

## Summary

- HTLV-1 : chronic retroviral infection
- Importance in certain geographical foci.
- Transmission from mother-to-child (breast feeding), sexually or via blood
- Clinical aspects: 95% of infected people remain asymptomatic, 5% become symptomatic
- Opportunistic infections: Norwegian scabies, tuberculosis, *Strongyloides stercoralis*, etc.
- Inflammatory syndromes: uveitis
- Evolution to neoplastic diseases in a minority of patients: adult T-cell leukaemia / lymphoma
- Neurological syndrome with abnormal gait pattern and urinary incontinence (HAM/TSP)

## General

The name retroviruses refers to the unique manner in which these viruses reproduce. Their genetic information is coded in RNA. This is not in itself unusual. However, they also possess an RNA-dependent DNA-polymerase (reverse transcriptase) which produces DNA from the RNA strand. This DNA can be integrated at random into the host genome. Using this new DNA as template, mRNA can be transcribed and then translated into viral proteins. Such a flow of genetic information (from RNA to DNA) does not occur in other organisms so far as is known.

The family of Retroviridae contains three subfamilies: the Oncovirinae (with HTLV-1 as the most important representative), the Lentivirinae (with HIV as the most important virus) and the Spumavirinae ("foamy viruses"). The group of viruses known as the Primate T-lymphotrophic viruses (PTLVs) is composed of simian and human T-lymphotrophic retroviruses (SLTVs and HTLVs respectively). The viruses are genetically closely related. It has been shown that hunter-gatherers, when hunting monkeys and/or apes, are regularly exposed to the simian viruses. In urban bushmeat markets in Cameroon, about 10% seroprevalence was found in the hunted wild monkeys. Studies have shown that the diversity of HTLVs is directly related to the genetic diversity of the SLTVs from which the primary zoonotic infection originated. The ease with which SLTVs seems to be able to cross species barriers warrants increased surveillance of these viruses. HTLV-1 has spread to many parts of the globe and is associated with adult T-cell leukaemia and myelopathy/tropical spastic paraparesis. In 1982 HTLV-2 was isolated in a patient with hairy cell

leukaemia. HTLV-2 is less pathogenic than HTLV-1. More than 99% of infected individuals will remain asymptomatic but a minority will develop myelopathy/tropical spastic paraparesis. HTLV-3 and HIV turned out to be the same virus. Less is known about HTLV-4, which was identified in 2005 in Cameroon.

HTLV-1 is genetically very stable. This stands in marked contrast with HIV which is so variable that it is sometimes called a quasi-species.

## Epidemiology

HTLV-1 was first isolated in 1980 from a T-cell lymphoma cell line, originating from a patient with adult T-cell leukaemia/lymphoma. It was the first time human retroviruses were shown to exist. Africa is the only continent where all different primate T-cell lymphocytotropic viruses have been found, from HTLV types 1 to 4, and the simian retroviruses STLV types 1 to 3. This suggests that the virus spread from Africa to the rest of the world. On the other hand, HTLV-1 genetic sequences have been found in a 1500-old Chilean mummy.

The seroprevalence fluctuates widely from region to region. HTLV-1 is endemic in certain geographical areas, such as Taiwan and the Southwest of Japan, Okinawa, Papua New Guinea, Melanesia (Solomon Islands, Vanuatu), Australia (in Aborigines), the Caribbean, West and Central Africa and the northeast of South America including Peru. In certain endemic areas, more than 1% of the population can be infected (e.g. Togo, Guinea-Bissau, the southern part of Cameroon). The highest prevalence is found in Southern Japan (up to 10%). Apart from Japan, Taiwan, a Chinese mainland province near Taiwan and Iran (seroprevalence 0.1 to 1%), the infection seems to be rare in other parts of Asia, although more study is needed. For many African regions, there are no good prevalence data available at present. The virus also occurs in some other regions such as Italy, Romania, Israel and the Arctic, but is less common there. It is rare in the rest of Europe and North America, although there are some small foci among Native Americans. In the first decade of the 21st century, it is estimated that 10 to 20 million people are infected worldwide. However, few population-based studies have been performed therefore prevalence data may be lacking. Studying the prevalence in blood donors, pregnant women or other groups might bias the data. One also must check the diagnostic criteria. Different techniques and strategies can give rise to different results.

## The virus

HTLV-I is a round, enveloped retrovirus which contains reverse transcriptase and integrase. Its genome is composed of positive single-stranded RNA. As with all retroviruses, this is converted to double-stranded DNA which is integrated into the host cell chromosomes. The virus exists predominantly as a cell-associated provirus and is transmitted as such. The plasma viral load is therefore often undetectable. Cytotoxic T-cells destroy infected cells by lysis. This results in the simultaneous production of inflammatory cytokines. The balance between these two processes leads to a more-or-less steady state in any given individual. HTLV-1 does not contain oncogenes. However, one of the viral encoded proteins induces abnormal cell growth. It blocks transcription of certain genes that are important for the control of the cell cycle, apoptosis and DNA repair. This results in mitosis without checking for chromosomal abnormalities. Genetically damaged cells with unstable chromosomes will not apoptose helping clonal outgrowth of these cells.

## Transmission

The virus is transmitted by at least three different mechanisms:

**From mother-to-child.** Transmission via breastmilk is the major route. The infection is transmitted via infected lymphocytes in the milk. Intra-uterine and peripartum transmission appears to be rare (less than 5% of children with infected mothers). Children of seropositive mothers have an approximately 15 to 20% risk of infection if they receive long-term breastfeeding, as is normal in many regions. **Via sexual intercourse.** This is bi-directional, yet transmission from man to woman is much more common than the reverse. After 10 years of sexual intercourse with an infected man, a woman has a 60% risk of becoming infected herself. The risk in the reverse situation is only 0.4%. The presence of genital ulcers increases the risk. The risk for men who have sex with men increases greatly depending on the number of years that there has been sexual contact and on condom use.

**Via infected blood transfusions** or infected medical material, chiefly when cellular elements are present (plasma-derived products do not represent a risk). The infectious titre in the cell-free plasma is very low. Blood for transfusion which has been stored for longer than one week has nearly zero percent chance of transmitting infection, due to the lack of

viable T-cells. Transfusion of contaminated blood results in seroconversion in more than 40% of patients. In endemic areas, candidate blood donors are screened for HTLV-1 antibodies.

**Via contaminated syringes and needles.** HTLV-1 infections are common among intravenous drug users in Brazil and New York, although in other North American and European IV drug users, HTLV-2 is more prevalent.

## Clinical aspects

### General

Several cell types may be infected, but T-cells are the most important of these. After infection various scenarios are possible:

1. latent infection without symptoms (the most common)
2. evolution to lymphoma / leukaemia
3. neurological syndrome with abnormal gait pattern and urinary incontinence
4. dermatitis
5. uveitis, arthropathy and other inflammatory processes, possibly with an auto-immune component
6. opportunistic infections

### Latent infection

Infection may leave a person with a latent disease. He or she is infectious to others, but exhibits no symptoms or problems. During his or her life there is an approximately 90 to 95% chance that no complications will arise. If not tested specifically for this virus, the person in question will have no idea that he or she is infected. A number of seropositive individuals will be found by chance e.g. during the control of donor blood. There are some preliminary data suggesting that infection with HTLV-1 is associated with a lower risk for development of stomach carcinoma in Japanese patients.

## Lymphoma / leukaemia

ATL (adult T-cell leukaemia/lymphoma). There are several histological subtypes, but the diffuse large cell lymphoma is the most common. The lifetime cumulative risk is roughly 2% (1 to 5%). The tumours consist of monoclonal proliferation of CD4-positive T-cells. The clinical course may be acute, lymphomatous, chronic or smouldering. A fifth form, primary cutaneous tumoral ATL, has also been described.

If the course is acute and aggressive, nearly all patients will have lymphadenopathy and 50% will have hepatosplenomegaly. Skin lesions can resemble those of mycosis fungoides (cutaneous T-cell lymphoma). The dermal abnormalities include nodules, papules and diffuse infiltrative lesions. About 70% of patients develop hypercalcemia and osteolytic bone lesions. Approximately 10% exhibit involvement of the cerebral meninges resulting in muscle weakness, disturbed behaviour and/or headache. Oddly enough the protein content in the cerebrospinal fluid may still be normal, while at the same time containing ATL cells. Peripheral blood contains pleomorphic atypical lymphoid cells with basophilic cytoplasm and convoluted nuclei (so-called flower cells). During the leukemic phase, leukocyte count may increase dramatically. Acute ATL has a poor prognosis, with a median survival time after diagnosis of 6 months.

The lymphomatous form occurs in approximately 20% of symptomatic patients. The course is the same as in the acute aggressive form. There is also lymphadenopathy. Neoplastic cells are found in the blood, yet there is no lymphocytosis. The average survival time is 10 months.

In the chronic form the disease lingers for two years on average, without bone lesions, hypercalcemia or neurological involvement. There is lymphocytosis. There may be hepatosplenomegaly, lymphadenopathy, skin and lung lesions.

In the smouldering form the disease lasts for more than 5 years. In this form skin lesions, and to a lesser extent pulmonary lesions, are prominent, while hypercalcemia, hepatosplenomegaly and lymphadenopathy are absent. Transformation from a smouldering or chronic form to an acute form may occur suddenly.

## HTLV-1 associated myelopathy (HAM)

HTLV-1 associated myelopathy (HAM) is also known as chronic progressive myelopathy or tropical spastic paraparesis (TSP). This is a progressive hypertonic and ataxic myelopathy. The cumulative risk to develop this after infection with HTLV-1 is 2%. The disorder is more common in women. The main pathological feature of this condition is chronic inflammation of the white and grey matter of the spinal cord. Mononuclear cells, mainly T-cells, cause perivascular cuffing and infiltrate the spinal cord, which in a later stage will lead to atrophy. It is possible that there is an auto-immune component in the destruction of nerve cells (cross-reactivity between HTLV-1 antigens and tissue antigens). Patients with rapidly progressing HAM/TSP have a higher proviral load than those with slow progression.

Most damage occurs in the lower thoracic spinal cord. Weakness and stiffness of the legs, back pain and urinary incontinence together with abnormal gait pattern, are characteristic of the disease. The sensory disturbances are usually limited, but there may be polyneuropathy with dysesthesia. Bladder disorders are an important cause of impairment among HAM/TSP patients. The course is progressive, so that many patients need to use a wheelchair and/or are bedridden within 10 years.

There is typical hypertonic symmetrical paraparesis or paraplegia with hyperreflexia and pronounced ankle clonus, for example when testing the Achilles tendon reflex or in sudden dorsiflexion of the foot. Babinski's sign can be elicited (spreading and extension of the toes instead of the normal plantar flexion upon stimulation of the sole of the foot). The reaction corresponding to this in the hands is Hoffman's sign. The cerebrospinal fluid may show an increased protein content and may contain mild pleiocytosis with "flower cells", anti-HTLV-1 antibodies and oligoclonal bands. Definite diagnosis of HAM/TSP requires the demonstration of HTLV-1 infection and exclusion of other causes of myelopathy.



Norwegian scabies in HTLV-1 patient. Copyright Alexander von Humboldt Institute, Peru.



HTLV-1 dermatitis. Copyright Alexander von Humboldt Institute, Peru

## Clinical aspects, miscellaneous

People infected with HTLV-1 have a high risk of dermatitis, often with superinfection by Gram-positive bacteria (*Streptococcus pyogenes* and *Staphylococcus aureus*). Lesions are often eczematous, and tend to be localized on the scalp, face (paranasal skin), ears, eyelids, neck, axillae and groins. Infective dermatitis is a chronic relapsing syndrome that mainly affects children. Co-morbidities include glomerulonephritis, bronchiectasis, lymphocytic interstitial pneumonia and anaemia. Norwegian scabies present with massive crusted skin lesions, mainly in pressure areas. Opportunistic infections due to immunosuppression are common, including *Pneumocystis jiroveci* and systemic fungal infections. There is a risk of hyper-infection with *Strongyloides stercoralis*, especially in those who are being treated with corticosteroids. Since the larvae mechanically carry bacteria from the colon, sepsis is common. Relapse after treatment with ivermectin is common. Herpes zoster is not so common as an opportunistic infection.



*Strongyloides stercoralis*, larva currens. Copyright ITM

People infected with HTLV-1 have an increased risk for tuberculosis, and patients tend to have more severe lesions due to tuberculosis.

In regions where HTLV-1 is endemic, various inflammatory and auto-immune disorders, including uveitis, the sicca syndrome, pneumonitis, arthropathy and thyroiditis are attributed to this virus. However, more research is needed into these matters. Patients with uveitis often present with blurred vision with floaters. Iritis and vitreous opacities are almost always present, often in association with retinal vasculitis, and sometimes with retinal exudates and haemorrhages. Bilateral lesions are as common as unilateral inflammation. The prognosis is good, since it tends to resolve spontaneously within weeks. Topical or systemic corticosteroid treatment hastens recovery. More than 90% of cases recur within 3 years. Complications include retinal degeneration, glaucoma and steroid-induced cataracts.

## Differential diagnosis:

The differential diagnosis is broad. HAM / TSP is similar to multiple sclerosis, with a slow, gradual onset. The disorder should be differentiated from lathyrism and konzo, both of which have an acute onset and are caused by toxins in the diet. The cauda equina syndrome, various neurodegenerative disorders such as amyotrophic lateral sclerosis, as well as infections such as syphilis, HIV, neurobrucellosis and tuberculous meningitis may be included in the differential diagnosis. The skin lesions are similar to mycosis fungoides (cutaneous T-cell lymphoma), leukemic skin lesions and those of non-HTLV-1-related lymphoma.

## Diagnosis

HTLV-1 is usually detected by carrying out serological tests because of clinical suspicion, screening at the blood bank or due to concerns by family members of HTLV-1 positive patients. Sometimes the diagnosis is made when a patient has a persistent *Strongyloides stercoralis* infection (faeces with larvae, cutaneous larva currens or signs of hyperinfection). In the family history, which is important due to the mother-to-child transmission, it is often possible to find maternal family members who suffered from lymphoma or who were wheelchair users.

The antibodies can be detected by enzyme immunosorbent assay (EIA). Polymerase chain reaction (PCR) can provide a definite diagnosis. With real-time PCR the proviral load can be quantified as the number of HTLV-1 DNA copies per fixed number of peripheral blood mononuclear cells. This is often used as a marker for prognosis and diseases progression.

The test for HTLV-1 also detects the majority of HTLV-II infections. MRI [magnetic resonance imaging] or a CT scan shows speckled white abnormalities in the spinal cord. In chronic ATL absolute lymphocytosis is found (more than  $3.5 \times 10^9$ /liter). In the acute form of ATL the blood count will suggest leukaemia. Blood smears may contain abnormal lymphocytes with a highly wrinkled nucleus, called "flower cells". A skin biopsy shows the malignant lymphocytes.

## Treatment

Oral or intravenous corticosteroids are used in the early phase of HAM/TSP, when inflammation is more prominent than demyelination. Motor disability, pain, and urinary dysfunction may be ameliorated, but improvement is not sustained in many patients. Valproic acid is an anti-epileptic with histone deacetylase inhibiting activity. It activates viral gene expression and exposes virus-infected cells to the immune system. Preliminary data show that the proviral charge initially increases, but subsequently decreases. Its exact place in therapy needs to be further clarified. Other drugs, such as interferon-alpha, daclizumab (humanized anti-Tac), plasmapheresis and intravenous immunoglobulins (IVIG) are used or being studied. The place of nucleoside analogues is unclear.

Hypercalcemia can be treated with cortisone and antineoplastic drugs. Calcitonin, for osteoclast inhibition, and etidronate or other bisphosphonates (also osteoclast inhibitors) will not usually be available. The tumour is initially highly sensitive to chemotherapy (e.g. CHOP [cyclophosphamide, hydroxydaunomycin/doxorubicin (Adriamycin), oncovin, prednisone]), but there is a serious risk of opportunistic infections. Relapse is common. Physiotherapy is important. For the hypertonicity, tetrazepam (Myolastan®), dantrolene (Dantrium®), baclofen (Lioresal®) and/or tizanidine (Sirdalud®) may be used. However, sometimes patients use their spastic legs as crutches and are able to walk. Antispasmodics can have the undesirable effect that walking in these patients suddenly becomes more difficult. In case of bladder hypertonia the patient is advised to begin bladder training. The idea is that the patient urinates at regular times, even if at that moment there is no urge to urinate. The intervals are gradually lengthened. In this way the bladder can become accustomed to retaining ever larger amounts of urine.

## Prevention

Breastfeeding by infected mothers should be discouraged. Blood donors should be screened for the virus. As with HIV, safe sex also has a role to play here. The repeated use and certainly sharing of needles should be avoided. Correct cleansing and sterilization of medical equipment should be obligatory.