Human T-Lymphotropic Virus Type II and Neurological Disease

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Human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II) are closely related retroviruses with similar biological properties and common modes of transmission. HTLV-I infection is endemic in well-defined geographic regions, and it is estimated that some 20 million individuals are infected worldwide. Although most infected individuals are asymptomatic carriers, some 2 to 5% will develop a chronic encephalomyelopathy, HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP). In contrast with HTLV-I, the role of HTLV-II in the development of neurological disorders is much less clear. HTLV-II is endemic in many native Amerindian groups and epidemic in injecting drug users (IDUs) worldwide. To evaluate the role of HTLV-II in neurological disease, we have critically reviewed all reported cases of HTLV-II–associated disorders. This has confirmed that although rare infection is associated with a disorder clinically similar or identical to HAM/TSP. However, most reports that have attributed infection to a range of other neurological disorders are difficult to evaluate in that in many cases either the association appears to be fortuitous or the presentations were confounded by a background of concomitant human immunodeficiency virus–1 infection and/or active IDU. In view of the many HTLV-II–infected individuals in urban areas of North America and Europe, neurologists should be aware of the potential clinical consequences of this infection.

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Human T-lymphotropic viruses type I (HTLV-I) and type II (HTLV-II) are closely related members of a family of mammalian retroviruses that have similar biological properties and an in vivo cellular tropism for mature T lymphocytes.[1,2] HTLV-I infection is clearly associated with the development of a range of inflammatory disorders of which the neurological disease HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP) is clinically the most significant. In contrast, the role of HTLV-II in neurological disease remains unclear. In this review, we summarize the evidence for such an association and describe the range of clinical features of the putative HTLV-II neurological disorders reported to date.

Epidemiology and Biological Properties

HTLV-I is endemic in several geographic regions which include Japan, the Caribbean basin, sub-Saharan Africa, South and North America and parts of Melanesia. It is estimated that globally some 20 million individuals are infected. Most infected individuals remain clinically asymptomatic throughout their lifetimes ("asymptomatic carriers") and have the potential to continue to transmit infection. No estimates are currently available for the global number of HTLV-II infections. HTLV-II infection is epidemic among injecting drug users (IDUs) in the United States, Europe, South America, and Asia and is endemic in many native American Indian populations.[2,3] In IDUs, infection rates vary widely and range from less than 1% in certain European countries to as high as 60% in parts of former South Vietnam. In many countries HTLV-II infection would appear to be more prevalent in IDUs coinfected with human immunodeficiency virus (HIV)–1, and as shall be discussed below this has confounded the accurate identification of HTLV-II–related neurological disorders. The origin of HTLV-II among native Indian groups is unclear, but it is likely that this was introduced to the American continent some 15,000 to 35,000 years ago, during migrations of ancestors of present-day Indian groups across the Bering Strait land bridge. It is probable that American IDUs initially acquired the infection from native Amerindians, and the spread of HTLV-II among IDUs is a recent event that probably has been facilitated by sharing of needles and other drug-related paraphernalia. Molecular analysis of HTLV-II isolates from Europe, the Americas, and South East Asia have shown the existence of three distinct subtypes IIa, IIb, and IIc, which can be differentiated on the basis of a combina-

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tion of phylogenetic analysis of nucleotide sequences of different regions of the provirus and phenotypic analysis of the viral regulatory protein Tax.[2] However, it is currently unclear if the different subtypes may have different pathogenic properties.

HTLV-I and II have common modes of transmission. Horizontal infection via contaminated cellular blood products is clearly an important route of transmission.[4–7] Whereas the policy of donor screening has markedly reduced transmission by contaminated blood in many countries, this remains a major mode of transmission in IDUs. As noted above, HTLV-II transmission in IDUs is significant in urban areas worldwide; in contrast, HTLV-I transmission in this population is essentially restricted to a few areas with endemic HTLV-I infection.[8,9] Sexual transmission also appears to be an important mode of HTLV-I and HTLV-II infection,[10–12] and studies in both HTLV-I and HTLV-II endemic areas have shown that heterosexual transmission is much more efficient from male to female.[11,13,14] Vertical transmission would appear to be central to the maintenance of infection in endemic areas. Mother to child transmission of both viruses occurs primarily through breast-feeding and as many as 25% of breast-fed infants become infected.[14–17] Perinatal infection occurs much less frequently, and although infection may occur in utero this also appears to be much less important than breast-feeding.[18]

Neurological Disease

In endemic areas, the range of HTLV-I–related illness extends from a group of lymphoproliferative malignancies to a range of diverse inflammatory disorders. The former, adult T-cell leukemia/lymphoma (ATLL) is a group of $CD4^+$ T-cell malignancies with distinct clinical subtypes.[19] Of the inflammatory diseases, the neurological disorder HAM/TSP is the most clinically significant.[20–25] HAM/TSP generally has an onset in the third and fourth decades of life but has been described in children as young as 6 years. The onset is usually subacute and insidious and occurs more frequently in female subjects. Initial symptoms include stiffness, weakness of the lower extremities, and frequency and urgency of urination. Physical findings include weakness of the legs with spasticity, hyperreflexia, and extensor plantar responses. Whereas strength usually is preserved, deep tendon reflexes tend to be brisk in the upper extremities, and sensory findings are usually minimal. Magnetic resonance imaging (MRI) has shown that thoracic cord atrophy with increased signals in the periventricular and subcortical white matter on T2-weighted images are the most commonly observed findings.[26–30] However, these are considered to be relatively nonspecific, and opinions differ on whether they can effectively be differentiated from changes due to aging, collagen vascular disease, or small lacunar infarcts. Recently, Howard and colleagues[30] retrospectively compared MRI findings in patients at various stages of HAM/TSP, asymptomatic seropositive family members, and patients with multiple sclerosis (MS). The typical nonspecific findings already noted were confirmed in HAM/TSP but also were observed in the asymptomatic carriers. Although more extensive abnormalities were observed in the former, these differences were not statistically significant. However, criteria were clearly established that effectively allowed the differentiation of HAM/TSP and MS.

Although the pathogenic mechanisms remain to clarified, HAM/TSP is characterized by a perivascular lymphocytic infiltration throughout the central nervous system and predominantly in the thoracic region of the spinal cord, and this is prominent in the early phases of the disease. Patients have very high HTLV-I proviral loads ranging from 10- to 100-fold greater than that observed in asymptomatic carriers.[22–32] Immunological studies have demonstrated high levels of circulating T-lymphocyte responses, and these appear to correlate with the high viral load levels in that their frequency is significantly higher in HAM/TSP compared with asymptomatic carriers.[22–25,31–35] Investigations on the pathogenesis of HAM/TSP initially were focused on the role of HTLV-I Tax-specific $CD8^+$ cytotoxic T lymphocytes (CTLs), and it has been suggested that during T-cell killing, cytokines and lymphokines released may be responsible for local parenchymal ("bystander") damage. More recently studies also have demonstrated high frequencies of HTLV-I–specific $CD4^+$ T lymphocytes directed to both Tax and Env proteins in patients with HAM/TSP, and it has been hypothesized that these responses also contribute to the pathogenesis.[36–39] Several studies also have suggested that autoimmune processes also may play a role. Specifically, it has been shown that HAM/TSP patients develop IgG antibodies which cross-react both with an immunodominant epitope in Tax and with a neuronal protein, heterogeneous nuclear ribonuclear protein–A1 (hnRNP-A1).[40,41] Thus, in addition to the contribution of markedly enhanced virus-specific T-lymphocyte responses, molecular mimicry involving viral and neuronal antigens also might contribute to the pathogenesis of HAM/TSP. It is unclear why certain individuals develop HAM/TSP and others ATLL. Although no specific virus properties have been identified, host genetic factors have been shown to be important, and in relation to HAM/TSP several HLA types have been identified that appear either to have a protective effect or that can predispose to the development of this disorder.[42–45] It is also unclear if concomitant HIV-1 infection might influence the development of HAM/TSP in dually infected individuals. In this regard, one report from Brazil compared the development of myelopathy in dually infected HIV-1/HTLV-I individuals with

that of single HIV-1 infection, and it was noted that a statistically higher proportion of coinfected individuals developed not only myelopathy but also peripheral neuropathy.[46] Currently, there would appear to be no consistently effective treatment for HAM/TSP. Treatment with corticosteroids, plasmapheresis, antioxidants, interferons, and, more recently, antiretroviral drugs have been attempted, but all have produced inconsistent and generally poor results. Early reports on the use of the HIV-1 reverse transcriptase inhibitor zidovudine (AZT) have produced conflicting results.[47,48] Virological improvement has been reported with the use of another reverse transcriptase inhibitor, lamivudine (3TC). Specifically, it was shown that treatment resulted in a 10-fold reduction in levels of proviral load in five patients with HAM/TSP, and in one there was also a decrease in the frequency of HTLV-I–specific CTL responses.[49] More recently, a study of two HAM/TSP patients treated with a combination of AZT and lamivudine showed that one patient had a two-log decrease in HTLV-I proviral load, whereas an increase of one log was observed in the second after several months of treatment.[50] The reasons for the conflicting data in these studies are unclear, but it is possible that the inhibitors used may have other activities perhaps involving cellular enzymes that could influence the study outcomes.

In contrast with HTLV-I, the role of HTLV-II in neurological disease remains poorly understood. However, there is increasing evidence that the infection may be associated with several different neurological disorders in some individuals.[2,51–69] To date, some 15 to 20 cases of possible HTLV-II–associated neurological syndromes have been published. The Table summarizes those reports with their clinical descriptions and where available the laboratory and immunological features of their presentation. The specific clinical classification used in the Appendix is based on that used by the authors in their original reports. Regrettably, however, many of the descriptions either have lacked sufficient neurological information to allow a confident diagnosis and/or have been limited by confounding elements. In addition, the descriptions of the same patient in more than one report make difficult the estimation of the real frequency of each of these syndromes. Further limitations in defining the role of HTLV-II in these disorders have been that information often has been based only on individual case reports and that many of the patients have had concomitant HIV-1 infection. As a result, it has been difficult in some instances to accurately assess the exact role of HTLV-II and to confidently define and establish contributing factors that might have arisen from HIV-1. In addition, because many HTLV-II–infected patients have a history of IDU, it is unclear if this or related activities also may have confounded the analysis and the interpretation of the clinical studies. The first descriptions of HTLV-II–associated neurological disorders were in two patients who were dually infected with HIV-1 and HTLV-II and who presented with a myelopathy indistinguishable from HAM/TSP.[51,52] Subsequently, a report[54] described two sisters infected only with HTLV-II, who had developed a chronic neurodegenerative process characterized by spasticity, paraparesis, and prominent ataxia. Overall, the clinical features were consistent with a syndrome of the olivopontocerebellar atrophy variant of multiple system atrophy. The association of HTLV-II with spastic ataxia was supported by two reports from Florida which described two and four female subjects, respectively[55,56] with a distinctive picture of ataxia, spasticity, and variable alterations in mental status. Although it is unclear if these two studies may have involved some of the same patients, they strongly supported an association of infection and disorders in which ataxia is a prominent feature. After this, at least seven other reports[57–61,68,69] have described patients with single HTLV-II infection who presented with symptoms resembling or identical to HAM/TSP and taken together have provided the strongest evidence that HTLV-II is, in fact, associated with such a disorder. Notably, most cases have occurred in female subjects, and this is similar to HTLV-I in which female subjects also are more likely to develop HAM/TSP. In view of the very low number of HTLV-II–infected individuals who have until now undergone detailed clinical evaluation, these observations suggest that a HAM/TSP-like illness is a significant feature of infection. The prevalence of HAM/TSP-like illness in HTLV-II infection cannot be ascertained currently. Orland and colleagues[69] recently reported on the long-term follow-up of a large cohort of blood donors in the United States (HOST cohort) with HTLV-I and HTLV-II infection. The prevalence of HTLV-II–associated myelopathy was reported as 1% compared with 3.7% for HTLV-I. Unfortunately, the clinical features of the HTLV-II–infected patients in this study were not described in detail. No information was provided on the evolution or the levels of neurological disability, and the disorders were described only as mild compared with HTLV-I–associated HAM/TSP. In addition, one patient had a low vitamin B12 level, and this could have contributed to the clinical presentation. Surprisingly, MRI findings were essentially normal and did not demonstrate any of the nonspecific changes noted in previous studies[30] in either the HTLV-I– or HTLV-II–associated myelopathies.

In addition to HAM/TSP-like illnesses, there has been one report of the development of a spinocerebellar syndrome in a HTLV-II–infected Indian subject from Panama.[62] Because similar disorders have been described in HTLV-I infection, it was suggested that this may represent a unique neurological manifestation

of either HTLV-I or HTLV-II infection. In a recent study of a cohort of HIV-1 coinfected individuals, the prevalence of antibodies to HTLV-II infection was found to be significantly higher in those with a predominantly sensory polyneuropathy (PSP) compared with asymptomatic controls.[64] In addition, patients with PSP were found to have higher proviral loads than those without PSP.[65] However, further studies are required to confirm an association with HTLV-II infection and the development of such neuropathies.

Although the studies to date suggest that HTLV-II may be rarely associated with a similar disorder to HAM/TSP, the description other clinical presentations (see Appendix) suggests, but does not prove, the potential existence of a wider spectrum of neurological syndromes. Most cases of putative HTLV-II–associated neurological disorders are in individuals who present with a mix of myelopathic and cerebellar features. This combination is particularly problematic in diagnostic neurology, and MS and hereditary spinocerebellar degeneration can present in an identical fashion. Therefore, it is possible that some of the clinical features attributed to HTLV-II may merely represent coincidental findings. In the case of hereditary spinocerebellar degeneration, genetic testing or the detection of noninfected relatives with similar clinical pictures could resolve this causative dilemma. In fact, this was the situation in a recently published case of an HTLV-II–infected woman with a slowly progressive clinical picture characterized by spastic paraparesis and cerebellar ataxia, and which had been initially reported as a case of HTLV-II–associated spinocerebellar degeneration.[66] Several years later, however, the authors reported that the patient's brother had an identical syndrome but was HTLV-II–negative, both serologically and on the basis of molecular testing.[67] These findings made the original association of the disease with HTLV-II infection unsupportable and serves as an example that cases of HTLV-II–related neurological disease must be carefully investigated before any causative associations can be made. MS is an inflammatory demyelinating disease of unknown cause, and the diagnosis remains based on clinical and paraclinical criteria of dissemination of neurological signs and symptoms in time and space. However, even with the assistance of highly sophisticated and precise methods for detecting demyelinating lesions in vivo, the exact diagnosis may require either long-term observation or neuropathological evaluation.[70,71] Reviewing the literature and the Appendix, one can observe that some of the HTLV-II–infected patients have had a clinical course similar to MS, with dissemination of the clinical symptomatology in time and space. In addition, one patient provided a strong family history of an "MS-like illness,"[58] and, according to large-scale studies, family cases of MS are not exceedingly rare.[70] This patient was also of special interest because this was the only individual in the literature who underwent a spinal cord biopsy. HTLV-II proviral DNA and *tax* mRNA were detected in spinal cord tissue, and neuropathological examination also showed granulomatous changes containing foreign body–type giant cells with inclusions of what appeared to be talc crystals.[59] Because this patient was an IDU, the talc granuloma were believed to be related to drug use, and the entrance of a foreign body (talc) into the nervous system compartment could well have triggered the influx of infected and uninfected lymphocytes. Therefore, it is possible that even with the finding of the HTLV-II genetic material in the spinal cord this does not necessarily prove that the HTLV-II was responsible for the clinical presentation. Rather, it shows that HTLV-II–infected cells are capable of entering the central nervous parenchyma during an inflammatory process, notwithstanding its specificity. If this is correct, even the finding of an HTLV-II polymerase chain reaction–positive cerebrospinal fluid would not necessarily imply an causative association between the virus and the neurological disease. Indeed, many infectious agents, viral, bacterial, and protozoal could in certain settings be considered "normal brain flora," because their presence in the nervous system may not be associated with disease.[72] Recent studies that have investigated in the presence of human herpesviruses (HHVs) −6, −7, and −8 viral sequences in fresh brain autopsy tissues obtained from 84 consecutive individuals, immunocompetent and free of clinical signs of viral diseases, demonstrated that HHV-6 was present in 43%, and that HHV-7 and HHV-8 DNA were present, respectively, in three and two patients.[73] Taken together, these data show that it is difficult to prove a clear relationship between HTLV-II and neurological disease based solely on the finding of the virus in the cerebrospinal fluid or in the nervous parenchyma. This problem is somewhat similar to that encountered in recent studies of MS in which over several years, several candidates have been nominated as the pathogens in this disease.[74]

In addition to the specific disorders noted above and in the Appendix, epidemiological studies have suggested that HTLV-II infection may produce various forms of generalized neurological dysfunction. Specifically, in a cohort of IDU, HTLV-II infection was shown to be independently associated with the development of global neurological disability.[75] However, the contribution of IDU to the latter could not be clearly ascertained. Thus, although there is now increasing support for the existence of a range of HTLV-II–associated neurological disorders, confounding elements often exist that make it difficult to definitely attribute infection to the clinical outcome. As noted above, HIV-1 can cause a variety of neurological disorders, and this may have played a role in some of the

Appendix. Neurological Syndromes Associated with HTLV-II Infection Findings

Syndrome[a]	Clinical Findings	Evolution	Risk Factors for HTLV Infection	Coinfections	CSF
TSP-like illness	34 yr old M; diffuse lymphadenopathy, spastic paraparesis, bilateral Babinski sign, T4 sensory level, Romberg sign	Spontaneous remission after 2 yr of disease	IDU	HIV-pos., syphilis treated in the past	First tap: mild pleocytosis, normal protein; negative VDRL and FTA-ABS. Second tap: mild pleocytosis, increased protein, increased IgG index, no oligoclonal bands
Chronic neurodegenerative disease	2 sisters, 59 and 46 yr old; cerebellar ataxia, spastic paraparesis, bilateral Babinski sign, no sphincter involvement, deep and superficial distal sensory involvement, dysautonomic signs	Chronic progressive	Pueblo Indians from New Mexico, HIV negative, no IDU history	Neg. HIV and syphilis	(1) Normal. (2) ND
Progressive spastic myelopathy	54 yr old, M; distal weakness of left arm, highly asymmetrical spastic paraparesis (> left leg), sphincter disturbances, bilateral Babinski sign, decreased vibration sense in UL and LL	20 years history, multiple relapses, no remissions	History of bisexual activity, denies IDU	HIV-pos., syphilis-negative	Normal cell count and protein, oligoclonal bands
HTLV-II–associated myelopathy	43 yr old, F; low back pain, spasticity without weakness in LL, patellar hyperreflexia, sphincter disturbances, unreactive plantar responses, normal sensory examination	Chronic progressive	IDU, married to HTLV-II –pos. IDU	Neg. HIV and syphilis	Normal, except for one oligoclonal band and pos. ELISA for HTLV
Spastic ataxia associated with HTLV-II	Two unrelated F (54 yr old and NI age); (1) spastic-ataxic gait, asymmetrical spastic paraparesis, bilateral Babinski sign, sphincter dysfunction, decreased superficial sensation distally in UL and LL, mental changes (dementia?). (2) Back pain, nocturia, spasticity in the LL (no objective paraparesis), hyperreflexia of ankle jerks, bilateral Babinski sign, end-gaze nystagmus, spastic-ataxic gait with poor tandem gait, no sensory deficients no Romberg sign, mental changes (dementia?)	Progressive	(1) Blood transfusions, married to IDU. (2) Frequent sexual contact with IDU	Neg. HIV	(1) Cellularity NI, normal protein, oligoclonal bands. (2) NI
Tropical ataxic neuropathy with HTLV-II	Four F (47, 34, 34, 49 yr old); gait ataxia (striking in cases 1 and 2), minor spasticity and sphincter disturbances (Cases 1–3)	NI	(Cases 1–4) Sexual contacts with IDU	Neg. HIV	(Cases 1 and 3) Cellularity NI, normal protein, pos. Western blot to HTLV-II
Chronic, progressive neurological disease clinically indistinguishable from HAM/TSP	52 yr old, M; weakness and pain of LL, sphincter disturbances, spastic-hyperreflexic paraparesis, bilateral Babinski sign, no ataxia, markedly impaired vibratory and position sense with milder superficial sensory deficits	Chronic progressive	IDU 20 yr earlier, Amerindian descendant	Neg. HIV, syphilis and Lyme	Normal cell count, increased protein and IgG, normal IgG index, no oligoclonal bands, pos. ELISA to HTLV-I/II
HTLV-II–associated myelopathy	3 M (53, 46, 70 yr old), 1 F (34 yr old); (1) See Castillo and colleagues.[62] After an episode of hyperglycemia–acute deterioration of strength of LL and T8 sensory level. (2) Transient left-sided weakness for 3 days, 1 yr latter spastic quadriparesis, right-sided T4 sensory level, hyperreflexia, bilateral Babinski sign. (3) Right-sided weakness that improved after steroids. Two years later, right-sided weakness progressing to quadriparesis over 10 days, partial T3 sensory level. Later, right retrobulbar neuritis. (4) Spastic paraparesis, distal sensory loss, sphincter disturbances	(1) Progressive over 3 yr, then acute deterioration. (2) Relapsing progressive. (3) Relapsing progressive. (4) Progressive	(1) See Castillo and colleagues.[62] (2) Same as 1. (3) Amerindian background (4) Transfusions	(Cases 1–4) Neg. HIV. (1, 2, 4) Pos. HCV	(1–4) Pos. HTLV-II. (1) Normal cell count, increased protein and IgG index. (2) Pleocytosis, increased protein and IgG index, oligoclonal bands. (3) Pleocytosis, increased proteins and IgG index, no oligoclonal bands. (4) Normal cell count, protein and IgG index ND

Appendix. Continued

Neuroimaging	EMG/NCS/EvP	PCR	Comments	Reference
Normal brain and spinal MRI	Mixed axonal-demyelinative, predominantly motor, neuropathy	Pos. in blood	Spontaneous remission is exceptional in TSP	52
(1) Normal myelogram and spinal MRI. Brain MRI: cortical and cerebellar atrophy. (2) Normal brain and spinal MRI	NI	Pos. in blood	Clinical picture more consistent with hereditary olivopontocerebellar atrophy	54
Normal myelography. Brain and spinal MRI: multiple, high-intensity, periventricular lesions	Left ulnar neuropathy. Normal visual and brainstem EvP	Pos. in blood	Family history (uncle and cousin) of an MS-like illness	53
Normal brain and spinal MRI	NI	Pos. in blood, neg. in CSF	This case will be described again in another article[61]	60
(1) Brain MRI: periventricular demyelination with central pontine, left cerebellar, bilateral thalamic, basal ganglia and subcortical white matter lesions. Normal spinal MRI; (2) NI		Pos. in blood (HTLV-IIa)	Both patients taking diphenylhydantoin because of epilepsy. This could account, at least in part, for the ataxia. Patient 2 had diabetes and was taking insulin. There are some evidences for a dementing state in both cases. At least the case of Patient 1 is related in another paper published almost simultaneously[56] (1) Slight improvement with danazol. (2) Lost to follow-up	55
NI	NI	Pos. in blood in all cases	Case 4 was subsequently found to have a colloid cyst of third ventricle, in which surgical removal improved ataxia. As a whole, the clinical description of the cases is superficial and does not allow further characterization of the cases. At least one of the cases had been already published some months before by the same group.[55]	56
Spinal MRI: severe cord atrophy at T1-9 without areas of enhancement. Brain MRI: scattered hyperintense, nonenhancing lesions in the subcortical white matter	Somatosensory EvP: absent in LL and delayed in UL	Pos. in blood (HTLV-IIa)	The follow-up of this case was subsequently published 3 yr afterward.[62]	58
(1) See Castillo and colleagues[62] for previous studies. New spinal MRI: intramedullary-enhancing lesion from T5–T6. (2) Brain and spinal MRI: unenhancing white matter lesions in the cerebrum and intramedullary region of C3–C7. (3) Brain MRI: unenhancing periventricular white matter lesions. Cervical cord MRI: mild cord swelling. (4) Brain CT: mild atrophy. Myelogram: thoracic cord atrophy	NI	Pos. in blood in all cases. (1, 2, 4) HTLV-IIa	Patient 1 underwent a laminectomy with removal of a thoracic spinal cord lesion, which showed noncaseating granulomas containing foreign body–type giant cells and lymphocytes. Small fragments of foreign material within the giant cells (talc crystals?); HTLV-II sequences have bee detected by PCR in this tissue.	59

Appendix. Continued

Syndrome[a]	Clinical Findings	Evolution	Risk Factors for HTLV Infection	Coinfections	CSF
Spinocerebellar syndrome	51 yr old, F; unsteady gait, dysarthria, intermittent diplopia, nystagmus, truncal ataxia, limb dysmetria, brisk tendon reflexes, flexor plantar responses, sphincter disturbances, paraparesis, normal muscle tone	Chronic progressive	Guaymi Amerindian blood transfusion	NI	Normal, HTLV serology NI
Chronic neurodegenerative disease	55 yr old, F; pain and weakness in the legs, ataxic gait, spastic paraparesis, hyperactive reflexes, bilateral Babinski sign, spastic bladder	Progressive			HTLV-II negative by ELISA and PCR
Myelopathy/tropical spastic paraparesis	49 yr old, F; pain and weakness in the legs, urinary incontinence, spastic paraparesis, hyperreflexia, bilateral Babinski sign	Progressive		Pos. *Trypanosoma cruzi* serology; Neg. syphilis, hepatitis B/C. HIV	HTLV-II–positive by particle agglutination, WB; pleocytosis increased protein content (1.18g/L)
HTLV-II–associated myelopathy	Four F (42, 47, 51, 54 yr old); increased patellar reflexes (Cases 1–4) and increased tone in the legs (Cases 1, 2); normal tone in the legs (Case 3)	Progressive	IDU (case 1); sexual contact with IDU (Cases 1–4)	Neg. HIV and syphilis	NI

Note: Some reports referenced in the text have not been included in the table because of either lack of enough data for a comparative analyses or replication of already published cases.

[a]As defined by the authors.

CSF = cerebrospinal fluid; CT = computed tomography; ELISA = enzyme-linked immunosorbent assay; EMG/NCS = electromyography/nerve conduction studies; EvP = evoked potentials; FTA-ABS = fluorescent treponemal antibody absorption test; HAM = HTLV-I–associated myelopathy: HCV = hepatitis C virus; HIV = human immunodeficiency virus; Pos/Neg. = positive/negative; IDU = intravenous drug user; MRI = magnetic resonance imaging; MS = multiple sclerosis; NI/ND = not informed/not done; PCR = polymerase chain reaction; TSP = tropical spastic paraparesis; UL/LL = upper/lower limbs; VDRL = Venereal Diseases Research Laboratory test.

putative HTLV-II–related disorders described. Moreover, because many HTLV-II–infected individuals independent of HIV-1 coinfection may be involved in drug usage, the effect of these or other compounds used in their preparation also may confound any study involving such individuals.[76,77]

Prospective studies of infected individuals known to be free of confounding elements such as HIV-1 and IDU will help elucidate the exact role of HTLV-II in neurological disease and will allow clear documentation of the prevalence of HAM/TSP-like illness. The pathogenesis and the specific role of cellular immune responses in HTLV-II infection both in asymptomatic carriers and in those with neurological disease remain poorly understood. However, these are likely to be important, and correlation of immunological investigations with prospective clinical studies in HTLV-II infection will provide a strong foundation for understanding the pathogenic properties of this virus and clarify its role in neurological disease.

To date, there has been limited experience in the treatment of HTLV-II infections and none in the setting of HTLV-II–associated neurological disorders. One report[50] evaluated the responses in two HTLV-II/HIV-1 coinfected patients receiving triple antiretroviral drug combinations including lamivudine and a protease inhibitor. Both patients showed an initial increase in HTLV-II proviral load shortly after beginning treatment, and this was followed by a slight decrease several months later. As expected, plasma HIV-1 RNA decreased to undetectable levels in both patients during therapy. Thus, it is unclear if antiretroviral therapy will prove to be of benefit in HTLV-II infection.

Conclusions

An extensive review of the literature has shown that, although rare, HTLV-II infection is associated with a chronic encephalomyelopathy similar to that of classic HTLV-I–associated HAM/TSP. In addition, there is limited but as yet an unproven association with a range of other neurological disorders. Unfortunately, possible misdiagnoses and in many instances confounding fac-

Appendix. Continued

Neuroimaging	EMG/NCS/EvP	PCR	Comments	Reference
Brain CT: diffuse cerebellar atrophy	NI	Pos. in blood	This patient had a history of multiple spontaneous abortions, which can be found in the antiphospholipid antibody syndrome. However, there is no information whether she has been ever tested for anticardiolipin antibodies or lupus anticoagulant.	62
Periventricular demyelination on CT scan		Pos. in blood (HTLV-IIa)	This patient was examined by one of the authors (A.A.), who did not detect the clinical signs described in this article.	63
NI	NI	Pos. in blood	Unusually high protein content for TSP/HAM; lack of neuroimaging studies to exclude spinal cord compression	68
Normal MRI (Cases 1, 2, 4); nonspecific increased T1 marrow signal (Case 3)	NI	Pos. in blood (Cases 1–4); neg. CSF (Cases 2 and 3); not available in CSF (Cases 1 and 4)	Case 4 showed a lower vitamin B12 level but with normal homocysteine and methylmalonic acid contents. One of these cases already described in previous articles from this group. Unfortunately, the clinical description of cases is superficial and does not allow their better characterization particularly regarding their evolution and level of neurological disability, which is said to be mild by the authors.	69

tors such as IDU or concomitant HIV-1 infection have not permitted the establishment of a clear association of HTLV-II infection with the latter. Prospective clinical studies of infected individuals free of such confounding elements will allow a clearer understanding of the neuropathological properties of this virus and the true incidence of neurological disease. Moreover, such studies will certainly contribute to our overall understanding of the immunopathogenic mechanisms of virus- induced disorders of the central nervous system.

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The authors regret that because of space restrictions many references and particularly those relating to the epidemiology of HTLV-II infection could not be cited.

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