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HTLV in Sweden

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Abstract

Sweden is a country with a low prevalence of human lymphotropic T-cell virus (HTLV) infection, estimated at < 0.005%, but the infection rate is notably higher in specific risk groups such as HTLV-2 among intravenous drug users (IVDU) and people originating from HTLV-1 highly endemic areas. Thus, in the most recent study from 2012, the prevalence of HTLV-2 among IVDU in Stockholm was 3.2%. However, much of the epidemiological data on HTLV in Sweden stems from studies conducted primarily between the 1990s and 2007, and the impact of migration to Sweden during the past 15 years has not been evaluated. Despite Sweden's status as a country with generally low prevalence of HTLV, it is prudent to anticipate and prepare for several potential challenges associated with HTLV infection in the future. Proactive measures to enhance awareness, alongside strategies to curtail transmission and mitigate complications, are crucial for addressing this relatively rare, but significant health issue. In this work, we review the current epidemiological knowledge about HTLV in Sweden and discuss future Swedish perspectives.

Keywords

HTLV-1. HTLV-2. Adult T-cell leukemia/lymphoma. Tropical spastic paraparesis. Intravenous drug users. Sweden.

Introduction

Background

Human lymphotropic T-cell viruses type 1 and 2 (HTLV-1 and HTLV-2) are members of the *Retroviridae* family and belong to the genus *Deltaretrovirus*. HTLV-1 was the first exogenous human retrovirus detected and isolated in 1979[1]. Although HTLV infection globally affects an estimated 10-20 million individuals, its prevalence is notably higher in specific regions. These regions include Japan, the Caribbean, and certain areas of West-Central Africa and South America, where HTLV infection is more commonly found[2].

HTLV primarily infects T lymphocytes, with DNA integration of HTLV-1 predominantly detected in CD4+ T-cells and HTLV-2 in CD8+ T-cells. The infection is lifelong, but 95% of carriers remain asymptomatic throughout life. HTLV is known to cause two main associated diseases: adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 infection can cause these serious conditions, whereas no firm association between HTLV-2 and severe clinical disease has been confirmed[3].

ATLL is an aggressive form of cancer that usually develops several decades after infection and affects T-cells, which might manifest as leukemia or lymphoma and eventually involve various organs. Conversely, HAM/TSP is a chronic neurological disorder characterized by inflammation of the spinal cord, leading to muscle weakness, spasticity in the lower limbs, and

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bladder dysfunction. It has been suggested that HTLV-1 proviral load (PVL) is a strong determinant for developing ATLL and HAM/TSP[2], and approximately 2-7% of individuals infected with HTLV-1 are estimated to develop ATLL and 0.25-3% to develop HAM/TSP over their lifetime[4]. Other HTLV-related manifestations include infective dermatitis which is observed mostly in children, Sjögren's syndrome, polymyositis, chronic inflammatory arthropathy, and ocular diseases such as uveitis[5], and also the broader spectrum of these HTLV-associated conditions may contribute to worse survival in affected individuals[3].

HTLV can be transmitted from mother to child during breastfeeding but also by sexual contact, blood transfusions or organ transplants, and exposure to other contaminated blood products. Studies suggest that the risk of vertical transmission is influenced by factors such as the mother's HTLV PVL in breastmilk and blood cells. Prolonged breastfeeding (> 6 months) has been the strongest factor associated with a higher risk of vertical transmission[6,7]. Overall, data indicate that the transmission rate through breastfeeding can range between 4 and 31%[8,9].

Prevention of mother-to-child transmission

To prevent HTLV transmission from an infected mother to her child, several measures can be taken. Pregnant women from high-endemic areas should be offered testing for HTLV infection during antenatal care, and if a woman is found to be HTLV-positive, she should receive appropriate counseling regarding the risks and preventive measures (proceedings of the 30th HTLV European Research Network [HERN 2023]). This is of particular importance in areas where HTLV prevalence is very high. Antenatal screening has been successfully introduced in Japan since 2011, leading to a substantial decline in new infections[10]. In HTLV-positive mothers, alternative feeding methods such as formula feeding should be considered to reduce the risk of transmission. If formula feeding is chosen, it is important to strictly adhere to exclusive formula feeding without any breastfeeding, thus avoiding any direct contact with breastmilk. Conversely, if breastfeeding is preferred, early weaning is recommended before 6 months of age. Gradually reducing and stopping breastfeeding as early as possible can help to minimize the risk of transmission. Finally, regular follow-up with health-care professionals is essential to monitor the health of both the mother and the child and to ensure appropriate management and support.

Treatment

At present, there are no specific antiretrovirals available for treatment or prevention of HTLV infection and the management focuses on addressing HTLV-associated complications and symptoms. Regular monitoring and follow-up with health-care professionals are recommended for individuals with HTLV infection. Antiretroviral drugs such as nucleoside-analogs reverse transcriptase-inhibitors and integrase-inhibitors have shown activity against HTLV-1 *in vitro*[11-13], but a beneficial *in vivo* effect in asymptomatic carriers has not been proved so far. The lack of clinical efficacy in this patient category relates to (I) the fact that HTLV-1 is not transmitted efficiently through cell-free viral particles, in contrast, transmission is facilitated by contacts between an infected donor cell and an uninfected target cell through the establishment of viral synapses and the transfer of viral biofilm and (II) a clonal expansion of HTLV-infected cells[14].

Treatment for specific HTLV-associated conditions, such as ATLL or HAM/TSP, should involve a multidisciplinary approach. For ATLL, treatment options may include zidovudine + interferon-alpha[15], combination chemotherapy regimens (e.g., CHOP and DA-EPOCH)[16], antibody therapies targeting CD30, immunomodulatory drugs such as interferon-alpha and the monoclonal IgG antibody mogamulizumab that targets the chemokine receptor CCR4 expressed in neoplastic cells in approximately 90% of ATLL cases[17]. Allogenic stem cell transplantation has been successful in patients with aggressive ATLL[18,19] and may be considered in selected cases. The choice of treatment depends on factors such as the subtype and stage of ATLL, as well as the patient's overall health including any comorbid conditions.

For HAM/TSP, management typically involves symptomatic treatment and physical therapy to improve mobility and manage spasticity. These interventions can enhance quality of life but do not change the course of HAM/TSP progression. Medications such as corticosteroids, immunomodulatory drugs, and antiretroviral therapy (ART) have been explored, but their effectiveness varies widely between individuals. High-dose pulsed methylprednisolone is recommended for induction and low-dose (5 mg) oral prednisolone as maintenance therapy for progressive HAM/TSP disease[20], and long-term improvement of symptoms in patients treated with corticosteroids has been observed in some cohorts[21]. The effect over 48 weeks of a T-cell activation inhibitor, cyclosporine A, was investigated in

a small study of seven patients with early or progressive HAM/TSP, with partial reversal of the clinical disease deterioration in some of the individuals[22]. Combination ART with zidovudine and lamivudine in 16 patients for 48 weeks in a placebo-controlled randomized clinical trial indicated no efficacy to reduce PVL or clinical improvement of the patients[23].

Global HTLV epidemiology

The global epidemiology of HTLV varies across different regions. HTLV-1 is more prevalent or endemic, in some focal geographic areas including Southwestern Japan, the Caribbean Islands, parts of South America, and some regions in Africa and the Middle East. The prevalence of HTLV-1 infection ranges from < 1% to over 30% in specific populations within these regions, e.g., in Australia among Australian aborigines[24]. However, it is important to note that the overall prevalence of HTLV-1 worldwide is relatively low. Most studies conducted in North America and Europe have found a prevalence of HTLV-1 infection of < 1% in the general population[25], apart from Romania where the prevalence of HTLV is high (5.33 at 10,000 blood donors in 2003-2008)[26].

HTLV-2 is less widespread compared to HTLV-1, and around 800,000 people are estimated to be infected with HTLV-2 worldwide. HTLV-2 infection has been associated with intravenous drug use in Northern America and is primarily found in certain African areas and indigenous populations in the Americas, particularly among native American tribes in North and South America[27]. Importantly, the epidemiology of HTLV is dynamic, and the prevalence rates can change over time due to various factors such as migration patterns, population movements, and changes in health-care practices such as testing frequency.

HTLV in Sweden

History

The initial studies of HTLV-1 infection in Sweden were published in 1985. The first reported the results from screening for antibodies to HTLV-1 among monkeys kept for scientific animal experiments at different Swedish universities and laboratories. Out of totally 252 monkeys, seven animals from the same colony had antibodies to HTLV. Several of the 28 animal caretakers or experimenters had been repeatedly exposed to infected monkey blood, but none had developed detectable HTLV-1 antibodies[28]. The second study, also from 1985, investigated the prevalence of HTLV-1 antibodies in 84 adult individuals with leukemia and 365 blood donors from Southern Sweden, but the results could not confirm any HTLV case in that cohort[29]. The first case report of a patient presenting with TSP in Sweden, a male originally from East Africa but living in Sweden since 1975, was published in 1987[30].

Blood donor HTLV-1/2 screening was introduced in February 1994, but later in the 1990s observational data indicated a low HTLV seroprevalence among both blood donors and intravenous drug users (IVDUs)[31-34], and HTLV screening was eventually recommended only for 1st-time blood donors.

The first case of HTLV-1-induced ATLL was reported in 1999, in a patient originating from the endemic area of Mashhad in Iran[35]. A mandatory national HTLV-1/2 screening program for all individuals seeking care at *in vitro* fertilization (IVF) clinics has been running since it was introduced in 2003 by the Swedish National Board on Health and Welfare.

HTLV seroprevalence

A survey of HTLV-1 antibody seroprevalence in Arctic regions, including three areas in Northern Sweden, was conducted in the mid-80s. The seroprevalence of HTLV-1 among 200 Swedish Lapps was 0.5%, whereas the prevalence among 100 healthy blood donors living near the Swedish-Finnish border was 5%[36]. After diagnosing the first HTLV-positive blood donor in Sweden in 1993, all national transfusion centers started to screen all donations by March 1, 1994. One year later around 650,000 donations, representing over 235,000 donors, had been screened. Six donors were found and confirmed to have HTLV-1 infection, and thus, the prevalence among all Swedish blood donors was around 2/100,000 (0.002%)[37]. The latest estimation of Swedish HTLV seroprevalence from 2012 includes several unique screening subgroups. A total of 550,000 new blood donors were included from 1995 to 2007. Overall, 16 were HTLV-1 positive and two were HTLV-2 positive. The overall HTLV prevalence in donors was 0.3/10,000 (0.003%). In antenatal screening of 11,997 pregnant women during the years 1995, 1998, 2000, and 2003 (all from the Örebro region), none was found HTLV positive. Among 35,000 IVF patients in the whole Sweden screened between 2003 and 2006, HTLV prevalence was 2.3/10,000 (including one HTLV-2). In patients who were diagnosed with hepatitis C in the Örebro region, 1/335 (0.28%) was positive for HTLV-1.

The highest seroprevalence was found in IVDU in the Stockholm area. Out of 1079 tested IVDUs, HTLV-2 was confirmed in 28 subjects and HTLV-1 in two subjects, giving an overall prevalence of 3.2% in this population[38]. The results from the Swedish epidemiological HTLV studies are summarized in table 1.

HTLV-2

HTLV-2 infection has been associated with intravenous drug abuse in many parts of the world. Furthermore in Sweden, HTLV-2 infections are mostly detected in IVDU. Already in 1994, when the first study assessing the prevalence of HTLV-2 in IVDUs in Stockholm was published, 10/134 screened IVDUs were shown to be seropositive and all the 10 subjects were of Scandinavian descent[32]. Evidence that HTLV-2 had entered the IVDU population also in the southern parts of Sweden (Malmö) was revealed in the same year[31]. In a larger IVDU cohort also from Stockholm, 27/1,158 (2.3%) of individuals screened during 1992 were HTLV-2 positive[33]. In another prospective study in Stockholm 1994, 29/905 (3.2%) of IVDUs were confirmed as HTLV-2 positives, and no case of HTLV-1 infection was reported. All but three were of Scandinavian descent. Interestingly, HIV-1 infection was identified as a risk factor for HTLV-2 in this study as the prevalence of HTLV-2 was highest in patients co-infected with HIV-1 (12%)[39]. As mentioned above, the most recent survey of HTLV-2 in IVDU from the Stockholm area published in 2012 showed a stable prevalence over time (3.2%).

Stockholm HTLV patient cohort

All patients with confirmed HTLV infection in the Stockholm region are followed at the outpatient clinic at Karolinska University Hospital. At present, around 90 patients with HTLV infection attend periodically clinical care, 90% HTLV-1 and 10% HTLV-2 positives. Almost 60% are women, and the average age in the cohort is 53.5 years. Overall, 25% of the individuals are born in Sweden, whereas the rest have other countries of origin (mostly from the Middle East, South America, African countries, and the Caribbean basin). The HTLV infection was diagnosed as part of contact testing and in blood donor screening in two-thirds, but also at IVF clinics and due to a diagnostic search for clinical symptoms. Only 2% of patients were IVDU.

Since the year 2000, 10 individuals have been diagnosed with HAM/TSP and two individuals with ATLL, in both latest cases with fatal outcome.

Future Swedish perspectives

Despite Sweden's status as a country with a low prevalence of HTLV, it is worth to anticipate and prepare for several potential challenges associated with HTLV in the future.

In other European non-HTLV-endemic countries, it has been demonstrated that the HTLV prevalence among individuals born in HTLV-endemic regions is significantly higher than among those born in European countries. For instance, the HTLV prevalence in women born in the Caribbean (1.4%) was significantly greater than that among women born in the United Kingdom (0.03%)[40]. In addition, recent data from Spain indicate that many HTLV-positive individuals (22%) present late to health care suggesting suboptimal testing strategies[41]. We assume that the situation in Sweden might be similar. Given the increased migration from HTLV-endemic areas to Sweden in recent years, there is a growing need for targeted testing strategies. This is particularly vital for high-risk groups such as pregnant women and IVDUs, to effectively identify and manage HTLV infections in these populations. We specifically want to point out:

- Increased awareness and screening: HTLV is less known compared to other chronic viral infections, which can make diagnosis and treatment challenging. Raising awareness among health-care professionals and the public is crucial for early detection and management.
- Blood transfusions and organ donations: HTLV can be transmitted through blood transfusions and organ donations. Ensuring keeping the rigorous screening processes for 1st-time blood and organ donors, and the introduction of repeated screening in individuals from HTLV-1 highly endemic regions is essential to reduce the risk of transmission.
- Antenatal screening: mother to child is the most common route of HTLV transmission in some endemic regions[42]. While screening for HTLV in individuals undergoing IVF care is already in place, it would be advisable to consider implementing antenatal HTLV screening for first- and second-generation female migrants from highly endemic countries. This proactive approach could significantly enhance early detection and management of HTLV in these high-risk groups.
- Global mobility: people travel worldwide, and HTLV can spread from one region to another. Increased global mobility may raise the risk of HTLV transmission. Over the past 15 years, 1,639,771 people have immigrated to Sweden, representing an increase of 18.4% compared to 2010 when the number of

Table 1. Characteristics and prevalence of HTLV infection in Sweden

Study (year)	Population (sampling period)	HTLV type included in screening	Sample size (number of individuals)	Number of infected	Overall prevalence (HTLV-1/2)
Blomberg et al. (1985)[28]	Monkey caretakers in Sweden (NA)	1	28	0	0
Robert-Guroff et al. (1985)[36]	Swedish Lapps (NA)	1	200	1	0.5%
	Healthy blood donors near Swedish-Finnish border in Norrbotten County (NA)		100	5	5%
	Healthy blood donors in Västerbotten County (NA)		100	0	0
Blomberg et al. (1985)[29]	Leukemia patients (NA)		84	0	0
	Blood donors (NA)	1	365	0	0
Blomberg et al. (1994)[31]	IVDU in Stockholm and Malmö (1986-1989, 1993)	1,2	648	2 (HTLV-1) 1 (HTLV-2)	0.5%
Krook et al. (1994)[33]	IVDU in Stockholm (1990-1992)	1,2	134	10 (HTLV-2)	7.4%
Andersson (1995)[32]	IVDU in Stockholm (1992)	1,2	1158	1 (HTLV-1) 27 (HTLV-2)	2.4%
Krook et al. (1997)[39]	IVDU in Stockholm (1994)	1,2	905	0 (HTLV-1) 29 (HTLV-2)	3.2%*
Tynell et al. (1998)[37]	Healthy blood donors (1994-1995)	1,2	201 000	6 (HTLV-1)†	0.002%
	New blood donors (1994-1995)		34 000	NA	
Malm et al. (2012)[38]	Pregnant women in Örebro County (1995,1998, 2000, 2003)	1,2	11 997	0 1 (HTLV-1)	0 0.28%
	Hepatitis C positive testing individuals in Örebro County (2002-2004)		335	4 (HTLV-1) 1 (HTLV-2) 3 (HTLV not typeable)	0.02% 0.003% 3.2%
	Individuals attending IVF clinics in Sweden (2003-2006)		34 555	16 (HTLV-1) 2 (HTLV-2)	
	New blood donors (1995-2007)		550 000	2 (HTLV-1) 28 (HTLV-2) 5 (HTLV not typeable)	
	IVDU in Stockholm (NA)		1079		

*The prevalence of HTLV-2 infection was 12% among HIV-1-seropositive.
†6 out of 235,000 blood donors were HTLV-1 positive. None was HTLV-2 positive.
IVDU: intravenous drug users; NA: not available.

immigrants was 1,384,929[43]. Between 2010-2019, migrants from highly HTLV-prevalent countries such as Iran and Iraq (n = 85,716), Romania (n = 18,943), and Brazil (n = 6,359) were registered in Sweden. During the same period, a total of 53,650 immigrants moved from Africa. During the COVID-19 pandemic, however, the number of immigrants to Sweden decreased, contributing to the lowest population growth in 15 years[44]. It is important to note that migration flows can be influenced by several factors, including global events and political changes. Recently, the World Health Organization (WHO) has called attention to the need for more HTLV-1 prevalence data globally[45]. Establishing an extended national surveillance program for transmissible diseases such as HTLV should be prioritized,

and updated epidemiological data on HTLV infection in Sweden need to be obtained to carry out optimal public health interventions and clinical follow-up.
- Treatment options: at present, there is no specific treatment that cures HTLV infection. Future research should focus on developing effective therapeutic options for those infected and for preventing HTLV infection, e.g., mother-to-child transmission. Studies on prevention of MTCT with antivirals should be designed and performed.
- Follow-up and long-term effects: many HTLV-infected individuals remain asymptomatic, but some may develop HTLV-1-associated diseases such as ATLL or HAM/TSP. Keeping retention into care with long-term follow-up of these individuals is essential to understand disease progression and manage any complications.

Conclusions

While the overall prevalence of HTLV in Sweden is relatively low, estimated at < 0.005%, the infection rate is notably higher in specific risk groups, with historical surveys indicating that around 3% of IVDUs are HTLV positive. Due to the increased migration to Sweden during the past decades, the current numbers might have changed, and an updated characterization of the HTLV prevalence in risk groups is important. No effective antiretroviral treatment has been proven effective *in vivo*, but some treatment options including corticosteroids and chemotherapy are available for HAM/TSP and ATLL. In the future, it is important that Swedish patients with HTLV have the possibility to be included in larger international collaborative studies, for instance in preventing vertical transmission with antiretrovirals.

In summary, continued monitoring of HTLV infection in Sweden, increased awareness, and efforts to reduce transmission and complications are crucial for addressing this relatively rare health problem.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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