Following on the use of the term "tropical spastic paraplegia" by Mani for cases in South India, Roman, in 1985, was the first to use the term "tropical spastic paraparesis" (TSP) to identify fifty cases in Tumaco, Columbia (19, 22). A link between TSP and HTLV-1 was established when Gessain demonstrated that blood samples from 10 of 17 (58.8%) TSP patients from Martinique had antibodies to HTLV-1 compared with 4% of controls (23). A few months later in November 1985, Rodgers-Johnson confirmed this association and was in addition the first to report the presence of HTLV-1 antibodies in CSF of TSP patients from Jamaica and Columbia (24). In 1986, Japanese researchers independently published the association of HTLV-1 with a condition of similar features to TSP which they termed HTLV-I associated myelopathy [HAM] (25). Two years later, the first electron microscopy report demonstrating viral-like particles morphologically identical to HTLV-1 in spinal cord cells in a TSP patient from Jamaica was published (26).

A consensus panel at the 1988 World Health Organization (WHO) HTLV-1 meeting in Kagoshima, Japan, agreed that TSP and HAM were identical conditions and that the syndrome should be designated HAM/TSP (27, 28). With the discovery of abnormal polylobated lymphocytes ("flower cells") in the peripheral blood of HAM/TSP patients by Morgan *et al* (29) and the reporting of HTLV-1 antibodies in Jamaican patients with adult polymyositis (30, 31), these features were included in the WHO guidelines for the diagnosis of HAM/TSP (Table).

Collaborative projects among researchers at the Trinidad and Tobago, Barbados and Jamaica campuses of

The University of the West Indies and researchers in Japan, South America and the United States of America led to rapid ex-pansion of understanding of HTLV-1 immunopathology and its association with ATL and HAM/TSP, TAN and polymyositis.

Human T-cell leukaemia/lymphoma virus type-1 epidemiology is one of geographic clustering with seroprevalence ranging from 2–6% in the Caribbean to 20% in South West Japan. The lifetime risk of developing HAM/TSP varies among different ethnic groups and ranges between 0.23% in Japan and 2% in Jamaica and Trinidad and Tobago. Popu-lation based data from Jamaica and Trinidad and Tobago suggest that HTLV-1 seroprevalence increases with age, with the mean age at onset of HAM/TSP being about 40 years, with women affected 2–3 times more often than men. Sexual intercourse confers a greater risk of transmission from an infected man than from an infected woman (32–38). HTLV-1 associated myelopathy/tropical spastic paraparesis may have an onset of weeks to years after transfusion-acquired HTLV-1 infection (39). Human T-cell leukaemia/lymphoma virus type-1 can also be transmitted through breastfeeding, from mother to child, and intravenous drug use.

Immunopathology

The mechanism by which HTLV-1 induces neurological disease is unknown. Human T-cell leukaemia/lymphoma virus type-1 is a single-stranded RNA retrovirus with reverse transcriptase activity leading to DNA transcription and inte-gration into the host genome (provirus). It is a complex virus having regions encoding not only the typical viral proteins encoded by gag, pol, and env but also other gene products including Tax protein. Tax is involved in stimulating viral gene expression and host cell proliferation and acts as an activator of inflammatory cytokines and their receptors.

The prevalence of HAM/TSP rises sharply once the proviral load (the amount of HTLV-I genome integrated into the DNA of host lymphocytes) exceeds 1% of peripheral blood mononuclear cells (PBMCs). Cross-sectional studies in a blood transfusion cohort in Jamaica show higher levels of HTLV-I proviral DNA in HAM/TSP patients than in asymptomatic HTLV-1 carriers. Proviral DNA levels in HTLV-1 infection indicate the pattern of an acute viral infection followed by a chronic persistent infection. Proviral DNA levels are high early in the course of infection then fall rapidly to a steady state within the first 90 days of infection. Proviral DNA levels then are highly correlated with HTLV-1 antibody titres (40). Proviral DNA levels are higher in asymptomatic HTLV-I carriers related to HAM/TSP patients than in those of unrelated asymptomatic carriers (41, 42). In-terestingly, despite higher HTLV-1 antibody titres and greater frequency of anti-Tax antibody in Jamaican as compared to Japanese subjects, the proviral DNA level was similar be-tween the two groups. The correlation between antibody titre and proviral load was greater among Jamaican subjects (43).

Many studies have demonstrated that both humoral and cellular immune responses are increased in HAM/TSP pa-tients. In HTLV-1 infection, HAM/TSP patients generally have a higher anti-HTLV-1 antibody (Ab) titre than asympto-matic carriers (ACs) with a similar HTLV-1 proviral load (40, 41). Both $CD4^+$ (mostly) and $CD8^+$ T cells are infected with HTLV-1 *in vivo*. $CD4^+$ infected cells and HTLV-1 specific $CD8^+$ cytotoxic T lymphocytes (CTLs) produce and induce release of cytokines which can damage CNS tissue. It is not known whether the CTLs act to promote inflammation and demyelination or are protective and lower the proviral load and risk for HAM/TSP. It is also still controversial whether the pathogenesis of HAM/TSP involves molecular mimicry between HTLV-1 and autoantigens in the CNS in an auto-immune mechanism similar to that for inflammatory diseases such as Guillain-Barre syndrome (43–49).

Histopathological findings in Japanese HAM/TSP patients have demonstrated findings similar to Montgomery and Cruickshank's descriptions of "Jamaican neuropathy" (49). The affected site was predominantly the thoracic spinal cord with the most severe damage in the lateral corticospinal tracts of the middle to lower thoracic regions. The so-called 'watershed' zones of the spinal cord were mainly affected. Perivascular and parenchymal T-cell ($CD4^+$ and $CD8^+$ T-cells) infiltration, macrophages, astrocytic gliosis and wide-spread loss of myelin and axons were found. Similar types of infiltrating cells were seen in the brain (deep white matter and in the marginal area of the cortex and white matter). HTLV-1 associated myelopathy/tropical spastic paraparesis patients with short duration (2.5 to 4.5 years) of illness showed an even distribution of $CD4^+$ cells, $CD8^+$ cells and macrophages. Patients with long duration (8 to 10 years) disease showed predominance of $CD8^+$ cells over $CD4^+$ cells and downregulated proinflammatory cytokine expression. Some reports show HTLV-I tax RNA localized within the neural tissue itself (astrocytes) while others localize HTLV-I tax RNA to perivascular infiltrating $CD4^+$ cells (49– 53). The frequency of HTLV-1 associated peripheral neuropathy ranges from 0–30% with a sensory-motor polyneuropathy being most common. HTLV-1 associated myelopathy/tropi-cal spastic paraparesis patients with sensory disturbance showed features of demyelination/remyelination, axonal degeneration/regeneration and perineurial fibrosis (54–56).

The Future

The natural history of HTLV-1 infection and the mechanism by which it causes neurological disease is still not well un-derstood. It is not known why the majority of HTLV-1 sero-positive individuals remain asymptomatic with only about 2% to 3% developing ATL and 0.3% to 2% developing HAM/TSP at usually late onset, adult age (32, 33). The annual incidence of HAM/TSP is reportedly higher among Jamaican individuals than among Japanese individuals. The explanation for the well-known geographic clustering of HTLV-1 prevalence is still unknown. The search for bio-

markers which could potentially identify carriers at high risk for progression to disease is ongoing. The HTLV-1 proviral load which has been viewed as important in the pathogenesis of HAM/TSP is present in a very wide range both in HAM/TSP patients and in asymptomatic HTLV-1 carriers and levels vary with race, gender and presence of co-morbid illnesses (40, 41).

Adult T-cell leukaemia and HAM/TSP are generally mutually exclusive conditions with only a few individual patients having both disorders being reported. Why does one group develop a neurological disease and another a leukaemia and then only usually after decades of an infection acquired in infancy? Current immunopathological mechanisms do not explain why in HAM/TSP the spinal cord is preferentially affected, in particular the thoracic cord. The list of other possible (some with stronger evidence than others) associations with HTLV-1 infection now includes *Strongyloides stercoralis* hyperinfection, pulmonary lymphocytic alveolitis, uveitis, keratoconjunctivitis sicca, Sjogren syndrome, thyroiditis, necrotizing vasculitis, Graves' disease, Behçet's disease and pseudohypoparathyroidism, polyneuropathies, Hansen's disease, tuberculosis and HTLV-1-associated chronic renal failure (57–64). The growing list probably reflects the role of HTLV-1 as a cofactor rather than a primary agent influencing host immune function.

Montgomery and Cruickshank in their initial reports on "Jamaican neuropathy" advanced the recognition and classification of chronic myeloneuropathies. Tropical ataxic neuropathy, thought to be the result of nutritional (vitamin) deficiencies and not linked to HTLV-1, is now, at least in Jamaica, practically non-existent (16). They described, as well, much more frequently occurring cases of a paraparesis or spastic paraplegia having pathology preferentially localized to the lateral and (less so) posterior columns of the thoracic cord but with lesser degrees of involvement of brain, cranial nerve and peripheral nerve roots. They highlighted the striking lymphocytic cellular infiltrate in cases with active but shorter duration disease and the "absent cellular response" when the clinical picture became static. Chronic inflammation resulted in gliosis and fibrosis of the spinal cord.

There is no effective specific treatment for HAM/TSP and management is directed at addressing complications such as spasticity, contractures and recurrent urinary tract, lung or skin infections. About 40% of HAM/TSP patients become wheelchair bound as a result of their chronic disease. Modern analytical approaches have not disproved Cruickshank's initial perspectives on the likely immunopathology of the disease which later would be designated as HAM/TSP. HTLV-1 associated myelopathy/tropical spastic paraparesis patients account for only a minority of HTLV-1 infected persons but represent patients who carry a high morbidity and (with ATL) mortality burden. Identification and management of additional triggers or cofactors, at an early stage, for what is a "complex autoimmune reaction within the nervous

Table: World Health Organization guidelines for diagnosis of HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP)

Clinical	
Age and gender	Sporadic and adult; female predominant
Onset	Usually insidious
Main neurological manifestations	Chronic spastic paraparesis, slow progression, sometimes static after initial progression. Weakness of the lower limbs, especially proximally. Bladder disturbance is an early feature; constipation occurs later; impotence and decreased libido. Sensory symptoms are more prominent than objective physical signs. Impaired vibration sense. Low lumbar pain with radiation to legs. Hyperreflexia of lower limbs often with clonus and Babinski's sign. Hyperreflexia of upper limbs with positive Hoffmann's and Tromner's signs; exaggerated jaw jerk
Less frequent neurological signs	Cerebellar signs, optic atrophy, deafness, nystagmus, cranial nerve deficits, hand tremor, absent or depressed ankle jerk
Other neurological manifestations	Muscular atrophy, fasciculation, polymyositis, peripheral neuropathy, polyradiculopathy, cranial neuropathy, meningitis, encephalopathy
Systemic non-neurological manifestations	Pulmonary alveolitis, uveitis, Sjogren's syndrome, arthropathy,vasculitis, icthyosis, cryoglobulinaemia, monoclonal gammopathy, adult T-cell leukaemia/lymphoma
Laboratory	Blood – HTLV-1 antibodies or antigens, lobulated lymphocytes, viral isolation when possible. CSF – HTLV-1 antibodies or antigens, lobulated lymphocytes, mild to moderate increase of protein, viral isolation when possible

system, of sensitized individuals" (21) will probably help to reduce much of the long-term sequelae of HAM/TSP.

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