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EPIDEMIOLOGY / *ÉPIDÉMIOLOGIE*

HTLV-I infection in the South West Indian Ocean islands, particularly in La Réunion and the Seychelles

Infection à HTLV-I dans le sud-ouest de l'océan Indien, particulièrement à La Réunion et aux Seychelles

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Abstract Data on HTLV-I are scarce in several Southwest Indian Ocean islands except for La Réunion and The Seychelles. The two cases of HTLV-I have been confirmed by Western-Blot in La Réunion, among blood donors. In Seychelles (87 400 inhabitants in 2012), where blood donors and some other cases are screened, HTLV-I was confirmed with a line immune assay in 43 persons and at least 10-20 patients are known to have tropical spastic paraparesia or adult T-cell lymphoma associated with HTLV-I. In the south-west Indian Ocean, a possibly important other issue may be co-infection of HTLV-1 with the *Strongyloides stercoralis* roundworm, which is endemic in all countries of the region and which can sometimes lead to severe symptomatic infestation.

Keywords HTLV-I · *Strongyloides stercoralis* · Strongyloidiasis · South West Indian Ocean Islands · La Réunion · Seychelles · Madagascar · Mauritius · Comoros · Mayotte

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Résumé Il existe peu de données fiables sur HTLV-I dans la plupart des pays du sud-ouest de l'océan Indien, à l'exception de La Réunion et des Seychelles. L'infection à HTLV-I y semble très rare, sauf aux Seychelles. Les deux cas dépistés à la Réunion (tests effectués sur tous les donneurs de sang) se sont avérés positifs par la méthode Western-Blot. Aux Seychelles (87 400 habitants en 2012), où HTLV-I est également dépisté chez tous les donneurs de sang ainsi que dans d'autres circonstances, 43 cas ont été confirmés au cours des cinq dernières années par Western-Blot et 10 à 20 cas de lymphome et de paraplégie spastique tropicale associés à HTLV-I sont répertoriés. La question de la coexistence morbide de HTLV-I et de l'anguillulose peut aussi se poser dans ces environnements tropicaux.

Mots clés HTLV-I · *Strongyloides stercoralis* · Anguillulose · Iles du sud-ouest de l'océan Indien · La Réunion · Seychelles · Madagascar · Mauritius · Comores · Mayotte

Background

Human T-cell lymphoma/leukemia virus type I (HTLV-I) is a type-C retrovirus affecting mature T-lymphocytes, originally isolated from patients with leukemia or lymphoma [10]. It was the first oncogenic retrovirus documented in humans (1980). It is the causative agent for leukemia/ T-lymphoma in adults (Adult T-cell Lymphoma/Leukemia [ATLL]), for tropical Spastic Paraparesis/HTLV-I Associated Myelopathy [TSP/HAM]. It is associated with several opportunistic infections, particularly disseminated *Strongyloides stercoralis* infestation [6,13].

At least five to ten million people are infected worldwide [7]. HTLV-I is present throughout the world, with clusters of high prevalence (over 2% of the adult population) located often nearby areas where the virus is nearly absent. The main HTLV-I highly endemic regions are the Southwestern part of

Japan, sub-Saharan Africa and South America, the West Indies, and foci in Middle East and Australo-Melanesia [7].

HTLV-I is transmitted from mother to child during prolonged breast-feeding, via sexual contact or through IV infusion. Three to seven per cent of infected persons develop a disease, mainly ATLL or TSP/HAM, and rarely, uveitis, infective dermatitis, polymyositis [6]. HTLV-1 is also associated with presence or exacerbation of *Strongyloides stercoralis* and possibly of tuberculosis [3].

HTLV-I is genetically stable, divided into seven genotypes encountered in specific geographical areas. The four main genotypes are [20]: sub-type A cosmopolitan with four sub-groups (transcontinental, Japan, West Africa, North Africa); sub-type B in Central Africa; sub-type C in Melanesia; sub-type D in western Central Africa (Cameroon, Gabon, Central African Republic). In La Réunion, the subtype A cosmopolitan, continental sub-group, was identified in 1994 [11,21].

HTLV-I presumably originated from the equivalent simian virus STLV-I, first identified in 1982. STLV-I is endemic in many Old World simian species. Cases of leukemia and T-lymphoma similar to ATLL have been reported in monkeys with STLV-I; as yet no cases of neuro-myelopathy similar to TSP/HAM have been reported in monkeys. No STLV-1 similar to the HTLV-I sub-type A has yet been described [8].

The purpose of this article is to review the existing data in the Southwest Indian Ocean.

Methods

We conducted a systematic computerized literature search on PubMed for publications requesting "HTLV", "Indian Ocean", "Madagascar", "Seychelles", "Comoros", "Mayotte", "Mauritius", "La Réunion". In addition, we interviewed the Seychelles national laboratory and the Ministry of health, the Pasteur Institute of Madagascar, l'Etablissement français du sang de La Réunion, the laboratory of the Centre hospitalier de Mayotte, The Ministry of Health in Comoros, and the Réseau surveillance des épidémies et gestion des alertes de l'océan Indien in Mauritius.

Results

Between 1984 and 2013, twenty-one publications mentioned HTLV and the South West Indian Ocean Islands (Table 1). Patients with TSP/HAM have been admitted to hospitals in the Seychelles in 1985 [15], in La Réunion, Mayotte, Madagascar [5,11] and Australia (a Seychellois immigrant) [19]. Blood donors positive for HTLV-I were recorded in La Réunion [4,5,11] and Madagascar [8]. In surveys conducted among the adult population in the Seychelles [9], a high HTLV-I prevalence was reported with 65 positive results among 1 055 people randomly selected from the population screened in 1989 using an EIA test and confirmed via a Western-Blot and radio-immuno-precipitation assay (RIPA). The prevalence increased from 3% at age 25-64 to 9% at age 55-65. A few years earlier, serological investigation of a case-series of TSP/HAM patients had shown a high percentage of infection: 17 among 20 patients tested [15,16].

To obtain current data on HTLV-I in the Seychelles, we examined results in 2008-2012 from the blood transfusion laboratory of the ministry of health, which is the only laboratory that tests HTLV-I in the country. HTLV-I is screened with an EIA test (HTLV-I/II Elisa 4.0, MP Diagnostics©) followed by a line immunoassay used to confirm the presence of antibodies against both HTLV-I and HTLV-II (INNO-LIA HTLV-I/II Score, Innogenetics©). Approximately 2800 HTLV-I tests are performed in Seychelles every year according to the central laboratory electronic database, mainly among blood donors (HTLV-I is screened in all blood collections). It can be estimated by the heads of the different units and departments that around 100-200 tests are done in HIV patients (HTLV-I tends to be tested in most new HIV patients) and a few hundreds of HTLV-I tests are done among in-patients and out-patients (HTLV-I tends to be tested only in persons with signs of symptoms of HTLV-I related disease in those patients). HTLV-I was confirmed in 43 persons in 2008-2013, which corresponds to at least 40 different persons (no name was available for 3 positive tests in the list of the laboratory form from which these figures are derived): blood donors (14 cases; mean age 36 years); patients undergoing hemodialysis (6 cases; mean age 60 years); patients from the communicable diseases control unit (4 cases; mean age 51 years); patients in different hospitals or health centers (19 cases; mean age 53 years). No case of HTLV-II was ever reported.

It must be emphasized that it is not possible to assess with accuracy the prevalence of positive HTLV-I serology in the population in 2008-2012 because figures on positive HTLV-I in 2008-2012 were obtained from the hospital laboratory on persons at increased risk of HTLV-1 (e.g. hemodialysis, HIV or patients presenting with signs of HTLV-I disease) -- unlike figures from the above mentioned population-based survey in 1989. However, a crude approximate estimation of the seroprevalence of HTLV-I in the general population may be drawn out of new blood donors in 2008-2012, considering they represent fairly well the general population and that most HTLV-I cases are likely to be diagnosed in new donors only, since repeaters are expected to be negative (positive cases are no longer eligible for blood donation). Since there were less than 150 new donors every year according to the head of the blood transfusion unit (hence 750 in 2008-2012), an upper limit for the current prevalence of HTLV-I among

Table 1 Publications citing HTLV1 infection in the Southwest Indian Ocean between 1984 and 2013 / *Publications citant l'infection à HTLV-I dans le sud-ouest de l'océan Indien entre 1984 et 2013*.

HTLV and Indian Ocean islands

Cnudde F, Gessain A, Dandelot JB, et al (1991) HTLV-1 in neurological patients from some Indian Ocean islands. J Acquir Immune Defic Syndr 4(7):734-5

Mahieux R, Gessain A, Truffert A, et al (1994) Seroepidemiology, viral isolation, and molecular characterization of human T cell leukemia/lymphoma virus type I from La Réunion Island, Indian Ocean. AIDS Res Hum Retroviruses 10(6):745-52

Montgomery RD (1993) The epidemiology of myelopathy associated with human T-lymphotropic virus 1. Trans R Soc Trop Med Hyg 87(2):154-9

Thyagarajan D, Bastian I, Stark RJ, et al (1993) HTLV-I associated myelopathy in a Seychellois immigrant. Med J Aust 159(1):29-31

Vidal AU, Gessain A, Yoshida M, et al (1994) Phylogenetic classification of human T cell leukaemia/lymphoma virus type I genotypes in five major molecular and geographical subtypes. J Gen Virol 75(Pt 12):3655-66

Voevodin A, Gessain A (1997) Common origin of human T-lymphotropic virus type-I from Iran, Kuwait, Israel, and La Réunion Island. J Med Virol 52(1):77-82

HTLV and La Réunion

Schaffar-Deshayes L, Chavance M, Monplaisir N, et al (1984) Antibodies to HTLV-I p24 in sera of blood donors, elderly people and patients with hemopoietic diseases in France and in French West Indies. Int J Cancer 34(5):667-70

Voevodin A, al-Mufti S, Farah S, et al (1995) Molecular characterization of human T-lymphotropic virus, type 1 (HTLV-1) found in Kuwait: close similarity with HTLV-1 isolates originating from Mashhad, Iran. AIDS Res Hum Retroviruses 11(10):1255-9

HTLV and Madagascar

Larouze B, Schaffar-Deshayes L, Blesonski S, et al (1985) Antibodies to HTLV-1 p24 in African and Portuguese Populations. Cancer Res 45(9S):4630s-4632s

HTLV and Seychelles

Arango C, Concha M, Zaninovic V, et al (1988) Epidemiology of tropical spastic paraparesis in Columbia and associated HTLV-I infection. Ann Neurol 23(Suppl):S161-5

Lavanchy D, Bovet P, Hollanda J, et al (1991) High seroprevalence of HTLV-I in the Seychelles. Lancet 337(8735): 248-9

Macchi B (1992) HTLV-I in neurological diseases. Ital J Neurol Sci 13(9 Suppl 14):31-6

Molgaard CA, Eisenman PA, Ryden LA, Golbeck AL (1989) Neuroepidemiology of human T-lymphotrophic virus type-I-associated tropical spastic paraparesis. Neuroepidemiology 8(3):109-23

Montgomery RD (1989) HTLV-1 and tropical spastic paraparesis. 1. Clinical features, pathology and epidemiology. Trans R Soc Trop Med Hyg 83(6):724-8

Oger JJ, Werker DH, Foti DJ, Dekaban GA (1993) HTLV-I associated myelopathy: an endemic disease of Canadian aboriginals of the Northwest Pacific coast? Can J Neurol Sci 20(4):302-6

Román GC (1987) Retrovirus-associated myelopathies. Arch Neurol 44(6):659-63

Román GC, Román LN (1988) Tropical spastic paraparesis. A clinical study of 50 patients from Tumaco (Colombia) and review of the worldwide features of the syndrome. J Neurol Sci 87(1):121-38

Román GC, Schoenberg BS, Madden DL, et al (1987) Human T-lymphotropic virus type I antibodies in the serum of patients with tropical spastic paraparesis in the Seychelles. Arch Neurol 44(6):605-7

Román GC, Spencer PS, Schoenberg BS, et al (1987) Tropical spastic paraparesis: HTLV-I antibodies in patients from the Seychelles. N Engl J Med 316(1):51

Vernant JC, Maurs L, Gessain A, et al (1987) Endemic tropical spastic paraparesis associated with human T-lymphotropic virus type I: a clinical and seroepidemiological study of 25 cases. Ann Neurol 21(2):123-30

Zaninovic V, Arango C, Biojo R, et al (1988) Tropical spastic paraparesis in Colombia. Ann Neurol 23(Suppl):S127-32

adults could be 14/750 = 1.9% (95% confidence interval: 1.0%-3.1%). The prevalence could be larger if there were actually less new donors in 2008-2012 than anticipated (which is likely) but smaller if some of the HTLV-I cases also occurred among repeaters who became positive for HTLV-I over time (this is possible).

As medical files cannot be traced from data available from the transfusion laboratory, we asked several senior clinicians about cases with HTLV-I associated diseases they were aware of. In the past few years, the oncologist reported around 5 patients with lymphoma associated with HTLV-I (including some young patients); senior physicians recalled

of at least 10-20 cases with spastic paraparesia (including some young patients); the head of the HIV Unit knew about around 5 HIV patients who also had HTLV-I (from a cumulative total of approximately 500 HIV cases in 2012); and 6 patients had HTLV-I among the 101 patients undergoing hemodialysis in 2012 (mostly middle-aged or old persons). Although the prevalence of all intestinal worms has dramatically decreased in the Seychelles over the last two decades [1,18], a few cases with strongyloidiasis associated with HTLV-I are known from local physicians, including a recent fatal case due to massive infestation.

In the Seychelles, it is worth noting that laboratory diagnosis had initially been based on the detection of antibodies using immuno-enzymatic ELISA tests that were unable to distinguish between HTLV-I and HTLV-II. Since 1991, the serological procedure has included Western-Blot supplemental testing, which is able to distinguish between the two viruses. The test line immune assay (e.g. Inno-Lia HTLV I/II Score, Innogenetics©) currently used in Seychelles for confirmatory purposes can distinguish between HTLV-I, HTLV-II and other HTLV strains, with 99.8% sensitivity and 99.7% specificity, according to the producer.

As a rule, examination for HTLV-I is systematically conducted on blood donors in the French territories, specifically in La Réunion [14]. The study conducted in La Réunion in 1994 has shown false positive ELISA results and nonspecific inconclusive findings from the Western-Blot technique [11], motivating the application of specific diagnostic tools using PCR genome detection in mainland France. In 1994 in La Réunion, off 3900 blood donors, only one was found to be positive, (prevalence estimate 0.025%) [11]. Concurrently, from 2007 to 2012, off 114 187 specimens from blood donors, 35 were positive on ELISA tests challenged for the HTLV-I/HTLV-II complex. The test in use in La Réunion is Architec rHTLV-I/II Reagent kit®. Whenever that test is positive, a Western-Blot test is performed. Notably, only two cases were confirmed using Western-Blot: one from an African and one from a Colombian individual.

Surprisingly, no systematic study of HTLV-I infection in the Southwest Indian Ocean Islands has been reported for the past twenty years and newer evidence is based on limited enquiries. We are not aware of studies that have assessed the frequency of HTLV-I in Mauritius, Comoros of Madagascar [2]. Comoros physicians have not reported to us medical cases that resemble HTLV-I infection. However, HTLV-I related lymphoma and paraplegia (particularly mild forms) might be missed or related to other causes in resource-constrained settings.

There is no blood donation in Mayotte and we are not aware of available data from blood donors in Mauritius, Madagascar and Comoros.

In the Seychelles, as mentioned above, HTLV-I is tested for all blood donors and for a few hundreds of other patients since at least two decades and positive tests are confirmed with a line immunoassay that can distinguish between different HTLV strains. Positive results on two different tests suggest true positivity. Since HTLV-I is not a notifiable disease, it is not reported in epidemiological quarterly reports, which mention only cases of HIV, hepatitis B and C and syphilis from screening of collected blood [12].

In mainland France, a 56-year old Caucasian man (originating from the department of Lot-et-Garonne) referred from Mayotte in October 2005, was recently identified as HTLV-1 positive as he developed a chronic progressive neuromyelopathy. He had lived in the South West Indian Ocean Islands region for 25 years: Comoros from 1980 to 1994 with a 6-month stay in Madagascar in 1990, and Mayotte from 1994 to 2006. In 2003, he insidiously developed urinary disturbances. During summer 2005, his clinical presentation worsened with difficulty in walking, pain, spastic paraparesia in the lower extremities and gait disturbances. Upon admission, he presented with spasticity, neurogenic muscular weakness, deep tendon hyperreflexia of the lower extremities, urinary bladder disturbance and severe constipation. Serologic examination for HIV, HCV, HBV, syphilis, serum antinuclear, anti-DNA and antineutrophil cytoplasmic antibodies were all negative. Examinations of the serum and CSF were positive for anti-HTLV-1 antibody by both ELISA and Western-Blot tests in both serum and CSF. He was diagnosed with advanced, crippling TSP/HAM. A high HTLV-1 proviral DNA load was measured in the peripheral blood. CSF analysis revealed a moderate increase of protein content (0.53 g/l) and an IgG level of 53.9 mg/l. Intrathecal production of IgG (10.54 mg/l) was ascertained, considering the oligoclonal IgG profile without evidence for hemato-encephalic barrier alteration. The cell count was elevated (11 lymphocytes/mm^3). Blood chemistry, other laboratory findings, brain and spinal magnetic resonance imaging (MRI) were unremarkable.

Thereafter, TSP/HAM tableau was associated with infective dermatitis, diabetes type 2 and IgA nephropathy with persistent proteinuria. Therapy with zidovudine in combination with pentoxiphylline was not effective. Intensive symptomatic treatment was the mainstay of therapy for supportive benefits and partial improvement. Of note, the patient reported multiple sexual partners between 1980 and 2000. His current partner, a Comorian woman, and three of their children were found to be uninfected (D. Malvy, personal data).

Discussion

In the Indian Ocean, only three countries conduct a regular HTLV-I surveillance, namely La Réunion, Seychelles and Mayotte. Notably, only two cases were confirmed in La Réunion among non-residents.

In the Seychelles there is a high prevalence reported earlier and nowadays. There are quite a few patients with conditions linked with HTLV-I with half a dozen cases of lymphoma and around 20 patients known to have spastic tropical paraplegia associated with HTLV-I, which are substantial numbers for a total population of 87'400. In many areas in the world, the high rates of HTLV-I infection are probably related to an ethnic repartition and to a founder effect in some groups with the persistence of a high viral transmission rate. In the Seychelles, it must be noted that when slavery was abolished in 1835, there were 6,600 slaves brought from several African countries, among the 7500 inhabitants. Then, the population substantially increased with many freed slaves by the Royal Navy, from captured slaves ships. Nowadays, it is estimated that approximately 65% of the inhabitants are of African origin, 5% Indian, 2-5% Caucasian, 2-3% Chinese. The remaining 25% are a mixture of these different groups, which is much less than in La Réunion and Mauritius.

Altogether, there is a paucity of data that limits inference on the actual prevalence of the HTLV-I infection in several Southwest Indian Ocean islands. Nevertheless, with the exception of Seychelles, there seems to be a striking contrast with the high prevalence in the French West Indies [14,17].

Although the frequency of Strongyloides and other intestinal worms has largely decreased in the Seychelles [1,18] and in La Réunion (there are no data in the other islands), co-infection with both HTLV-I and *Strongyloides stercoralis* can be an issue, as there are several reports of lethal malignant cases [2,4] and as modulating effects of HTLV-I on the immune response may facilitate and predispose to *Strongyloides stercoralis* multiplication. HTLV-I can exacerbate the clinical severity of mixed infections [13] or, it has also been suggested, early manifestations of ATLL. Furthermore, Brazilian authors have recently suggested that HTLV-1 is associated with increased susceptibility to Mycobacterium tuberculosis infection and severity of tuberculosis [3].

Conclusions

HTLV-I seems to be rare in the region, except in the Seychelles where substantial numbers of people have a positive HTLV-I serology and non-negligible numbers of patients have lymphoma or paraparesia related to HTLV-I. Screening is conducted routinely in La Réunion but only very few positive cases were confirmed with Western-Blot; further surveillance along this high diagnostic standard is warranted. Very little data on HTLVI are available in Mauritius, Comoros and Madagascar. Data from these countries are warranted to assess the situation of HTLV-I in the region.

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