Tropical Spastic Paraparesis and Polymyositis – A Still Unfolding Story

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INTRODUCTION

The description of a neurological entity termed "Jamaican peripheral neuritis" by Strachan (1) in 1888 marked the beginning of more than a century of systematic clinical and scientific investigation into an endemic neurological syndrome that is now recognize as tropical spastic paraparesis. It required the work of Scott (2) in 1918 and finally Cruickshank (3) in 1956 to better clinically characterize this entity. Cruickshank identified that "a neuropathic syndrome with features which do not conform to any recognized pattern has been known to occur in the West Indies for some years". The clinical distinction between a predominantly spastic and an ataxic form was first delineated by Montgomery *et al* (4) in 1964 with the observation that the proportion of ataxic patients was steadily declining over time.

The clinical features of tropical ataxic neuropathy (TAN) were described in detail (3–4). Symptoms were primarily of failing vision, deafness and weak legs. Clinical findings were of optic neuropathy, nerve deafness and prominent posterior column signs with lesser pyramidal signs and mild bilateral peroneal wasting. Cases examined at post mortem demonstrated symmetrical demyelination of posterior columns especially *fasciculus gracilis* and optic nerves, particularly the papillomacular fibres. Significantly, there were no inflammatory changes with occasional mild patchy demyelination of peripheral nerves.

In comparison, the clinical features of the spastic group were quite different with pyramidal findings (100%), bladder symptoms (71%), constipation (65%) and posterior column findings(56%) dominating the clinical picture. Optic atrophy, nerve deafness and wasting were seen in less than 15% of patients (4–5). Pathologically, patchy thickening and opacity of the meninges of the base of brain and especially the spinal cord was observed. Microscopically, a mainly perivascular lymphocytic cellular infiltrate with parenchymal small vessel proliferation and reactive gliosis in damaged neuronal tissue was noted. Demyelination was most prominent in lateral and posterior columns and could extend into the posterior and anterior nerve roots.

Aetiology

From an aetiological perspective, it had been recognized that TAN/TSP was more common in lower socio-economic groups and that these disorders were more prevalent in rural regions than the coastal populated zones where syphilis was more prevalent (5). This epidemiologic observation also reduced the likelihood that the Jamaican myeloneuropathies were due to *Treponema pallidum* despite the high prevalence of positive serological tests for syphilis in Cruickshank's series (4). Positive serology was also postulated to be due to yaws (*Treponema pertenue*) but there was no epidemiological or clinical evidence that yaws caused neurological disease (5).

The possibility of dietary deficiencies of the B vitamins or dietary excesses (cyanogenetic glucosides in cassava) were considered (5) but no definite evidence in support of these theories was ever found.

And so the matter stayed until a chance observation in 1985 by Gessain *et al* demonstrated that 10/17 TSP patients being used as controls for another study demonstrated positive ELISA antibody tests for the HTLV-1 virus (6). The significance of this finding was rapidly confirmed by the demonstration of a high prevalence of HTLV-1 antibodies in Jamaica in serum (67%) and cerebrospinal fluid (CSF) (55%) and both (77%) (7). Abnormal polylobated lymphocyes were observed by Morgan *et al* in peripheral blood in TSP patients (8), a finding subsequently included in the 1990 WHO criteria for the diagnosis of HTLV-1 associated myelopathy (HAM)-Tropical Spastic Paraparesis (HAM-TSP).

Differential Diagnosis and Investigation

In a review article, Morgan *et al* stated that the emergence of TSP as a 'pure' clinical syndrome owed much to improvement in nutrition and also to decline in post-primary syphilis, thereby reducing the likelihood of diagnostic confusion although the differential diagnosis was wide (9). In this regard, the differential diagnosis of a non-compressive myelopathy includes the following (non-exhaustive) considerations:

* Syphilis
* Diabetes mellitus
* Transverse myelitis
* Human Immunodeficiency Virus (HIV) myelopathy
* Motor neurone disease – especially primary lateral sclerosis
* Familial spastic paraplegia
* Adrenoleucodystrophies
* Multiple sclerosis (MS)
* Lupus erythematosus involving the spinal cord
* Midline parasagittal mass lesions
* Spinal AVM

Patients therefore must be properly investigated, firstly to exclude causes of compressive myelopathy (by myelography in the past and nowadays by MRI of the cervico-thoracic cord) as well as to confirm the diagnosis of TSP by exclusion of the other causes of non-compressive myelopathy. The diagnosis of TSP will be suggested in the context of the appropriate clinical history and physical findings with a positive HTLV-1 antibody test (10).

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This antibody test demonstrates the presence of IgG antibodies to HTLV-1 by an enzyme-linked immunosorbent assay (ELISA) technique employing disrupted virions produced by HTLV-1 producing cell lines, such as the HUT 102 cell line, as antigen. This ELISA tests is also utilized on CSF. Confirmation by Western Blot may be performed. In this test, nitrocellulose strips containing HTLV-1-specific proteins (fractionated according to molecular weight) are washed with phosphate-buffered saline (PBS) and Tween-20, incubated with PBS containing heat-inactivated normal goat serum and nonfat dry milk to minimize nonspecific immunoglobulin binding and then reacted with serum or CSF specimens in dilution and washed again. Human immunoglobulins to HTLV-1 proteins are visualized using biotin-labelled goat antihuman immunoglobulin, avidin-horseradish peroxidase conjugate and 4-chloro-1-napthol solution as developer. HTLV-1 proteins detected include the group antigen (gag) – encoded proteins p19, p24 and p53, the envelope-encoded glycoproteins (gp) gp61 and gp46, and p42 protein encoded in part in the long open reading frame portion. Other supplementary findings often seen include a positive VDRL serology, the detection of polylobated lymphocytes and abnormalities of CSF.

An increasingly important cause of non-compressive myelopathy in the Caribbean is multiple sclerosis (MS), now a diagnosis more commonly made with the improved availability of appropriate investigative techniques. However, caution is required. In an area of high HTLV-1 seroprevalence, the diagnosis of MS particularly of the primary progressive type may be missed if the patient happens to be HTLV-1 seropositive. The diagnosis of MS in this context can be challenging. This issue has been considered by many workers (9, 11) with additional difficulties noted in relation to spinal cord and brain MRI findings in TSP which may mimic MS (12). Even further, the diagnosis of HTLV-1 negative TSP may be made instead of MS or *vice versa.* There remains no MRI features specific to TSP. Therefore, careful attention to history and physical examination along with appropriate investigations including MRI, CSF and evoked potentials (EPs), where appropriate, will help to reduce diagnostic confusion.

In this regard, electrophysiological investigations have been used in the further investigation of patients with TSP. In the first electrophysiological study to be published on TSP and TAN, the findings were essentially of normal peripheral nerve conduction in TSP. This pointed further to the central involvement of the disease. In the single TAN case studied, this revealed features of a peripheral sensorimotor axonal neuropathy (13).

To prove that central pathways were affected neurophysiologically, and not peripheral pathways, patients with TSP were examined by trans-cranial magnetic stimulation (TCMS). In this study, significant delay in central conduction times were observed, with maximal delay noted in the thoraco-lumbar segment with no evidence of peripheral nerve involvement, confirming the central site of dysfunction in this disease (14).

Pathogenesis

It was therefore clear that TSP was a disorder affecting the central nervous system (CNS), in particular the thoracic cord, and that it was associated aetiologically with the HTLV-1 virus. However, the mechanism by which this virus produced neurological disease required elucidation. In a paper published in 1988, 47 patients with TSP were examined for the presence of antibodies to the virus in serum and CSF. Positive tests were noted in 82% of serum and 77% of CSF samples. Importantly, despite this being a cell-associated retrovirus, viral particles morphologically similar to the HTLV-1 virus were isolated from the CSF study of only one patient (15).

One of the first issues that required clarification was that of the relevance of positive antibody tests for treponemes. It had been reported that antibodies to *B Burgdorferi*, the causative agent of Lyme disease were more prevalent in TSP patients (15) and it was speculated that TSP might be a neurological manifestation of Lyme disease. However Morgan *et al* demonstrated a prevalence of 12.5% positive antibody titres to *B Burgdorferi* in TSP patients *versus* 10% in controls. In addition, none of the sera was positive by Western Blot studies (16).

Furthermore, in regard to the possibility of *T pallidum* infection, a positive serological test for syphilis (STS) was observed in 35% of TSP patients *versus* 14.5% of controls. Also, the frequency of a positive STS was higher in the > 40 years age group (16).

The aetiology of a positive STS was felt to be multifactorial and not directly related to syphilitic infection. The higher prevalence of STS in the older group suggested the possibility of yaws as a cause of the positive serology. Yaws had been eradicated in 1960 and has not been associated as a cause of CNS disease (16). In regard to the positive STS, the data of a further study (17) in patients with HAM-TSP suggest that IgA anticardiolipin (aCL) antiphospholipids are frequent and are associated with HTLV-1 infection and that the positive STSs are false positives rather than true-positives. Yet, the observation (12) that patients with TSP were significantly older than Afro-Caribbean patients with MS and had a much higher seroprevalence of STS suggests that exposure to treponeme either syphilis or yaws was the likely explanation for the positive STS, as both of these conditions were either now eradicated (yaws) or much less prevalent suggesting that the TSP patients did contract yaws at a time when it was highly endemic but that the younger MS patients did not have the chance for exposure.

The possibility of humoral autoimmunity in the possible pathogenesis of TSP was then examined (18). In 76 TSP patients compared to 60 asymptomatic HTLV-1 sero-

positive carriers and 100 seronegative healthy blood donors, high prevalences of autoantibodies (51%), reactive serological tests for syphilis (30%), hypergammaglobulinemia (90%) and complement immune fixing complexes (58%) were increased when compared to seropositive carriers and much more so than healthy blood donors. These findings suggested that enhanced immune activation might generate auto-antibodies with specificity for antigens of the spinal cord.

The immune system is however very complex and other mechanisms have been considered. The virus itself may contribute to disease.

HTLV-1 has a gene pX with four open reading frames of which Tax and Rex (the transactivating and regulating genes of the X region) have been well characterized. The protein product of the Tax gene is important not only for activating viral transcription but also because it is able to transactivate a large number of human genes including MHC class I and many cytokines, clearly therefore increasing the likelihood of pathogenicity. Possible immunopathogenetic mechanisms include:

* Direct toxicity – virus infects glial cells which are lysed by cytotoxic T lymphocytes (Tc)
* Autoimmunity theory – $CD4^+$ lymphocytes mistake a self antigen expressed by glial cells as foreign and release cytokines.
* Innocent bystander theory
* Circulating anti-Tax-specific Tc migrate through spinal cord or cerebrum.
* Encounter HTLV-I infected $CD4^+$ lymphocyte.
* Cytokines directed against infected lymphocyte cause "collateral" damage to glial cells.

Irrespective of the mechanism, antigen still has to be presented to the immune system to promote any of the immune responses listed above. One of the most potent antigen presenting systems in the immune system is the dendritic cell (DC). It had been previously shown that DC obtained from HTLV-1 positive TSP patients when co-cultured with autologous T lymphocytes produced a markedly enhanced mixed lymphocyte reaction (MLR). The requirement for DC to be infected to promote this enhanced MLR has been confirmed (19). It is speculated that infection of DC by HTLV-1 may be an initial step in altering the immune system in seronegative patients, and that persistent T cell stimulation in those with genetic susceptibility may underlie the production of neurological disease.

T cells remain the effectors of the immune system in viral diseases and as such in collaborative work with the NIH (20) it was demonstrated that fully 10% of circulating $CD8^+$ T cells were Tax11-19 peptide reactive.

Other Effects of HTLV-1 infection

The health effects of apparently asymptomatic HTLV-1 infection were examined in a study of 201 members of the Jamaican cohort. Tropical spastic paraparesis/HTLV-1 associated myelopathy was in fact diagnosed in 0.5% of these patients and subtle effects on body mass and blood eosinophil counts were noted, indicating that even apparently asymptomatic infection can produce clinical effects when these individuals are carefully examined (21). The possible prevalence of HTLV-1 in other chronic neurological diseases was therefore investigated. No association with any other chronic disease was noted with the exception of seropositivity in all seven cases of polymyositis (22).

This led to further study. In a paper by Morgan *et al* (23) 6 patients were studied, 4 of whom were HTLV-1 positive. In a review paper in 2001, Gilbert *et al* (24) indicated that HTLV-1 seropositive patients tended to follow a more protracted course with less systemic effects and a poorer response to corticosteroid therapy, underscoring the importance of determining antibody status in these patients.

A critical question remains – what is it that makes only a small percentage (1–2%) of patients go on to develop neurological disease? Clearly there are host and viral factors and the complex interplay between the two in those with a genetic proclivity. HLA allele typing may eventually indicate more clearly those at most risk. The GLUT-I receptor as putative HTLV-1 receptor if confirmed may help to unravel the host factors responsible for disease genesis (25).

Virus-host related factors include the following:

* Immunological abnormalities arising from a high proviral load
* Heightened transmigrating activity of HTLV-I infected $CD4^+$ T lymphocytes
* Bystander damage to CNS parenchymal cells by $CD8^+$ HTLV-1-specific Tc against infected lymphocytes
* High pro-inflammatory cytokine concentrations in CSF (INF, TNF) from $CD8^+$ HTLV-1-specific Tc

Of these, an area of current active interest is that of proviral load. This measure of viral DNA integrated into the host genome in peripheral lymphocytes may be of important prognostic information. Its relationship to antibody concentrations was studied with an inverse relationship noted over time (26) but with levels consistently higher in TSP patients than the asymptomatic carrier. A change in these levels in the carrier may therefore herald the possibility of transformation to disease.

From a clinical perspective, it is also important to know what behavioural cofactors may predispose to developing the disease. Early age of initial heterosexual contact and having more than five lifetime sexual contacts increased the risk of developing TSP-HAM in HTLV-1 positive individuals (27) These are important issues in regard to counselling the asymptomatic patient.

A recent interesting finding of Tax gene products in CSF of two HTLV-1 seronegative TSP patients in Chile (28) may indicate that either a closely related virus is responsible

for this entity or that the HTLV-1 virus may occasionally produce CNS disease with little humoral immunological response.

Treatment and Prevention of TSP-HAM

In any immunologically mediated disease process, the aim is to limit the degree of damage from the inflammatory process induced by these mechanisms. In TSP, clinical disease tends to mirror the progression of the neuropathology with initial progression and then stability with plateau of function or slow deterioration. The latter is likely related to axonal loss with ageing as well as smouldering disease (10). Histologically, the infiltrate in the first five years of disease is characterized by $CD4^+$ and $CD8^+$ T cells, B cells and foamy macrophages with a high expression of inflammatory cytokines. Later these change as the number of inflammatory cells decrease substantially with mainly $CD8^+$ T cells and markedly reduced expression of inflammatory cytokines, except IFN-gamma.

Similarly, CSF abnormalities are seen in TSP. These are:

* Mild lymphocytosis
* Normal or increased protein
* Oligoclonal bands with evidence of local synthesis
* Anti-HTLV-1 antibodies
* Beta-2 microglobulin
* Neopterin[29]
* TNF-alpha, IFN-gamma, IL-1, IL-6

Among the first agents to be used in the treatment of TSP were corticosteroids utilizing its direct anti-inflammatory properties in view of the inflammatory nature of the disease. Most success has been seen in Japan where the majority of patients reported benefit. This was short lasting with modest degrees of improvement and symptoms worsened as the dose of steroids was reduced (10). Results have not been as good outside of Japan. This may be due to many factors including the earlier treatment of Japanese patients and perhaps cultural factors such as better compliance with the treatment protocols. In Jamaica, a short steroid trial by Morgan 1989, (unpublished data) appeared to have no benefit, perhaps again because these were patients with long-standing disease. Steroids are still used in early disease on a case-by-case basis and particularly when there is significant lumbar pain but the benefits are not sustained.

For similar reasons, Danazol, a synthetic derivative of 17-alpha-ethinyltestosterone, has been used in the treatment of TSP with the hope that the beneficial aspects of corticosteroids could be seen without the problems associated with long-term corticosteroids. Improvement in motor and bladder function was reported in two studies (30, 31). The benefits were not sustained.

Other immunomodulatory modalities utilized in the past include plasmapheresis, interferon-alpha and the use of anti-retrovirals (lamivudine, zidovudine) (10). Benefit was again noted in those with early disease but "these modalities are plagued with problems of high cost and the high frequency of side effects" (32). An interesting recent study examined the utility of interferon-beta 1a in HAM-TSP patients (33). In a single-centre, open-label trial, 12 patients with HAM/TSP were treated with doses of interferon-beta1a of up to 60 micrograms twice weekly. Primary end points were immunological and virological measures. Interferon-beta 1a therapy reduced the HTLV-1 tax messenger RNA load and the frequency of potentially pathogenic HTLV-1-specific $CD8^+$ cells. The HTLV-1 proviral DNA load remained unchanged. Spontaneous lymphoproliferation, a marker of T-cell activation in HAM/TSP, was reduced also. Some measures of motor function were improved, and no significant clinical progression occurred during therapy. Cost may be a significant limiting factor in the more widespread use of this agent as most individuals with the disease are of lesser economic means.

In summary, management of TSP requires the following: accurate diagnosis, general medical care such as: symptomatic relief of spasticity, bladder and bowel care, mobility aids and psychological support. Specific medical management *ie* disease-modifying treatment includes the following: reducing proviral DNA load and treating early to prevent subsequent cascade of immunologic events and thus preserve the spinal cord. There is little place for anti-viral or anti-inflammatory treatment in more advanced disease.

Prevention of TSP and HTLV-1 infection must remain the goal for now while effective treatment remains unavailable. The efforts of the Japanese to eradicate the virus from their population may succeed in reducing and eventually eliminating the consequences of infection *ie* TSP and ATLL. In the Caribbean, targeted screening of all donated blood, pregnant mothers, food handlers, commercial sex workers and other identified groups may be more realistic. In addition, infected individuals must be counselled on the risks of transmission to partners as well as to offspring. The infants of HTLV-1 positive mothers should not be breast fed as the risk of transmission appears high (34). However in countries with extreme poverty, malnutrition and diarrhoeal diseases represent problems more often faced in the non-breast fed infants.

The lifetime risk of carriers transforming to HAM/TSP is 0.25% in Japan but is several times as high in Africa, the Caribbean and to a lesser extent North America. While genetic factors must certainly be relevant, it is also likely that infectious diseases in these endemic areas may act as co-factors in increasing the risk of transformation to clinical disease states, perhaps by increasing the range of immunological activation and the chances of expansion of potentially autoreactive T cells.

The vexing question of the significance and possible relevance of positive STS to pathogenesis will have to be resolved by prospective studies of new patients with TSP and

determining if the seroprevalence of STS in these patients is stable or declines with time. Stability may imply causation by exposure to treponeme or false positivity if the same methods of testing are used, whereas a declining prevalence will prove that the cause of positive STSs was simply due to previous exposure, to yaws at least, in view of its eradication some 30 years ago. The difference in seroprevalence of STS between patients with TSP (30%) and HTLV-1 positive asymptomatic carriers (10%) is well known (18) and the difference implies causation. Alternatively, this may reflect an enhanced state of immune activation as the patient transforms to clinical disease.

Despite all the progress over the past 20 years the closing words of Professor Morgan in a review article (9) remain relevant today: **"**Recent discoveries, while opening up a new vista in virology, may only point towards its full pathogenesis. Above all …….. we need effective prevention and treatment."

ACKNOWLEDGEMENT

I am indebted to Professor Owen Morgan for supplying important historical articles and reprints of his papers, as well as for advice in the writing of this review. I also thank Professor Everard Barton for inviting me to submit this article to the Journal for publication.

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