HTLV: a new issue in prenatal screening?

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Abstract

Human T-cell leukemia virus-1 (HTLV-1) is the first infectious agent proven to cause cancer, and it is considered among the most potent carcinogens for humans. HTLV-1 is estimated to have infected 5-10 million individuals, with only about 5% of people that contract the virus expected to develop any associated disease. Within Europe, Romania appears to be the only region endemic to HTLV-1. There are two primary diseases associated with HTLV-1, T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy (HAM), or tropical spastic paraparesis (TSP). Each is linked to a distinct mode of transmission: ATL with breastfeeding, and HAM/TSP with blood transfusion. The main ways of viral transmission are from mother to child by breastfeeding, via blood transfusions, or through sexual intercourse. Vertical infection rate has been found to be 14.2%. In Romania, HTLV is included in the screening for blood donors, but not in prenatal screenings. Vertically transmitted infections can be reduced with up to 87% by avoiding breastfeeding. New research supports the effectiveness of prenatal screening followed by avoiding breastfeeding in reducing new cases of HTLV in endemic areas, and such measures must be taken in Romania as well.

Keywords: *human T-cell leukemia virus, prevention, vertical transmission, prenatal screening*

Rezumat

Virusul HTLV-1 este primul agent infecțios care s-a dovedit a provoca neoplazii, fiind considerat unul dintre cei mai puternici agenți carcinogeni pentru om. Se estimează că HTLV-1 a infectat între 5 și 10 milioane de indivizi, însă doar aproximativ 5% dintre aceste persoane pot dezvolta o boală asociată. În Europa, România pare a fi singura regiune endemică pentru HTLV-1. Există două boli primare asociate cu HTLV-1: leucemia/limfomul cu celule T (ATL) și mielopatia asociată cu HTLV-1 (HAM), sau parapareza spastică tropicală (TSP). Fiecare este asociată unui mod de transmitere distinct: ATL cu alăptarea la sân și HAM/TSP cu transfuzia de sânge. Principalele căi de transmitere a virusului sunt de la mamă la copil prin alăptare, prin transfuzii de sânge sau prin contact sexual. S-a constatat că rata de infecție verticală este de 14,2%. În România, HTLV este inclus în screeningul pentru donatorii de sânge, dar nu și în screeningul prenatal. Infecțiile cu transmitere verticală pot fi reduse cu până la 87% prin evitarea alăptării. Dovezile recente susțin eficiența screeningului prenatal urmat de evitarea alăptării în reducerea cazurilor noi de infecție cu HTLV în zonele endemice, iar astfel de măsuri trebuie luate și în România.

Cuvinte-cheie: *virusul leucemiei umane cu celule T, prevenție, transmisie verticală, screening prenatal*

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HTLV: un nou subiect pentru screeningul prenatal?

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Introduction

Human T-cell leukemia virus-1 (HTLV-1) is the first infectious agent proven to cause cancer, and research suggests that HTLV-1 may be considered among the most potent carcinogens for humans[(1)]. Furthermore, this virus is responsible for a wide range of illnesses, such as myelopathy and immunodeficiency, leading to significant morbidity and mortality globally[(1)]. HTLV-1 is the most clinically significant and well documented, and it belongs to the retrovirus family. Presently, four distinct types of this virus have been recognized for their ability to infect humans and induce pathological effects: HTLV-1, HTLV-2, HTLV-3, and HTLV-4[(2)].

HTLV-1 is estimated to have infected 5-10 million individuals, with only about 5% of people that contract the virus expected to develop any associated disease, with a heterogenous distribution worldwide[(3-5)]. Indeed, it is found often within concentrated clusters of high prevalence in proximity to areas where the virus is scarce. The major highly endemic regions include the southwestern part of Japan, certain areas in the Caribbean, and adjacent regions, as well as focal points in South America, some areas in intertropical Africa and the Middle East[(3)]. Within Europe, Romania appears to be the only region endemic to HTLV-1[(3)]. In a study published in 2009, the authors found the prevalence of HTLV-1 among first-time blood donors (confirmed by Western Blot or Immunoblot) to be 5.33 in 10,000 donors in Romania, as opposed to 0 in Denmark, Finland, Ireland and Norway[(6)]. The origin of this complex geographic and ethnic distribution is not fully understood, but it is likely associated with a founder effect in certain groups, followed by the sustained high transmission of the virus.

HTLV-associated diseases

HTLV-1 exhibits numerous parallels with human immunodeficiency virus type 1 (HIV-1), yet it diverges significantly in terms of the diseases it causes and the mechanisms through which it induces them. Two

virological distinctions between HIV-1 and HTLV-I are the following:

- The relatively low viral burden and the high genetic stability of HTLV-1, stemming from its low replication rate and the high replication fidelity, minimizing the likelihood of immune escape[7].
- While both viruses affect the T cells, HTLV-1 employs a cell-to-cell transmission pattern, the most frequent and efficient model, and it does not prompt the death of T cells; instead, it stimulates cell proliferation and transformation[2,8].

The two primary diseases associated with HTLV-1 – T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy (HAM), or tropical spastic paraparesis (TSP) – seldom overlap[9,10].

ATL encompasses four identifiable clinical forms: acute, lymphomatous, chronic, and smoldering[11]. Each of these disease variants presents differently and has various prognoses. Acute ATL, the most prevalent clinical manifestation, is associated with the least favorable overall survival, typically around six months[11]. The clinical findings are: skin lesions (nodules, ulcers, generalized papular rash), lytic bone lesions, hypercalcemia, pulmonary infiltrates, and up to 10% of individuals have central nervous system manifestations[11].

HAM/TSP is characterized by a subtle and gradual onset of worsening weakness and spasticity in one or both legs, ankle clonus, extensor plantar responses, hyperreflexia, and lower back pain[12].

Additionally, each is linked to a distinct mode of transmission (ATL with breastfeeding, and HAM/TSP with blood transfusion), each having different pathogenic and immunologic correlates[2]. It is also well-known that these infection models are linked to a specific age group, so it is not far fetched to assume that the age of the individual at the time of infection might be a factor in this pathological process. In essence, this suggests that HTLV-1 infection can lead to two fundamentally distinct diseases.

Transmission

The main ways of viral transmission are from the mother to the child by breastfeeding, *via* blood transfusions, or through sexual intercourse[13].

In a study published in 2018, the authors found the mother-to-child infection rate to be 14.2%, with the following independent risk factors: breastfeeding for more than 12 months, age of the mother at delivery over 26 years old, and having two or more children previously infected with HTLV-1[14]. The authors suggest that, given such a high transmission rate by breastfeeding and the dire consequences of the infection, admittedly in a small percentage of infected individuals, screening programs and breastfeeding counseling for mothers should be implemented in endemic areas. However, a meta-analysis showed that even bottle feeding does not guarantee non-transmission: there was a 0.6% transmission rate at one year in exclusively bottle-fed infants from infected mothers, but we must notice the significant difference in transmission rates[15].

Regarding infection by sexual intercourse, we know that seroconversion is almost four times more likely in the case of male-to-female transmission; the incidence of this transmission model is not well known[16].

As to infection by blood transfusion, a study found a rate of seroconversion of 44% in recipients of HTLV-1-positive cellular donor units[17]. As we have previously mentioned, HTLV employs a cell-to-cell transmission pattern, so acellular units do not pose a risk of infection.

Diagnosis and screening

The main tool for HTLV diagnosis is antibody detection, using an enzyme-linked immunosorbent assay (ELISA) test[18]. Also, multiplex RT-PCR is a very useful test, as it is not only diagnostic, but it also allows the possibility of quantifying the proviral load, a significant factor in the pathogenesis of HTLV-1[19].

In some European countries, HTLV is not included in the routine testing of donated blood as the prevalence is too low and, after a trial of universal screening, the evidence supported the discontinuation of HTLV screening[20]. However, as we discussed, Romania is an endemic region and, therefore, all cellular blood components are checked for HTLV[21]. When it comes to prenatal screening, HTLV is not taken into account in European countries in general or in Romania in particular[22].

Discussion

With evidence that vertically transmitted infections can be reduced with up to 87% by avoiding breastfeeding, action to reach as many infected people is imperative[23]. One of the key factors is knowing one's carrier status. This condition must be met before any preventive measures, such as counseling to avoid breastfeeding, can be implemented. It is rather apparent that, in order to meet this goal, antenatal screening in endemic regions, such as Romania, is needed, a topic supported by multiple authors[14,20,24]. An example is set by Nagasaki, Japan, where, after implementing the prenatal screening, the prevalence of infected pregnant individuals went from 7.1% in 1987 to 1% in 2007, affirming the efficacy of this approach[25].

Conclusions

The infection with HTLV poses a significant challenge in certain areas of the world, including Romania, and considering the morbidity and mortality of the associated diseases, efforts to reduce the incidence of infection must be made. The vertical transmission component must be addressed by implementing an antenatal screening policy, because knowing one's status is the first step in interrupting the chain of transmission, and for avoiding the risks and potential consequences of HTLV infection altogether. ■

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