HTLV-1-associated myelopathy/tropical spastic paraparesis

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Abstract | Human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a progressive disease of the CNS that causes weakness or paralysis of the legs, lower back pain and urinary symptoms. HAM/TSP was first described in Jamaica in the nineteenth century, but the aetiology of the condition, infection with the retrovirus HTLV-1, was only identified in the 1980s. HAM/TSP causes chronic disability and, accordingly, imposes a substantial health burden in areas where HTLV-1 infection is endemic. Since the discovery of the cause of HAM/TSP, considerable advances have been made in the understanding of the virology, immunology, cell biology and pathology of HTLV-1 infection and its associated diseases. However, progress has been limited by the lack of accurate animal models of the disease. Moreover, the treatment of HAM/TSP remains highly unsatisfactory: antiretroviral drugs have little impact on the infection and, although potential disease-modifying therapies are widely used, their value is unproved. At present, clinical management is focused on symptomatic treatment and counselling. Here, we summarize current knowledge on the epidemiology, pathogenesis and treatment of HAM/TSP and identify areas in which further research is needed. For an illustrated summary of this Primer, visit: http://go.nature.com/tjZCFM

Human T-lymphotropic virus 1 (HTLV-1) is a retrovirus that infects T lymphocytes (BOX 1; FIG. 1). The virus was first named human T cell leukaemia virus type 1 because it causes an aggressive malignant disease of $CD4^+$ T cells known as adult T cell leukaemia/lymphoma (ATL)[1,2] in ~5% of infected individuals. Approximately 1% of HTLV-1-infected people develop a chronic inflammatory disease of the CNS, known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 is transmitted by sexual contact, breastfeeding or blood transfusions. HTLV-1 infection causes the activation and clonal proliferation of infected T cells, a process for which the viral proteins Tax and HBZ (HTLV-1 basic zipper factor) are essential (BOX 1). HTLV-1 is almost entirely cell-associated *in vivo*; cell-free virus particles are usually undetectable, and accidental transmission of HTLV-1 by blood transfusion has only been recorded after the transfusion of cellular blood products[3–6]. A single host typically possesses 10^4 to 10^5 distinct clones of HTLV-1-infected T cells[7,8], each clone being defined by the unique genomic integration site of the HTLV-1 provirus. These clones are not equally abundant in the blood; certain clones reach very high abundance and can persist for many years[9,10].

HTLV-1 infection is initially asymptomatic and this stage can last for several years or even decades, after which subsequent inflammatory and malignant diseases usually occur. HAM/TSP was first described as a form of multiple neuritis in Jamaica in the late nineteenth century, but the aetiology remained obscure. For many years the disease was believed to be caused by a nutritional deficiency, a toxin or another infectious agent such as *Treponema pallidum*[11,12]; the connection with HTLV-1 infection was discovered by French[13] and Japanese[14] research groups in the 1980s.

HAM/TSP is characterized by progressive spastic weakness of the lower limbs, lower back pain and urinary symptoms. The pathology in HAM/TSP shows a biphasic pattern. An initial inflammatory phase is characterized by perivascular lymphocytic infiltration of the spinal cord. The inflammatory phase is followed by a stage in which scarring, atrophy and neurodegeneration prevail[15,16]. Although the disease is not directly life-threatening, life expectancy is substantially shortened[17], there is no satisfactory treatment and the disease imposes a considerable health burden in areas where HTLV-1 infection is endemic, such as Japan, the Caribbean, Africa and some regions in central and southern America[18]. In this Primer article, we summarize the main features of HTLV-1 biology and the pathogenesis and clinical features of HAM/TSP, and identify key areas in which further clinical and basic research is needed.

Epidemiology

There are no data on the incidence of HTLV-1 infection because the primary infection is asymptomatic.

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The most widely quoted prevalence figure for HTLV-1 infection is 10–20 million individuals worldwide, as estimated by de Thé and Bomford in 1993 (REF. 19). This estimate was based primarily on data from the 1980s. More recently, Gessain and Cassar[18] estimated that a total of 5–10 million individuals are infected with HTLV-1. However, these authors remarked that most of the data were from areas where HTLV-1 was already known to be endemic, and omitted many large populations. Even in the regions where HTLV-1 prevalence is best described, few studies are based on the general population. Consequently, the prevalence of HTLV-1 is unknown for 80% of the global population[20].

With the increasing mobility of both populations and tissues or organs for transplantation, an understanding of the risk of transmission requires more-robust prevalence data. The European Centre for Disease Prevention and Control has defined areas with more than one HTLV-1 infection per 10,000 blood donors or per 1,000 people in the general population as high-prevalence areas[21]. The population prevalence of HTLV-1 ranges from less than 1 per 10,000 people to more than 10%: it is highest in Japan, South America, the Caribbean basin, central Australia, and in western, central and southern Africa[18] (FIG. 2). The countries with the highest estimated total numbers of HTLV-1-infected people are Japan and Brazil, each with more than 1 million individuals. Even in countries such as Japan, Brazil and the United States (a low-prevalence country), considerable regional variation has been reported. Populations in which HTLV-1 infection is common in otherwise low-prevalence regions include certain Australian aboriginal groups[22], first-nation North Americans[23] and, in Europe, Romanians[18]. This variability in prevalence is attributed to the fact that HTLV-1 is predominantly transmitted vertically by close or prolonged contact.

Certain features of HTLV-1 epidemiology are consistently observed in different populations. The prevalence in children increases up to the age of 2 years and thereafter remains stable until puberty[24]. The prevalence in adults increases steadily with age and is higher in females than males; the female to male ratio increases after the age of 50 years[25].These observations are explained by the known routes of HTLV-1 transmission: from mother to child by prolonged breastfeeding, and by sexual contact, with a higher rate of transmission from males to females than vice versa.

Lifetime risk of HAM/TSP

The lifetime risk of developing HAM/TSP has been reported as 0.25% in HTLV-1-infected individuals in a southern Japanese population[26]. The risk in people of Afro-Caribbean descent is higher: a cross-sectional study of HTLV-1-infected North American blood donors[27] reported a risk of 2.4%, increasing to 3.7% after 10 years of follow-up study[28]. In Trinidad and Tobago, the risk is 1.9%[29]. In a Brazilian cohort study, the incidence of HAM/TSP was 5.3 cases per 1,000 person-years[30], which is much higher than the 17.3 to 24.7 cases per 100,000 person-years reported for Trinidad and Tobago[29]. Ethnic differences have been observed in the susceptibility to HAM/TSP; for example, in Zaire, HAM/TSP primarily affects a minor group of the Mundunga ethnic group[31].

The complete spectrum of diseases that is associated with HTLV-1 infection has not been fully described, and even for recognized associations, such as uveitis, the frequency of events is poorly documented. The lifetime risk of developing HTLV-1-associated disease is, therefore, usually based on the two most common and best described conditions: HAM/TSP and ATL. The lifetime risk of developing ATL was estimated to be 2–6% in population-based studies in Japan, with the higher rate observed in males[32]; similar rates have been noted in other endemic regions. Although the risk of developing HAM/TSP is lower than that of ATL, the disease burden of HAM/TSP is higher because of its long and progressive course.

Box 1 | **HTLV-1 biology**

Retroviruses have a genome consisting of two copies of single-stranded, plus-sense RNA, ~9 kb in length. A distinguishing feature of retroviruses is the possession of reverse transcriptase, an enzyme that transcribes RNA into DNA. Reverse transcriptase transcribes the virus genome, forming a double-stranded DNA copy known as the provirus, which is then integrated into the genome of the host cell by the virus-encoded enzyme integrase. Human T-lymphotropic virus 1 (HTLV-1) integrates a single copy of the DNA provirus in each cell it infects[46]; it is not known what prevents a second copy from becoming integrated. The genomic location of the provirus is identical in every cell of one clone but differs between clones (see FIG. 1 and REF. 166 for further details of the structure and life cycle of retroviruses).

HTLV-1 is classified in the *Deltaretrovirus* genus of the *Orthoretrovirinae* subfamily of retroviruses. Similar to the distantly related HIV-1, HTLV-1 is a complex retrovirus because, in addition to the *gag*, *pol* and *env* genes possessed by other exogenous replication-competent retroviruses, HTLV-1 encodes several genes whose products regulate viral transcription, replication and spread[167–169]. The most important of these regulatory genes are *tax* and *HBZ*[170,171]. Tax transactivates transcription of the provirus itself, providing a strong positive feedback loop. In addition, Tax transactivates many host genes, notably those encoding the IL-2 receptor α chain (CD25), interferon-γ and intercellular adhesion molecule 1 (ICAM1). As a consequence, Tax exerts a remarkable range of effects on the infected cell, including activation, proliferation, inhibition of cell cycle checkpoints and inhibition of DNA repair[168,169,171]. HBZ acts both at the RNA level and the protein level to promote proliferation of the infected cell[172] and oppose many of the actions of Tax[170].

HTLV-1 can infect most nucleated cell types *in vitro*, but *in vivo* ~95% of the proviral load is located in $CD4^+$ T cells, followed by $CD8^+$ T cells and, infrequently, dendritic cells. HTLV-1 propagates by cell–cell contact: engagement of ICAM1 on the infected cell by lymphocyte function-associated antigen 1 (LFA-1, also known as integrin α-L) on the 'target' cell triggers budding of the virus towards the cell contact area in a specialized structure with organized protein microdomains called the virological synapse[173].

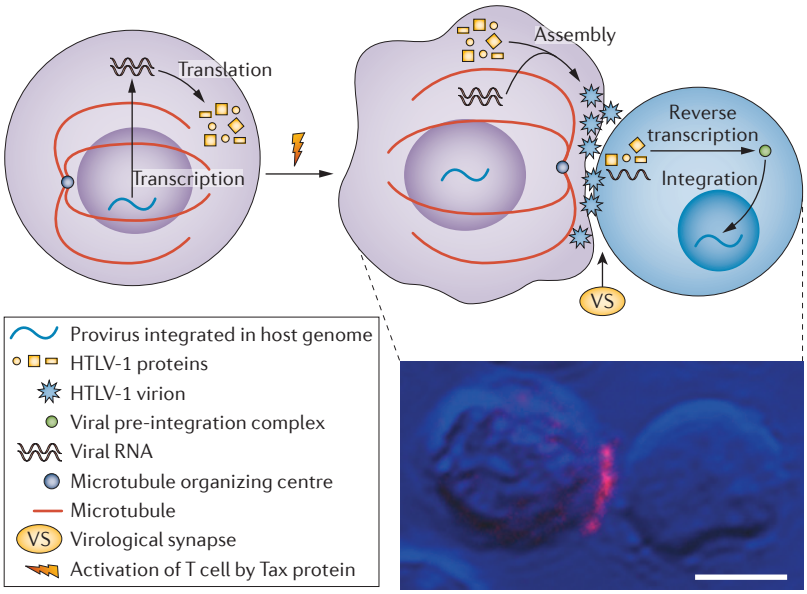

Figure 1 | **HTLV-1 life cycle.** In a human T-lymphotropic virus 1 (HTLV-1)-infected cell, the HTLV-1 provirus integrated in the host genome is transcribed into RNA and translated to form the structural and regulatory proteins of the virus. HTLV-1 expression activates the cell, which becomes large and irregularly shaped, and upregulates the adhesion molecule intercellular adhesion molecule 1 (ICAM1) on its surface. Contact between the HTLV-1-expressing cell and another cell activates a signalling pathway in the infected cell by engagement of ICAM1 (REF. 174) on the cell surface. This signal synergizes with a second signalling pathway — activated by the HTLV-1 Tax protein[175] in the cytoplasm — to trigger the formation of a specialized cell–cell contact known as a virological synapse[173] and polarization of the microtubule cytoskeleton towards this contact zone. The viral proteins and RNA genome are transported by the microtubules to the synapse, where the virions are assembled and bud through the plasma membrane. The virions then cross the short extracellular space within[173,176] or at the periphery[177] of the synapse, fuse with the membrane of the 'target' cell, and release their contents into the cytoplasm. The RNA genome is then reverse-transcribed into double-stranded DNA, which associates with the viral integrase enzyme to form a pre-integration complex. The pre-integration complex gains access to the host genome when the nuclear envelope disassembles during mitosis, and a single copy[46] of the provirus is then integrated into the host genome[110,178]. Inset panel shows polarization of the HTLV-1 Gag protein (red) in the infected cell (left) towards the virological synapse (scale bar represents 5 μM). Inset is from Fig. 1E of Igakura, T. *et al.* Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. *Science* **299**, 1713–1716 (2003). Reprinted with permission from AAAS.

Mechanisms/pathophysiology

Neuropathology

The signs and symptoms of HAM/TSP are caused by focal inflammatory lesions in the CNS[33]. Inflammatory infiltrates of mononuclear cells can be widely dispersed throughout the CNS[34], but are found most frequently in the upper thoracic spinal cord. The infiltrate is dense around blood vessels, but can spread diffusely throughout the parenchyma. The cause of this distribution of lesions is not completely understood. T cells are thought to enter the CNS in 'watershed' areas of the circulation, where the blood flow rate is low, especially at the borders between regions supplied by different spinal arteries[35]. The mononuclear cell infiltrates consist primarily of T lymphocytes; $CD4^+$ T cells predominate in early, active lesions, and the proportion of $CD8^+$ T cells rises progressively as the lesion progresses[33,36,37]. The inflammatory process culminates, after months or years, in macroscopic changes in the CNS — in particular, a loss of spinal cord volume is evident on MRI[38,39] (FIG. 3).

The CNS is not the only system affected by HTLV-1-associated inflammatory diseases: several other inflammatory conditions have been described, notably uveitis[40], polymyositis[41], infective dermatitis[42], arthritis[43] and bronchiectasis[22]. The prevalence of these inflammatory diseases, including that of HAM/TSP, varies widely between HTLV-1-infected populations, presumably owing to differences in host genetics and in the ascertainment of the diseases.

Risk factors predisposing to HAM/TSP

Proviral load. The HTLV-1 proviral load is the strongest predictor of developing HAM/TSP[16,44,45]. Therefore, it is essential to identify the factors that determine an individual's proviral load in order to understand between-individual variation in the risk to progression to HAM/TSP. The HTLV-1 proviral load is measured as the number of HTLV-1 DNA copies per peripheral blood mononuclear cell (PBMC), and is usually expressed as the percentage of infected PBMCs, assuming that each cell carries a single proviral copy[46]. After the acute phase of infection, the proviral load reaches a stable value or 'set point', which is characteristic of each individual. The evidence, summarized below, shows that the set point proviral load is determined largely by the efficacy or 'quality' of that individual's T cell response to the virus[47], which in turn is determined by the host genotype.

In each individual, the set point HTLV-1 proviral load can fluctuate by a small factor (twofold to fivefold) over time. However, the proviral load varies widely between individuals, ranging from <3 copies per million PBMCs to >1 copy per PBMC in some cases of ATL[48]. HAM/TSP is rarely diagnosed in carriers with a proviral load of <1%, and there is an exponential increase in the prevalence of HAM/TSP at higher proviral loads[16,44]. However, a high proviral load alone is insufficient to cause the disease: patients who develop HAM/TSP have typically maintained a high proviral load for many years before the onset of symptoms[49], and 50% of asymptomatic carriers also have proviral loads of >1%. Thus, only a minority of carriers with a high proviral load develop HAM/TSP. Furthermore, once the proviral load exceeds the apparent threshold value of 1%, an even higher proviral load has not consistently been associated with faster disease progression[17,50,51].

Virus genetics. Globally, the most common HTLV-1 genotype is subgroup A. In contrast to HIV-1, HTLV-1 varies little in its sequence both within and between hosts[52], although minor variations exist between geographical isolates[53–55]. No single strain or sequence variant of the virus is uniquely associated with HAM/TSP[52,53], but certain variants are associated with a slight difference in the risk of the disease[56]. However, the bulk of the variation in risk between hosts is due to variation in the host, not in the virus. This conclusion focuses attention on host genetics and the immune response.

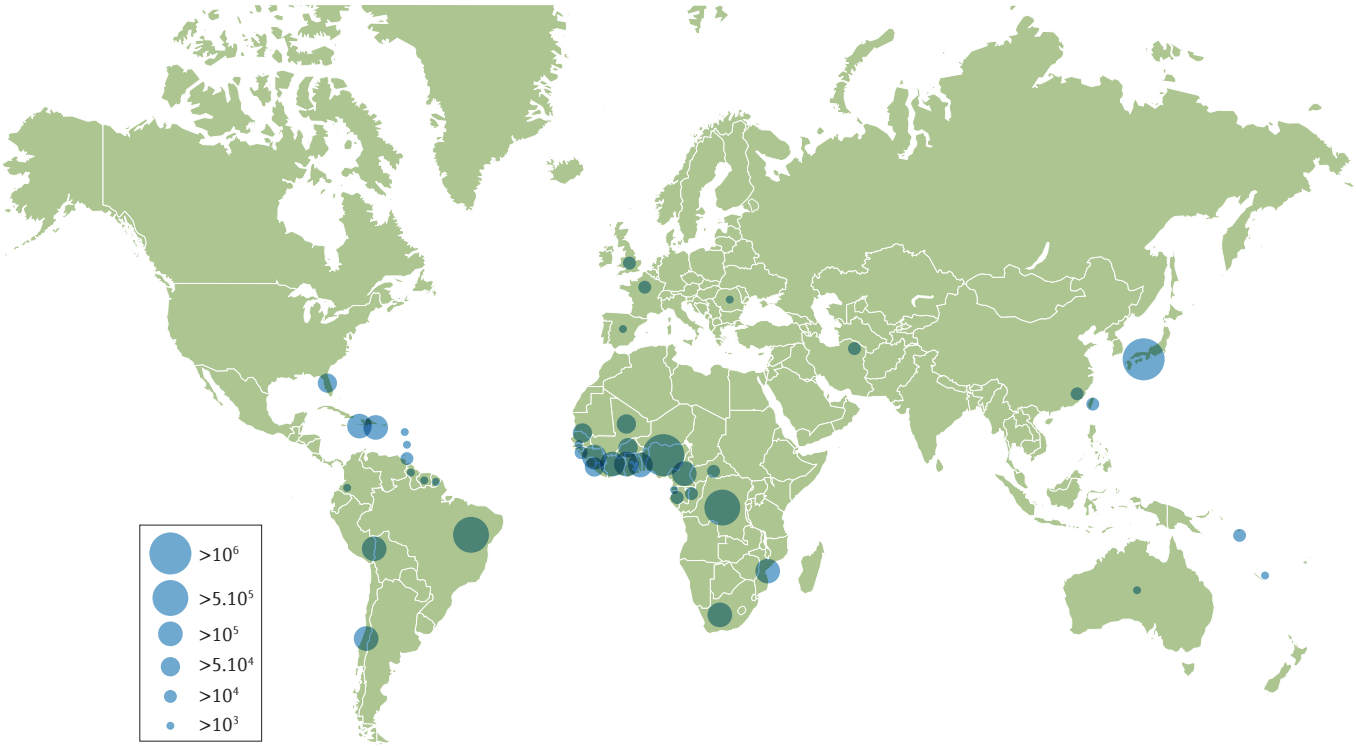

Figure 2 | **Global prevalence of HTLV-1 infection in endemic areas.** Circles show the estimated numbers of human T-lymphotropic virus 1 (HTLV-1)-infected individuals. HTLV-1 infection is most prevalent in Japan, South America and the Caribbean basin, and in west, central and southern Africa. Reproduced from REF. 18.

Host genetics. HTLV-1 infection is a prerequisite for both the development and diagnosis of HAM/TSP. However, as mentioned above, differences in the lifetime incidence of HAM/TSP among carrier populations suggest that additional environmental or host factors determine the risk.

The HLA class I genotype of an individual determines the specificity and the efficacy of their $CD8^+$ T cell response to a virus. In turn, the $CD8^+$ T cell response determines the proviral load set point and, therefore, the individual's risk of developing HTLV-1-associated disease. A protective effect of the class 1 allele *HLA-A*02* was observed in southern Japan[44,57,58] (see below), in a predominantly Afro-Caribbean cohort in the United Kingdom and in a Brazilian cohort[59]. *HLA-A*02* was not shown to be protective in studies in Peru[60], Iran or the French West Indies[61]; however, small cohort sizes and genetic admixture in these studies preclude a definitive conclusion. In a study in Spain, *HLA-DRB1*0101* and *HLA-B*07* were associated with higher proviral loads and with HAM/TSP[62].

In addition to the HLA genotype, single nucleotide polymorphisms (SNPs) in a small number of genes have been associated with the outcome of HTLV-1 infection. A polymorphism in the promoter of the inflammatory cytokine interleukin-6 (*IL6*-634C) was present at a higher frequency in patients with HAM/TSP than in asymptomatic carriers (odds ratio 5.3; 95% CI 1.6–17.5) in Salvador, Brazil[63]. A SNP at position −592 in the promoter of the immunosuppressive cytokine IL-10 (*IL10*-592A) was associated with a twofold reduction in risk of HAM/TSP in Japan, where it was calculated that the presence of *IL10*-592A prevented 44% of possible cases of HAM/TSP[64]. This association was not observed in the study from Brazil[63].

A promoter polymorphism (*TNF*-963A) in the gene encoding another inflammatory cytokine, tumour necrosis factor (TNF), was found to be associated with HAM/TSP in southern Japan, with an odds ratio of 9.7 (95% CI 1.3–74) in subjects with HTLV-1 proviral loads of >3 copies per 100 PBMCs[45]. In addition, a polymorphism in the 3UTR of the chemokine stromal cell-derived factor 1 (*SDF1*+801A) was associated with a 50% reduction in the risk of developing HAM/TSP. In the same population, the 191C allele of *IL15* conferred protection against HAM/TSP through an association with a lower proviral load[45]. A SNP in the *IL28B* gene was reported to be associated with HAM/TSP in Brazil[65].

There is some evidence of familial clustering of HAM/TSP cases[66], but the contribution of individual genes to this clustering has not been quantified.

Other risk factors for HAM/TSP. Age, sex and the route of HTLV-1 acquisition are known to influence the risk of developing HAM/TSP. HAM/TSP is rare in children; it has a peak incidence in the fifth decade of life[29]. Among patients with HAM/TSP, the ratio of females to males is 3:1 in Trinidad and Tobago[29] and 4:1 in the United Kingdom[51]. In a study of 88 patients with HAM/TSP from Brazil, the disease progressed faster in women than in men[67]. The higher risk of developing HAM/TSP in women is partly due to a higher frequency of infection,

but the reason for the apparently greater susceptibility of women to the disease is not known. Finally, there have been reports of HAM/TSP developing within months of HTLV-1 infection acquired through blood transfusion or through solid organ or bone marrow transplantation[68–71]; in some patients, the disease progressed rapidly. However, the small number of these cases precludes a robust estimation of the absolute risk of HAM/TSP in transplant recipients. In general, HTLV-1 acquired by any route can result in the development of HAM/TSP after an interval that ranges from months to decades.

Host response to HTLV-1

Inflammation. The presence of a lymphocytic infiltrate in CNS lesions suggests that the immune or inflammatory response to HTLV-1 causes the observed tissue damage. The innate immune response has been relatively little studied in HTLV-1 infection, but some work has revealed the important roles of interferons[72–74]. A gene expression microarray study of peripheral blood provided strong evidence that interferons are a major pathway of pathogenesis; the study revealed a transcriptional signature of interferon-stimulated genes in patients with HAM/TSP[74]. However, whether this signature is due to type 1 or type 2 interferons, or both, is unclear because most interferon-stimulated genes are regulated by both types of interferon, and the half-life of interferons themselves *in vivo* is too short to enable accurate quantification. Interferon-γ (IFNγ; a type 2 interferon) probably has a pathogenetic role in the disease because the HTLV-1 Tax protein induces a T helper 1-like state[75] and IFNγ expression[76] in infected CD4$^+$ T cells. By contrast, IFNβ (a type 1 interferon) can impair HTLV-1 replication *in vitro*[77], and IFNα (a type 1 interferon) inhibits HTLV-1 infection through an effect of the interferon-stimulated gene *PKR* (also known as *EIF2AK2*) on late (post-transcriptional) stages of viral replication[78].

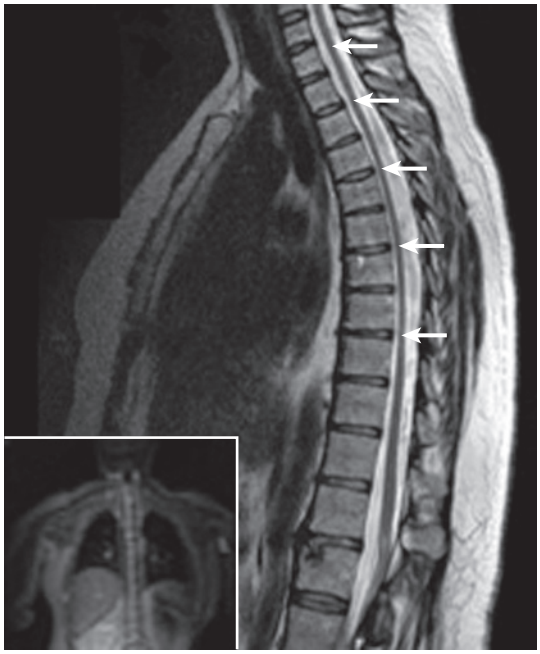

Figure 3 | **MRI scan of an atrophic spinal cord in a patient with human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis.** The abnormally thin spinal cord (dark) is indicated with arrows. Inset shows anteroposterior view of the cervical and thoracic spine. Image courtesy of the Imperial College Healthcare NHS Trust, UK.

Cytotoxic T lymphocytes. The CD8$^+$ cytotoxic T lymphocyte (CTL) response to HTLV-1 has been intensely studied (reviewed in REFS 47,79,80). HTLV-1-specific CTLs are typically abundant in the peripheral blood, and their abundance is proportional to the HTLV-1 proviral load. The CTLs are chronically activated, which suggests that the virus is not latent *in vivo* but is expressed persistently or at frequent intervals. The dominant antigen recognized by the anti-HTLV-1 CTLs is the Tax protein[81–83]. The finding of persistently activated CTLs in patients with HAM/TSP led to the hypothesis that these cells cause the inflammatory tissue damage observed in this disease[80]. However, CTLs are usually necessary, and often sufficient, to limit the replication of a virus *in vivo*. In fact, antiviral CTLs can exert both protective and pathogenetic (inflammatory) effects, for example, in infection with lymphocytic choriomeningitis virus in the mouse[84].

In HTLV-1 infection, the dynamic nature of the persistent infection precludes a simple conclusion about the balance between the beneficial (virus-killing) and detrimental (inflammatory) effects of the CTL response[79,85,86]. Nevertheless, clear evidence for a beneficial effect of the CTL response emerged from studies of host immunogenetics[44,57,58,87,88]. In an endemically HTLV-1-infected population in Kyushu, southern Japan, possession of either of the two class I MHC alleles *HLA-A*02* or *HLA-Cw*08* is associated with a lower proviral load and a lower risk of HAM/TSP[44,58] (FIG. 4). Class I MHC molecules are responsible for presenting antigen to CTLs, whereas class II molecules present antigen to CD4$^+$ T cells. This class I MHC-associated protection is enhanced by the possession of the killer immunoglobulin-like receptor allele *KIR2DL2* (REF. 88), but the mechanism of this enhancement is not yet known. Efficient control of viral replication is associated with CTL recognition of the poorly immunogenic HBZ protein of HTLV-1, not the immunodominant antigen Tax[87]. These observations imply that the genetically determined responsiveness[86] or 'quality'[47] of the host CTL response, rather than the magnitude of the response, determines the set point proviral load and, consequently, the risk of inflammatory diseases such as HAM/TSP in that individual. However, the abundant but inefficient anti-HTLV-1 CTLs found in patients with HAM/TSP could contribute to the inflammatory tissue damage in the CNS[80]. This possibility is strengthened by the observation[44,58] that another class I HLA allele, *HLA-B*54*, is associated with a higher risk of HAM/TSP in southern Japan.

T helper cells. The role of the CD4$^+$ T helper cell response is less clear, but several observations suggest that these cells play an important part in the pathogenesis of HAM/TSP. First, CD4$^+$ T cells predominate in early HAM/TSP lesions[33]. Second, HTLV-1-infected CD4$^+$

T cells secrete IFNγ[75,76], and the frequency of IFNγ-secreting HTLV-1-specific CD4+ T cells has been shown to be higher in patients with HAM/TSP than in asymptomatic HTLV-1 carriers with a similar proviral load[89]. Third, a class II MHC allele, *HLA-DRB1*0101*, is associated with a high risk of HAM/TSP in Kyushu, southern Japan[44]. An attractive hypothesis has been advanced recently by Ando *et al.*[90] whereby IFNγ secreted by infected CD4+ T cells causes astrocytes[91] to secrete the chemokine CXCL10 (also known as IP-10). CXCL10 then recruits additional infected CD4+ CXCR3+ T cells to the lesion. Thus, a positive feedback loop is established, resulting in a high local concentration of IFNγ and subsequent damage to the neural tissue (FIG. 5).

Regulatory T cells. CD4+ T cells that express the transcription factor forkhead box protein P3 (FOXP3) can act as regulatory T cells, which inhibit the activation and proliferation of other T cells. HTLV-1 induces and maintains a high frequency of FOXP3+CD4+ T cells, especially in patients with HAM/TSP[92] or ATL[93]. This high frequency of FOXP3+CD4+ T cells is caused by the HTLV-1 Tax protein[94]. Tax induces CD4+ T cells to produce the chemokine CCL22, which prolongs the survival of regulatory T cells by binding to the CCL22 receptor (CCR4), which is characteristically expressed on the surface of regulatory T cells. Some evidence indicates that these FOXP3+CD4+ T cells impair the efficiency of the CTL response to HTLV-1 (REF. 92), thereby conferring a survival advantage on the virus. The chemokine receptor CCR4 is expressed on a majority of HTLV-1-infected T cells, both CD4+ and CD8+, and clinical trials are now underway to test the efficacy of a CCR4-specific monoclonal antibody in the treatment of both HAM/TSP[95] and ATL[96]. Although many of the FOXP3+CD4+ T cells are uninfected, HTLV-1 seems to favour infection of these cells compared with FOXP3−CD4+ T cells[97]. The uninfected FOXP3+CD4+ T cells act as regulatory T cells; inhibition of FOXP3 function by HTLV-1 Tax[98] or HBZ[99] might in fact enhance the inflammatory phenotype of infected CD4+ T cells[75].

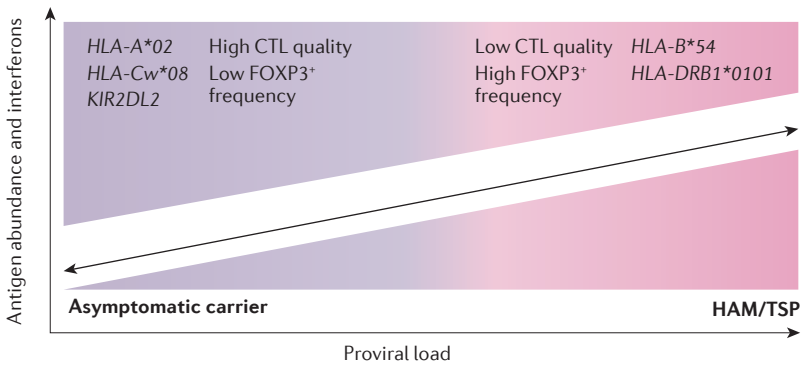

Figure 4 | **Risk factors for HAM/TSP development.** The host genotype (primarily of the HLA class I and the killer-cell immunoglobulin-like receptor (KIR) loci) determines the quality of the cytotoxic T lymphocyte (CTL) response against human T-lymphotropic virus 1 (HTLV-1). The CTL response and the frequency of forkhead box protein P3 (FOXP3)+ T cells determine the number of HTLV-1+ T cell clones — and, therefore, the proviral load set point — in that individual. The proviral load is an important risk factor for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP); asymptomatic carriers tend to have lower proviral loads than those who develop HAM/TSP. Antigen abundance is correlated with proviral load. HAM/TSP is associated with a strong, chronically activated interferon response.

Natural killer cells. The abundance and activity of natural killer cells in the circulation is typically lower in patients with HAM/TSP than in asymptomatic carriers[74,100–102]; however, the causes and consequences of this phenomenon are not understood. Further research is required to understand the natural killer cell response in HTLV-1 infection.

Antibody response. Antibodies reduce the efficiency of HTLV-1 transmission from mother to child by breast-feeding[103], and reduce HTLV-1 propagation in nonobese diabetic/severe combined immunodeficiency mice[104] and in rabbits[105]. The titre of HTLV-1-specific antibodies in infected individuals is frequently very high, especially in patients with HAM/TSP, but there is no evidence to suggest that these antibodies contribute to pathogenesis. The high antibody titre possibly reduces the infectious spread of HTLV-1 in the host, and instead favours maintenance of the proviral load by proliferation of infected cells (mitotic spread)[106]. One group suggested that mimicry of a self-antigen (heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1)) by HTLV-1 Tax might lead to antibody-mediated autoimmune damage in HAM/TSP[107]. However, there is some evidence that the presence of hnRNPA1-specific antibodies in the cerebrospinal fluid (CSF) is not specific to this disease[108].

Clonality of HTLV-1 *in vivo*

HTLV-1 drives a strong proliferation of infected T cells, as shown by Southern blot analyses of genomic DNA from PBMCs[109] and linker-mediated PCR analyses of PBMC DNA[10]. Until recently, it was believed that oligoclonal proliferation of HTLV-1-infected cells contributed to the pathogenesis of HAM/TSP. However, evidence from a high-throughput analysis of HTLV-1 clonality has shown that a typical individual with non-malignant HTLV-1 infection possesses between 10^4 and 10^5 different infected T cell clones[8,9,110]. Furthermore, the HTLV-1 proviral load, which is the strongest risk factor for developing HAM/TSP[16,45], is correlated with the number of distinct HTLV-1-infected T cell clones but not with the extent of oligoclonal proliferation[9]. These observations imply that oligoclonal proliferation itself does not contribute to HAM/TSP development. The high proviral load in a patient with HAM/TSP consists of a large number of low-abundance clones[8,9] and the frequency of spontaneous Tax expression is considerably higher in low-abundance clones than in those of high abundance[8]. Thus, HAM/TSP is associated with a large number of low-abundance, Tax-expressing clones.

Mechanism of tissue damage in HAM/TSP

The evidence reviewed here strongly suggests that the host immune response causes the tissue damage observed in the CNS in HAM/TSP. But what is the mechanism underlying this damage? The absence of a good animal model of HAM/TSP precludes direct proof; accordingly, the likely

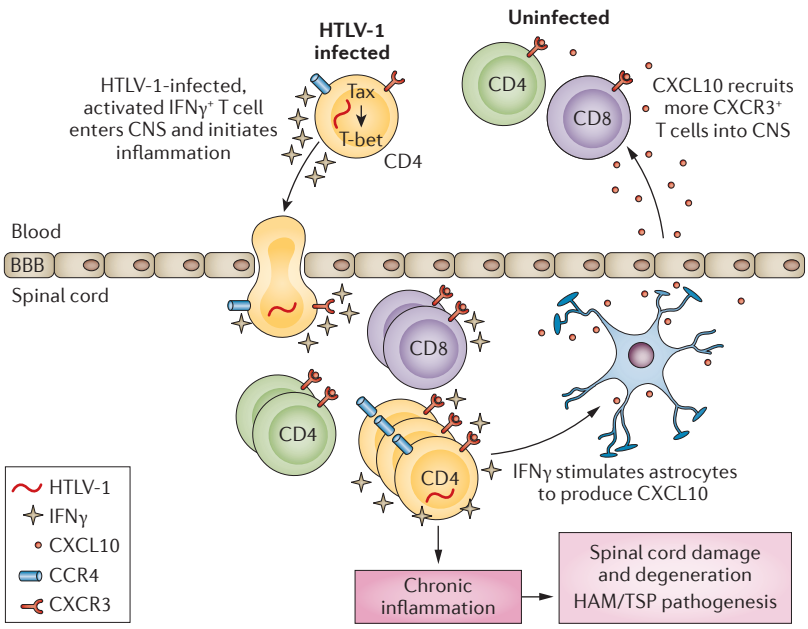

Figure 5 | **Proposed mechanism of tissue damage in HAM/TSP.** Expression of the human T-lymphotropic virus 1 (HTLV-1) Tax protein activates the infected T cell (top left of figure), which crosses the blood–brain barrier (BBB) into the CNS. Interferon-γ (IFNγ) secreted by the infected T cell stimulates astrocytes to secrete the chemokine CXCL10, which recruits more T cells that express the cognate receptor CXCR3, thereby establishing a self-perpetuating focus of inflammation. Infected $CD4^+$ T cells are shown in yellow, uninfected $CD4^+$ T cells in green. T-bet is a transcription factor that directs lineage commitment of T helper 1 (T_H1) $CD4^+$ cells. CCR4 binds the chemokine CCL22, which is secreted by HTLV-1 Tax-expressing T cells and increases survival of $CCR4^+$ cells. HAM/TSP, HTLV 1-associated myelopathy/tropical spastic paraparesis.

mechanism must be inferred. Three categories of mechanism can be considered: infection with HTLV-1 of resident cells in the CNS, that is, neurons and glial cells; mimicry of a host antigen by HTLV-1; or bystander damage. No convincing evidence shows that cells normally resident in the CNS become infected, and more evidence is required to make a case for antigen mimicry. Thus, by exclusion, the disease most likely results from bystander damage[111,112]. In this hypothesis, neurons and glial cells are damaged by toxic or inflammatory products released from the HTLV-1-infected T cells and the responding CTLs present in the cellular infiltrates in the CNS. IFNγ probably plays a significant part[90] in tissue damage, and other inflammatory cytokines, such as TNF and IL-6, might also contribute. It is uncertain whether type 1 interferons have a protective or pathogenetic role.

To summarize, current evidence favours the following causal sequence of tissue damage in HAM/TSP: a genetically determined inefficient immune response, especially the CTL response[44,47,58], results in a large number of infected T cell clones[8,9], which frequently initiate spontaneous expression of the proviral plus-strand DNA[8]. This proviral expression leads to a high abundance of viral antigen at equilibrium (or set point)[86], and a subsequent strong persistent stimulation of both $CD4^+$ and $CD8^+$ T cells to produce potentially inflammatory products, especially IFNγ, the expression of which is also directly induced by the HTLV-1 Tax protein[76].

Diagnosis, screening and prevention

Use of risk factors in diagnosis

As mentioned above, the genotype, age and sex of the host and the proviral load and strain of HTLV-1 contribute to the risk of developing HAM/TSP. However, application of these risk factors and clinical or laboratory features has not proved helpful in making a diagnosis in individual cases. In a Japanese analysis, the only clinical correlates of the diagnosis of HAM/TSP were detection of brisk patellar tendon reflexes, which might reflect subclinical disease, and the presence of 'flower cells'[113], which are HTLV-1-infected lymphocytes with a characteristic multilobular nuclei (FIG. 6). However, atypical lymphocytes with an abnormal nuclear morphology can be observed in individuals with any clinical manifestation of HTLV-1 infection; their presence is associated with inflammation rather than with a higher risk of developing ATL[114].

Clinical diagnosis of HAM/TSP

Criteria for the diagnosis of HAM/TSP were agreed by the WHO in 1990 (REF. 115). A proposal for an updated, staged approach to the diagnostic criteria[116] of HAM/TSP is summarized in BOX 2.

The characteristic features of HAM/TSP are subacute or chronic onset lower-limb weakness or stiffness, which can initially be unilateral but invariably becomes bilateral and is associated with generalized hyper-reflexia and extensor plantar responses. Weakness of the lower limbs progresses to an abnormal, spastic gait. In a 14-year clinical follow-up study in Martinique[17], the median time from onset to use of a unilateral walking aid was 6 years; the median onset to wheelchair dependency was 21 years. Older age at onset (>50 years) and a high proviral load were associated with faster disease progression. Lower back pain is common, often radiating to the legs and often with neuralgic features. Ill-defined sensory symptoms, such as distal paraesthesia in the lower limbs, are also common[117]; however, objective sensory signs are unusual and, when they are present, usually reflect the involvement of the posterior columns of the spinal cord and are associated with diminished vibration and position sense. A well-defined sensory level (sensory dysfunction corresponding to the 'level' of the lesion in the spinal cord) is rarely observed in HAM/TSP. Constipation is common, as are increased urinary frequency, nocturia, urgency and sometimes incontinence; in men, erectile dysfunction is common[118]. The urinary symptoms are usually attributable to bladder hyperactivity, but 15% of patients have flaccid bladders, with urinary retention and a risk of obstructive nephropathy[119]. HAM/TSP is the most common cause of chronic, non-traumatic, non-compressive myelopathy in many endemic countries, and is highly incapacitating over time[119–121]. Some evidence shows mild cognitive impairment in both asymptomatic HTLV-1 carriers and in patients with HAM/TSP[122], but further studies are needed on the impact of HTLV-1 infection on cognitive function.

A common pitfall is to misdiagnose HAM/TSP as disseminated multiple sclerosis, usually of the primary progressive subtype, particularly if the patient is not in

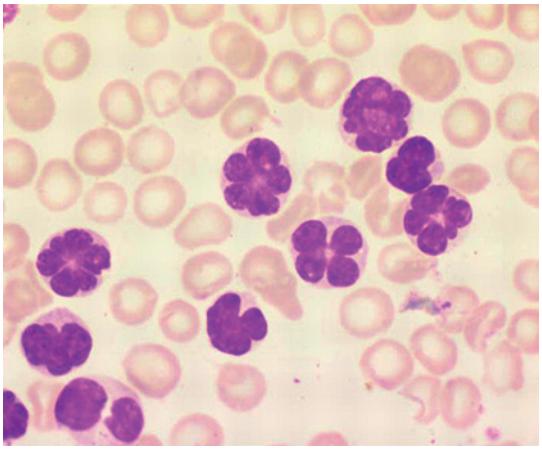

Figure 6 | **Flower cells in HTLV-1 infection.** Some human T-lymphotropic virus 1- (HTLV-1)-infected T lymphocytes develop morphologically abnormal, multilobular nuclei, sometimes giving the appearance of a flower. These morphologically abnormal cells, including 'flower cells', were previously thought to be diagnostic of adult T cell leukaemia/lymphoma caused by HTLV-1. However, these cells are also present in some asymptomatic HTLV-1 carriers and patients with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[179,180]. Republished with permission of the American Society of Hematology, from Flower cells of leukemia, *Blood* **115**(9), 1668 (2010) (REF. 181); permission conveyed through Copyright Clearance Center, Inc.

a group at high risk of HTLV-1 infection. Even detailed family, transfusion and sexual histories might not identify a risk of HTLV-1 infection. Indeed, rare case reports have documented HTLV-1-seronegative TSP[123], but the relationship of such cases to HAM/TSP remains unclear.

Box 2 | **Diagnostic guidelines for HAM/TSP**

Diagnostic criteria for human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) are presented according to the level of ascertainment[116].

Definite

- A non-remitting progressive spastic paraparesis with sufficiently impaired gait to be perceived by the patient. Sensory symptoms or signs can be present. When present, they remain subtle and without a clear-cut sensory level. Urinary and anal sphincter signs or symptoms can be present.
- Presence of HTLV-1 antibodies in serum and CSF confirmed by western blot analysis and/or a positive PCR for HTLV-1 in blood and/or CSF.
- Exclusion of other disorders that resemble HAM/TSP.

Probable

- Monosymptomatic presentation: spasticity or hyper-reflexia in the lower limbs or isolated positive Babinski sign with or without subtle sensory signs or symptoms, or neurogenic bladder only confirmed by urodynamic tests.
- Presence of HTLV-1 antibodies in serum and/or CSF confirmed by western blot analysis and/or a positive PCR for HTLV-1 in blood and/or CSF.
- Exclusion of other disorders that resemble HAM/TSP.

Possible

- Clinical presentation with some or all of the symptoms described above.
- Presence of HTLV-1 antibodies in serum and/or CSF confirmed by western blot analysis and/or a positive PCR for HTLV-1 in blood and/or CSF.
- Disorders that resemble HAM/TSP have not been excluded.

Laboratory investigations

Detection of HTLV-1 antibodies is required for the diagnosis of HAM/TSP, and a positive antibody result from an enzyme-linked immunoassay must be confirmed either by western blot analysis or by detection of viral nucleic acid. Although not essential, quantification of the HTLV-1 proviral load in PBMCs can be helpful, particularly in patients with atypical or incomplete clinical features. CSF protein concentration and lymphocyte count can be normal or mildly raised. The HTLV-1 proviral load in CSF lymphocytes is usually high, higher even than in the PBMCs[124], and an algorithm based on the combination of CSF HTLV-1 antibody titre, antibody index (the ratio of the antibody concentrations in CSF and circulation), HTLV-1 proviral load and inflammatory response has been reported to have a 100% positive predictive value and 98% negative predictive value for HAM/TSP[125]. The concentration of CXCL10 is higher in the CSF of patients with HAM/TSP than in control subjects or patients with disseminated multiple sclerosis[126], and the CSF concentrations of CXCL10, CXCL9 and neopterin have been proposed as prognostic biomarkers for HAM/TSP[127]. High concentrations of CXCL10 and CXCL9 and low concentrations of CCL2 in the serum have also been associated with HAM/TSP, rather than asymptomatic carriage of HTLV-1 infection[128]. High plasma concentrations of β_2-microglobulin and calgranulin B, and low apolipoprotein A2 levels distinguish patients with HAM/TSP from asymptomatic HTLV-1 carriers independently of HTLV-1 proviral load; plasma β_2-microglobulin and calgranulin B together correctly identified 81% of patients with HAM/TSP[129]. The high plasma concentration of β_2-microglobulin reflects the high frequency of activated $CD8^+$ T cells, which recognize antigens presented by class I MHC molecules. Class I MHC molecules are noncovalently associated with β_2-microglobulin in the cell membrane. The role of the chemokines and biomarkers discussed above in the pathogenesis of HAM/TSP is unknown.

Neuroimaging and CSF examination are essential to exclude other diseases, but do not reveal any features that are unique to HAM/TSP. The spinal cord can be swollen, normal or atrophic (FIG. 3) depending on the stage of disease, with or without changes in the MRI signal. However, MRI changes are frequently observed[130,131]; in particular, the presence in the spinal cord of T2 signal hyperintensity, which is characteristic of oedema, is associated with more rapidly progressive disease[132] and, accordingly, has prognostic implications.

Screening and prevention of HAM/TSP

With the exception of the screening of blood and tissue donors, screening programmes for HTLV-1 infection are rare, and even blood-donor screening is not conducted in all countries. Consequently, the only people aware of their HTLV-1 infection status are donors who have been screened, patients already diagnosed with HTLV-1-associated disease and the sexual partners and relatives of these index cases if they have been offered, and have accepted, HTLV-1 tests. These people should be offered clinical review for evidence of HAM/TSP, other

Table 1 | **Drugs and other therapies used in the treatment of HAM/TSP**

Drug or therapy*	Comments	Refs
Corticosteroids	• Most used drugs to treat HAM/TSP • No placebo-controlled study conducted; most data are from case series • Work better in recent-onset cases, although seem to lose efficacy with time • Difficult to maintain in high doses owing to adverse effects	141, 154
Interferon-α	• Positive result in one double-blind, placebo-controlled study ($n = 48$, only 28-day duration) • Efficacy in one open-label study ($n = 167$, efficacy ratio at 4 weeks of 66.2%)	182, 183
Interferon-β	• Improvement in some measures of motor function; no clinical progression during therapy in one open trial ($n = 12$)	184
Cyclosporin A	• One open-label pilot study ($n = 7$ with either <2 years' duration of disease or progressive disease, 48 weeks of therapy) • Five patients showed objective evidence of clinical improvement, 2 patients restarted cyclosporine A during follow-up, owing to relapse	148, 185
Danazol	• Two open-label trials ($n = 6$ and $n = 8$, respectively); 'favourable response' achieved: 2 patients who had been in a wheelchair became ambulatory • In one study, improvement was noted within 15 days of administration; in one study, beneficial response was preferentially found in female participants • Slight elevation in liver enzymes responded to a decrease in dose	151, 186
Vitamin C	• One open-label trial ($n = 7$, intermittent high-dose) • Disability score decreased (9.7 months after the therapy, from grade 7.1 to grade 3.6)	187, 188
Plasmapheresis	• Sporadic case reports • Short-lived (2-4 weeks) improvement in 11 of 18 patients • Lowered titres of HTLV-1 antibodies in serum but not in CSF (no correlation with the effects of plasmapheresis)	189
Monoclonal antibodies specific for the IL-2 receptor (anti-Tac or daclizumab)	• Selective downregulation of activated T cells and a decrease in the HTLV-1 PVL in peripheral blood lymphocytes in one open-label trial ($n = 9$, no significant clinical response)	190
Antiretroviral drugs	• Scattered reports of clinical improvement or reduction in PVL with lamivudine or zidovudine • No clinical response and no difference in PVL and T cell activation and proliferation in one randomized, double-blind, placebo-controlled study ($n = 16$, 6 months combination therapy with zidovudine and lamivudine) • No differences in PVL, WTT, visual analogue pain score and $CD4^+$ or $CD8^+$ lymphocyte counts in one open-label study ($n = 6$, tenofovir)	143, 144, 193
Valproic acid	• One 2-year open-label trial ($n = 19$); no change in PVL, expression of CD38 or HLA-DR on lymphocytes, $CD8^+$ T cell-mediated lysis efficiency or mean disability score • WTT worsened in 3 patients (>20%, due to adverse drug effects including drowsiness and tremor, reversible after stopping treatment)	192
Green tea	• Reduced PVL (asymptomatic HTLV-1 carriers, 37 received fixed amount of green tea extract powder, 46 controls)	193
Lactobacillus casei	• Increased natural killer cell activity, improvements in spasticity and urinary symptoms in an open-label trial ($n = 10$, fermented milk containing viable *L. casei* strain Shirota for 4 weeks)	194
Pentoxifylline	• One open-label trial ($n = 15$, 4 weeks) • Improved motor disability, especially spasticity in 13 patients • Suppressed spontaneous proliferation of peripheral blood mononuclear cells in 14 patients	150
Heparin	• One small open-label trial ($n = 10$); motor dysfunction improved substantially and the effect continued for >1 month after discontinuation of therapy in 7 patients	195
Prosultiamine	• One open-label label trial ($n = 24$, treated for 12 weeks) • In most patients there was a reduction in spasticity and an improvement in WTT and urodynamic parameters; the PVL in the peripheral blood decreased by 15.4% compared with pretreatment levels	152
Pentosan polysulfate	• Improvement in lower-extremity motor function and WTT, based on reduced spasticity in an open-label trial ($n = 12$, subcutaneous administration) • No change in PVL or chemokine CXCL10 and CCL2 levels, increased serum concentration of sVCAM1, positive correlation between the increase in sVCAM1 and the reduction in WTT	153

CSF, cerebrospinal fluid; HAM/TSP, human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis; PVL, proviral load; WTT, walking time test; sVCAM1: soluble vascular cell adhesion molecule 1. *For more details on doses, schedules, costs and adverse effects of drugs as well as the magnitude of effect of the main trials mentioned above, the reader is referred to REFS 154,196.

HTLV-1-associated inflammatory diseases and chronic asymptomatic ATL. HTLV-1 proviral load quantification is useful to identify those at high risk of disease, who can then be offered more frequent clinical follow-up care. The prevalence of subclinical signs or mild symptoms of HAM/TSP varies between populations. Family history frequently reveals a possible HTLV-1-associated disease in a sibling or older relative, although often without a clear diagnosis. Carriers with a high HTLV-1 proviral load as well as patients with HAM/TSP are at greater risk of developing ATL[114].

To date, there is no evidence that HAM/TSP can be prevented in those already infected with HTLV-1, and therefore prevention of infection is paramount. Data from Japan showed a 16% reduction in the incidence of HAM/TSP 2 years after the introduction of blood-donor screening[69], which emphasizes the importance of transfusion-transmitted infection as a cause of HAM/TSP. Depletion of leukocytes substantially reduces the proviral load in cellular blood products[133] and the risk of transmission[6], but is only suitable for red-cell products. Transfusion of cell-free blood products does not transmit HTLV-1 infection. As mentioned above, case reports of rapid-onset and aggressive HAM/TSP suggest that infection acquired through organ transplantation carries a particularly high risk of developing HAM/TSP, perhaps compounded by immune suppression[134]; however, the risk compared with other routes of infection is unknown. Up to 80% of mother-to-child transmissions of HTLV-1 are prevented by the avoidance of breastfeeding[135–137], but antenatal screening programmes are rare outside Japan.

Management

The clinical management of HAM/TSP is based on the treatment of symptoms such as back pain and muscle spasm, measures directed at the putative underlying pathological process, and counselling of patients, their families and contacts. But, as discussed above, the pathogenetic mechanisms are incompletely understood. In particular, it is unclear to what extent symptoms are due to inflammation, subsequent neurodegeneration or disuse atrophy. This distinction is important because HAM/TSP behaves as a biphasic illness in most patients. The disease usually progresses without remission, but there is intra-individual and inter-individual variation in the rate of disease progression[17,50,51,138,139]. This variation in disease progression is important because it can explain the variable therapeutic success rates reported in the literature. These discrepancies could be largely attributable to the timing of pharmacological immunosuppression, because it is widely believed that the therapeutic window in HAM/TSP lies within the first few years of the disease[140]. Thus, both early diagnosis and prompt treatment are essential for successful management of patients with the disease.

So far, most therapeutic trials in HAM/TSP have attempted to suppress or modulate the immune response, or to reduce the HTLV-1 proviral load in an attempt to decrease the risk or modify the course of the disease. Several drugs have been evaluated, but most have not been subjected to properly designed, randomized, double-blind, placebo-controlled trials. Oral or intravenous corticosteroids remain the mainstay of HAM/TSP treatment, particularly in the initial phase of the disease when inflammation is more prominent than demyelination and gliosis[141]. Motor disability might be ameliorated with steroids[141,142], but improvement is usually not sustained; the impact of steroids on pain and urinary dysfunction is less well documented.

As HAM/TSP is associated with a high HTLV-1 proviral load, reducing this load could treat or even prevent disease. However, despite *in vitro* evidence indicating that certain nucleoside/nucleotide analogue reverse transcriptase inhibitors are active against HTLV-1, *in vivo* results have been disappointing[143,144]. Valproic acid has been tested as a potential treatment for HAM/TSP because this drug can activate HTLV-1 proviral gene expression and subsequently expose virus-infected cells to the immune system, leading to a reduction in the proviral load[145]. However, the drug was ineffective in

Table 2 | **Symptomatic drug treatment for HAM/TSP**

Symptom or sign	Drug or therapy*	Refs
Spasticity	Baclofen, tizanidine, botulinum toxin injections	197
Neurogenic bladder	Oxybutynin, doxazosin mesylate, imipramine, bethanechol (when urinary retention predominates), intermittent catheterization, intradetrusor injections of botulinum toxin, specific physiotherapy	198
Prophylaxis of urinary tract infections	Intermittent catheterization, low daily dose of sulfamethoxazole or nitrofurantoin (controversial)	198
Constipation	Fibre-rich diet, increased fluid intake, oral psyllium mucilloid, mineral oil, lactulose, prucalopride, lubiprostone, intermittent use of suppositories or enemas in more-severe cases, specific physical therapy	199
Neuropathic pain	Tricyclic antidepressants, gabapentin, pregabalin	200–202
Non-neuropathic or mechanical pain	NSAIDs	200–202
General motor disability	Physical therapy	17,203

HAM/TSP, human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis. *For details of doses, schedules, costs and side effects of treatments, the reader is referred to REF. 154.

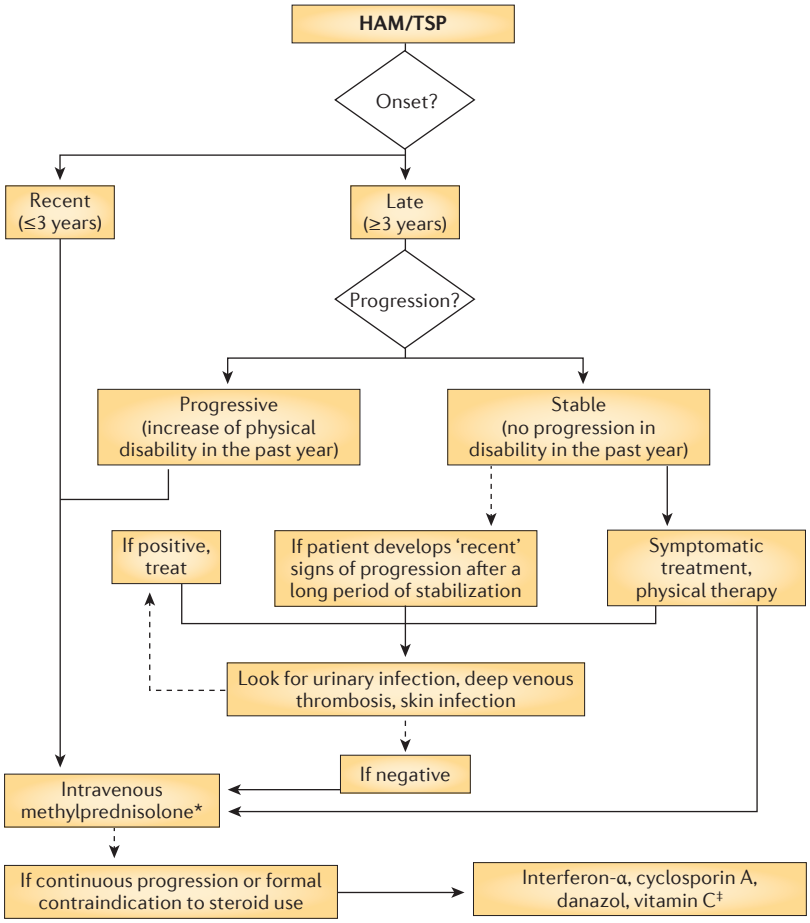

Figure 7 | **Flowchart for the treatment of HAM/TSP.** This flowchart represents the current approach of one of the authors (A.A.), based on more than 25 years of experience in the clinical management of human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP). This algorithm has not been formally validated; its use in everyday practice should be based on careful clinical judgment and in an individualized approach. *1 g per day for 5 days, followed by oral prednisolone or prednisone 1 mg per kg per day for 2 months, followed by slow tapering until the lowest possible maintenance dose is reached without worsening of symptoms. ‡No comparison between drugs available; choice is only based on costs, local availability and personal experience.

improving motor and other disabilities, and the reduction in proviral load was not sustained. Other reagents such as IFNα[146,147], cyclosporin A[148], methotrexate[149], pentoxifylline[150], azathioprine[141] and danazol[151] might be tried if steroids fail or cannot be tolerated, but they should be only used after a careful risk–benefit analysis. More recently, small open trials of prosultiamine, a vitamin B_1 derivative known to induce apoptosis in HTLV-1-infected cells, and of pentosan polysulfate sodium, a heparin derivative that reduces blood viscosity, have provided evidence of some clinical improvement in HAM/TSP[152,153]. Larger, double-blind studies are needed to confirm these results. Symptomatic treatment using drugs and physical therapy to alleviate pain (which strongly correlates with a low quality of life in individuals with HAM/TSP), spasticity and to improve bladder control is the current mainstay of clinical management.

TABLE 1 and TABLE 2 summarize the main treatments and their specific purpose (reversing or delaying the progression of the disease or relieving symptoms); for a more detailed discussion of different drug options refer to REFS 154,155. A current algorithm for the management of HAM/TSP is shown in FIG. 7.

The reasons for the absence of good clinical studies in HAM/TSP include the difficulty in enrolling patients, inadequate or nonstandardized scales to evaluate neurological improvement or deterioration, and the lack of interest in research agencies of more developed countries to fund large, multicentre and rigorous clinical studies. The lack of positive clinical results, notwithstanding some improvement in biomarkers of inflammation or viral activity, might be because treatment is typically started in the late phase of the disease, when inflammation has subsided and scarring, gliosis and neurodegeneration explain the clinical deficit. Thus, future clinical trials should take into account the phase of the illness before assessing a specific drug.

In summary, early diagnosis and appropriate timely therapeutic intervention are critical factors in ensuring a favourable long-term outcome. Reliable biomarkers are needed that predict the development of HAM/TSP in high-risk populations and to facilitate early therapeutic intervention to prevent irreversible clinical deficit. As the rate of progression of HAM/TSP in an individual patient is unpredictable, there is also a need for biomarkers that correlate with the activity of the disease in the spinal cord. Such biomarkers must reflect the two apparent modes of neurological damage: the early, predominantly inflammatory phase, and the later neurodegenerative phase. For example, markers that correlate with neuronal, axonal and glial loss, such as microtubule-associated protein tau, neurofilaments and *N*-acetylaspartate should be investigated, as well as proteins involved in remyelination and regeneration, such as reticulon-4A (also known as Nogo A)[156]. Finally, serum or urine biomarkers that monitor the response to treatment should also be developed.

Quality of life

HAM/TSP is characterized by lower-limb dysfunction, so mobility presents the greatest challenge to the quality of life for patients; the primary complaint is impairment of gait[121,157]. Patients progress at varying speeds from canes to crutches and walkers, and eventually to wheelchairs; in the worst cases, the patient is bedridden[51]. The patient's physical disability and dependence limit their activities of daily life and impair their emotional and social status[158].

The impact of another prominent symptom of the disease, neurogenic bladder dysfunction, has been underestimated. A detailed investigation revealed that management of bladder function was the category in which the fewest patients with HAM/TSP were independent, even fewer than in mobility categories such as walking and stairs[121]. Bladder symptoms cause not only discomfort and embarrassment, making it difficult to participate in social and work events, but also severe sleep disturbances[159], which can further degrade both

Box 3 | **Open research questions**

Virology

- What regulates the latency of the integrated human T-lymphotropic virus 1 (HTLV-1) provirus *in vivo*?
- What is the contribution of infectious spread to the maintenance of the proviral load and to the inflammation observed in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)?

Immunology

- How does the HLA class I restricted T cell response confer protection? The reduced risk of developing HAM/TSP associated with certain HLA class I genes (for example, *HLA-A*02*) is not wholly attributable to a reduction in proviral load.
- How does *HLA-B*54* increase the risk of developing HAM/TSP?
- How does *KIR2DL2* (killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 2) enhance HLA class I-mediated protection in HTLV-1 infection?
- Why is HTLV-1 basic zipper factor (HBZ) such a weak immunogen for cytotoxic T lymphocytes? Can the response to HBZ be enhanced, for example, by a therapeutic vaccine?

Pathogenesis

- Is there subclinical inflammation in asymptomatic HTLV-1 carriers with a high proviral load?
- What distinguishes patients with HAM/TSP from asymptomatic carriers with a high proviral load?
- What triggers the onset of the CNS inflammation?
- How extensive and how durable is inflammation in HAM/TSP?
- Does a reduction in proviral load lead to a reduction in inflammation and amelioration of symptoms?
- Does neurodegeneration contribute to the decline in neurological function that is typical of HAM/TSP?
- How do the known causes of neurodegeneration, such as hypoxia inducible factor, nuclear factor-κB, peroxisome proliferator-activated receptors and reactive oxygen species, contribute to HAM/TSP?

Management

- What is the best combination of specific biomarkers, independent of the proviral load, of disease incidence and activity?
- Can early intervention with anti-inflammatory measures or an antibody against the C-C chemokine receptor type 4 (CCR4) limit the tissue damage in HAM/TSP?
- Is it possible to reset the equilibrium between the virus and host to cause a sustained reduction in the proviral load?
- Can the putative vicious circle of inflammation (FIG. 5) be interrupted with clinical benefit?

physical and psychological health. Indeed, nocturia can be so severe that patients must insert their own catheters in the evenings before sleep. Urinary incontinence substantially impairs the quality of life of patients, decreasing their general perception of health and imposing serious limitations on their daily life activities, social relationships, sleep and mood[160].

Chronic pain is another well-documented consequence of HAM/TSP that affects quality of life. One study showed that nearly 90% of patients with HAM/TSP had chronic pain: most reported that the dominant pain was felt in the lumbar region, followed by the lower limbs[161]. Although patients without pain experienced no detectable change in mood, up to half the patients reporting chronic pain showed signs of anxiety, depression or both. In fact, many patients described how the pain strained their relationships with friends and family and disrupted their work, leisure and sleep. Pain relief is complicated because patients can experience both neuropathic pain[162] from the spinal cord damage and nociceptive pain from musculoskeletal comorbidities.

In addition to the physical symptoms and their consequences, patients also bear the knowledge that they have a progressive disease with no cure, facing a future of steadily worsening symptoms, often culminating in an early death. One study in Martinique reported that patients with HAM/TSP live 15 years less than the average person[17]. As a consequence, anxiety and depression are frequent in patients with HAM/TSP[121,157,161].

With a cure remaining out of reach, it is important to provide patients with as much palliative care as possible, both physical and psychological, to improve quality of life. Participating in patient groups and peer counselling are widely considered to be important for mental health. Surveys suggest that exercise and physiotherapy can improve the health of patients with HAM/TSP; those who regularly exercised demonstrated better mental health, energy levels and social function, and experienced reduced pain[157]. However, more-detailed studies are necessary to quantify the effect in a controlled setting and define an effective regimen.

Several factors that are thought to influence the quality of life of patients with HAM/TSP require further examination. To our knowledge, only one study to date has directly analysed the effects of existing pharmaceutical HAM/TSP treatments on quality of life[148]. Steroids, for example, might slow the progression of physical disability but can also add unpleasant adverse effects to the existing symptoms. Similarly, comorbidities such as osteoporosis have been identified but remain understudied. Sexual dysfunction is a particularly under-reported and neglected issue. Finally, to appeal for government aid, data must be gathered to demonstrate how financial difficulties due to disability can exacerbate poor living conditions for patients with HAM/TSP.

Outlook

HTLV-1 has existed in the human population for tens of thousands of years, and consequently the virus is highly adapted for persistence at the individual and the population level. Eradication of the virus from an infected host might be impossible because HTLV-1 establishes a secure genetic foothold in the host with many thousands of infected T cell clones. However, the prevalence of the virus in the population can be reduced by serological screening of high-risk groups and by counselling of infected individuals and their families and contacts.

The clinical management of HAM/TSP remains particularly challenging, and further work is required in both basic and clinical research. In BOX 3 we summarize some of the most important outstanding questions.

Anticipated advances

The increasing knowledge of the regulation of eukaryotic chromatin structure and gene expression will result in a better understanding of the factors that regulate the expression of HTLV-1 and, therefore, its

mechanism of persistence and its potential to cause inflammatory disease.

Clinical studies of biomarkers will lead to more-accurate diagnosis and prognostication in HTLV-1-infected individuals. In particular, as HAM/TSP can progress very slowly, surrogate markers are needed to rapidly and accurately evaluate the effects of treatments in patients.

Clinical trials of therapeutic agents directed at specific components of the cellular immune response or specific inflammatory pathways or at reducing proviral loads (for example, CCR4-specific antibodies) might lead to improvement in symptomatic treatment in HAM/TSP and possibly to a better preservation of neurological function.

The rapidly advancing techniques of neuroimaging are anticipated to have a major impact on the diagnosis of HAM/TSP, the monitoring of the response to treatment, and, by functional neuroimaging, on the understanding of pathogenesis.

Perhaps the most exciting prospect for HAM/TSP therapy is the growing evidence demonstrating that neuroregeneration can restore some function in the adult CNS[163–165].

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Competing interests statement
The authors declare no competing interests.