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8.5.25 HTLV-1, HTLV-2, and associated diseases 941 fever, weight loss, night sweats) at each clinical encounter, and those who do not have active tuberculosis should be offered isoniazid preventive therapy. Routine screening for cryptococcal antigen prior to ART, followed by pre-emptive antifungal treatment if crypto- coccal antigen positive, should be considered for people with CD4 counts less than 100 cells/μl where the prevalence of cryptococcal antigenaemia in the population is greater than 3%. Interventions to prevent malaria are described earlier. Appropriate vaccines include those against hepatitis B, pneumococcal disease, influenza, and tet- anus. Nutritional support should be provided for the malnourished. To reduce infective diarrhoea, household-based water treatment methods are recommended, along with proper disposal of faeces and hand washing with soap. KDC's work towards this publication was made possible by support from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) to the U.S. Centers for Disease Control and Prevention (CDC), Division of Global HIV & TB (DGHT). The opinions and conclusions in this chapter are those of the authors and do not necessarily represent the official position of the funding agencies. FURTHER READING World Health Organization (2018). Latent TB Infection: Updated and consolidated guidelines for programmatic management. https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ World Health Organization (2015). Consolidated guidelines on HIV testing services. 5Cs: consent, confidentiality, counselling, correct results and connection. http://apps.who.int/iris/bitstream/10665/179870/1/9789241508926_eng.pdf?ua=1&ua=1 World Health Organization (2016). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach, 2nd edition. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_ eng.pdf 8.5.25 HTLV-1, HTLV-2, and associated diseases Kristien Verdonck and Eduardo Gotuzzo ESSENTIALS Human T-cell leukaemia virus (HTLV)-1 and HTLV-2 belong to the genus Deltaretrovirus of the family Retroviridae. They only infect humans, produce a lifelong infection, and can be transmitted from mother to child, through sexual intercourse, and via cellular blood components and organ transplantation. Both viruses are present in all continents and have a heterogeneous distribution. HTLV-1-endemic foci (general population prevalence >1%) are found in Japan, the Caribbean, South America, Africa, and

Australo-Melanesia. There are endemic foci of HTLV-2 among native Amerindians and Central African populations. HTLV-1 and 2 also occur among people who inject drugs. It is unclear why some infected people develop associated diseases while others remain asymptomatic. Clinical features—(1) HTLV-1—up to 10% of carriers develop clin- ical manifestations, including adult T-cell leukaemia/lymphoma, HTLV-associated myelopathy/tropical spastic paraparesis, and in- fectious diseases such as strongyloidiasis, scabies, and tuberculosis. (2) HTLV-2—can cause HTLV-associated myelopathy/tropical spastic paraparesis, arthritis, bronchitis, and pneumonia. Diagnosis and prevention—HTLV enzyme-linked immunosorbent assays are used for screening, followed by confirmatory testing of positive results. Mother-to-child transmission of HTLV-1 can be re- duced by avoiding breastfeeding; condom use protects against sexu- ally transmitted infection; screening of blood donors is performed in many countries. No vaccine is available and there are no effective antiviral drugs. Historical perspective In 1979, human T-lymphotropic virus 1 (HTLV-1) was isolated from a patient with a T-cell malignancy. In the years that followed, several syndromes, previously considered idiopathic, were linked to this virus: adult T-cell leukaemia/lymphoma (ATL), tropical spastic paraparesis, uveitis, and infective dermatitis. HTLV-2 was discovered in 1982, and HTLV-3 and HTLV-4 in 2005. It is not yet known whether HTLV-3 and -4 cause human disease. Epidemiology HTLV originated several millennia ago. There are six molecular sub- types of HTLV-1 and four of HTLV-2, several of which have spread from Africa to the rest of the world. The sequence variation in these viruses is linked with specific populations and geographical loca- tions, but not with disease outcome. It has been estimated that more than 5–10 million people are in- fected with HTLV-1 worldwide and that the number of HTLV-2- infected people also amounts to several millions. These estimates should be interpreted with caution because most of the HTLV prevalence studies were done in blood donors, pregnant women, and other selected population groups, and because data are lacking in large areas of the world. HTLV-1 infection is present throughout the world, but its distri- bution is heterogeneous. The highest HTLV-1 prevalence (up to 10% of the general population) has been found in southwestern Japan. HTLV-1-endemic foci (1–10%) have also been reported in the Caribbean (Jamaica, Haiti and Martinique), South America (Peru, Colombia, and French Guyana), West and Central Africa (Guinea- Bissau, Côte d'Ivoire, Ghana, Nigeria, Gabon, Cameroon, the Central African Republic and the Democratic Republic of the Congo), the Middle East (Iran), and Australo-Melanesia (Aboriginal popula- tions of Australia, Papua New Guinea, and the Solomon Islands). In Brazil, Mozambique, Iran, Taiwan, and Romania, the prevalence is 0.1 to 1%. HTLV-1 infection is uncommon in Western Europe and the United States; here, the infection is concentrated in immigrants from endemic regions and people who inject drugs.

942 section 8 Infectious diseases For HTLV-2, there are two endemic foci: native Americans (prevalence 1–58%) and Central African populations (prevalence up to 14%). The virus also occurs among people who inject drugs in all continents (prevalence up to 20%). In endemic populations, the prevalence of HTLV-1 and HTLV-2 tends to be higher in elderly than in young people, and is higher in women than in men. Other risk factors include prolonged breast- feeding, unsafe sex practices, blood transfusion, and injection drug use. Pathogenesis The genomes of HTLV-1 and HTLV-2 consist of RNA, which, during infection, is transcribed to DNA and inserted as provirus into the DNA of human cells. HTLV-1 infects mainly CD4 and HTLV-2 CD8 lymphocytes. HTLV-1 produces almost no cell-free virus particles in vivo. Instead, the virus spreads from an infected cell to another cell via a tight and organized cell–cell contact (virological synapse). In early stages of HTLV-1 infection, dendritic cells have a central role. During chronic infection, there is little

production of mature vir- ions, and the viruses propagate via mitosis of infected lymphocytes (clonal expansion). As a consequence, HTLV-1 has a remarkable genetic stability, which is unusual for a retrovirus. HTLV-1 encodes several regulatory gene products, of which Tax and the HTLV-1 bZIP factor (HBZ) are the most important. Tax and HBZ control proviral transcription, mRNA splicing and transport, and the expression of different host genes. Tax and HBZ gene prod- ucts make the infected CD4 cells proliferate and are involved in the pathogenesis of the malignant as well as the inflammatory complica- tions of HTLV-1 infection. HTLV-1 infection is a necessary but insufficient condition for the development of associated diseases. As most of the HTLV-1-infected people (about 90%) remain asymptomatic, other viral, host, genetic, or environmental factors must contribute to the risk of disease. The strongest correlate of disease risk is the proviral load. The proviral load (the proportion of peripheral blood mononuclear cells carrying integrated HTLV provirus) remains relatively stable in any given subject, but varies between subjects. A high HTLV-1 proviral load is related to the risk of HTLV-associated myelopathy (HAM)/tropical spastic paraparesis (TSP), and perhaps also of ATL. The main deter- minant of an individual's proviral load and risk of HAM/TSP is the cytotoxic T-lymphocyte response against HTLV-1. Diagnosis of infection HTLV enzyme-linked immunosorbent assays are available for screening purposes. In samples with a positive result, confirmatory testing with western blot, line immunoassay, immunofluorescence, and/or polymerase chain reaction is recommended to eliminate false- positive reactions and to discriminate between HTLV-1 and HTLV-2. Prevention and treatment of infection HTLV-1 mother-to-child transmission can be reduced from 15– 25% to less than 5% by avoiding breastfeeding. The incidence of sexual transmission among stable partners is about 1 per 100 person-years for HTLV-1 and -2. Condom use pro- tects against infection. Transfusion of HTLV-1-contaminated cellular blood components leads to infection in more than 40% of recipients. In many coun- tries, candidate blood donors are screened for HTLV, as are donors of solid organs. There are no vaccines and no effective antiviral drugs against HTLV-1 and HTLV-2. HTLV-1 disease outcomes The lifetime risk for HTLV-1 carriers to develop ATL is 1% to 5% (see Table 8.5.25.1). HAM/TSP occurs in 0.3% to 4%, and for HTLV-1-associated diseases in general, the risk is estimated in 10%. Adult T-cell leukaemia/lymphoma (ATL) ATL is an aggressive malignancy of HTLV-1-infected CD4 lymphocytes. Clinical features include lymphadenopathy, hepatosplenomegaly, skin lesions, and opportunistic infections. Hypercalcaemia and lytic bone lesions are found in up to 70% of patients. Peripheral blood smears might show lymphoid cells with large, multilobed nuclei ('flower cells'). HTLV-1-induced ATL is classified as acute, lymphoma-type, chronic, and smouldering, based on total lymphocyte count, pres- ence of abnormal lymphocytes in peripheral blood, calcium and lactate dehydrogenase levels, lymphadenopathy, and solid organ involvement. Despite advanced care, including intensive chemotherapy, the median survival after diagnosis of the acute and lymphoma-type ATL is only 7–13 months. Chronic and smouldering forms have a better prognosis, but can evolve to acute ATL. The combination of zidovudine with interferon-α improves survival in patients with leu- kaemic subtypes of ATL. Allogeneic haematopoietic stem cell trans- plantation can be curative but is not always possible. HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) HAM/TSP is a chronic, debilitating condition characterized clin- ically by spastic weakness of the legs (Fig. 8.5.25.1), pain, bladder problems, sensory signs and symptoms, constipation, and/or sexual dysfunction. The main pathological feature is an inflamma- tion of the white and grey matter of the spinal cord. Cerebrospinal fluid examination might show mild lymphocytosis and protein increase. The diagnosis of HAM/TSP requires demonstration of HTLV- 1 and exclusion of other causes of myelopathy, such as spinal cord compression, vitamin B12 and folate deficiency, multiple sclerosis, amyotrophic lateral sclerosis, and lathyrism. Several treatment

strategies have been proposed, including cor- ticosteroids, interferon-α, interferon-ß-1a, reverse transcriptase inhibitors (e.g. zidovudine, lamivudine, and tenofovir), histone deacetylase inhibitors (valproate), NF-κB inhibitors, fucoidan, ciclosporin, and monoclonal antibodies to CD25 or interleukin- 15. There are case reports of good response to zidovudine and lamivudine in combination with corticosteroids in patients with rapidly progressive disease. However, only two of these treatment strategies (interferon-α and zidovudine and lamivudine) have been

 tested in randomized controlled studies. They showed no satisfac- tory effect on symptoms or proviral load. Infective dermatitis Infective dermatitis is a chronic, relapsing disease that affects mostly children. Clinical characteristics include a papular rash, with exud- ates and crusting, mainly on the scalp, but also on the ears, eyelid margins, paranasal skin, neck, axilla, and groin (Figs. 8.5.25.2, 8.5.25.3). Watery nasal discharge and crusting of the nostrils are fre- quent. Clinical and histopathological images may resemble atopic dermatitis. The response to corticosteroids and antibiotics is generally good, but relapses are frequent after withdrawal of treatment. Case reports suggest that HTLV-1-infected children with infective derma- titis have an increased risk to develop HAM/TSP and ATL. Other diseases An increasing body of evidence shows that symptoms and signs sug- gestive of neurological disease are frequent among HTLV-1-infected people, also among those who do not have a formal diagnosis of HAM/TSP. Arthropathy, uveitis, dry eye syndrome, thyroiditis, polymyositis, and alveolitis are other inflammatory conditions linked to HTLV-1. Carriers of HTLV-1 are also at increased risk of infectious complications, notably strongyloidiasis (Chapter 8.9.4), scabies, tuberculosis, and perhaps also leprosy, onychomycosis, paracoccidioidomycosis, periodontal disease, and bronchiectasis. These infectious complications of HTLV-1 appear to be associated with more morbidity and mortality than was previously appreciated. When HTLV-1 carriers live in an overcrowded and contaminated environment with inadequate sanitation, they are more likely to suffer severe infectious outcomes. This has been reported among Aboriginal people of central Australia and is likely to occur in other HTLV-1-endemic areas as well. HTLV-2 disease outcomes HTLV-2 is less pathogenic than HTLV-1 (see Table 8.5.25.1), but has been linked with HAM/TSP, arthritis, pneumonia, and bronchitis. A prospective study of HLTV-2-infected candidate blood donors in the United States of America found a twofold increase in mortality compared to uninfected control subjects. Likely future developments Developments in the near future will probably include the following: • Treatment trials for HAM/TSP and ATL • Clearer picture of HTLV-1, -2, -3, and -4 epidemiology and dis- ease outcomes • Better understanding of pathogenesis of associated diseases (role of viral, genetic, and environmental factors) • Biomarkers to predict disease progression • Better understanding of interaction with HIV and hepatitis B and C • Research into preventive and therapeutic vaccines and antiviral therapy Table 8.5.25.1 HTLV-1 and HTLV-2 disease outcomes and main clinical features HTLV-1 Malignant disease ATL Lymphadenopathy, hepatosplenomegaly, skin lesions, opportunistic infections, hypercalcaemia. Poor prognosis. Affects more men than women, mostly adults. Inflammatory syndromes HAM/TSP Weakness of the legs with signs of pyramidal tract involvement (hyperreflexia, clonus, spasticity, Babinski’s sign), loss of vibration sense, pain, urinary problems, constipation, and sexual disorders. Progressive disease. Affects more women than men; mostly adults, sometimes children. Occurs mostly sporadically, sometimes in families. Uveitis Blurred vision with floaters, iritis, vitreous opacities, retinal vasculitis, uni- or bilateral. Intermediate uveitis in >50% of cases. Sometimes preceded by an episode of thyroiditis. Resolves spontaneously, but more rapidly with corticosteroids. Relapse is frequent. Affects more women than men; mostly adults, sometimes

children. Arthritis Resembles rheumatoid arthritis. Infectious complications Strongyloidiasis Disseminated, life-threatening strongyloidiasis can develop. Relapse after treatment is common. Infective dermatitis Generalized papular rash, with exudates and crusting on scalp, ear, eyelid margins, paranasal skin, neck, axilla, and groin. Watery nasal discharge, lymphadenopathy. Chronic syndrome; good response to antibiotics but frequent relapse. The syndrome has an inflammatory as well as an infectious component. Affects usually young children. Scabies Severe forms can occur, with extensive, crusted lesions, located mainly in pressure areas. Tuberculosis Increased risk of active tuberculosis. Specific clinical features remain to be clarified. Bronchiectasis Reported among indigenous people in Central Australia. High mortality. Linked to recurrent respiratory tract infections. HTLV-2 HAM/TSP Similar symptoms as in HTLV-1, but milder and more slowly progressive disease. Acute bronchitis and pneumonia Specific clinical features remain to be clarified. Arthritis ATL, adult T-cell leukaemia/lymphoma; HAM/TSP, HTLV-associated myelopathy/tropical spastic paraparesis.

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