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VERTICAL TRANSMISSION OF HTLV-I/II: A REVIEW

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SUMMARY
The vertical transmission of the human T-cell lymphotropic virus type I (HTLV-I) occurs predominantly through breast-feeding. Since some bottle-fed children born to carrier mothers still remain seropositive with a frequency that varies from 3.3% to 12.8%, an alternative pathway of vertical transmission must be considered. The prevalence rate of vertical transmission observed in Japan varied from 15% to 25% in different surveys. In Brazil there is no evaluation of this form of transmission until now. However, it is known that in Salvador, Bahia, 0.7% to 0.88% of pregnant women of low socio-economic class are HTLV-I carriers. Furthermore the occurrence of many cases of adul T-cell leukemia/lymphoma and of four cases of infective dermatitis in Salvador, diseases directly linked to the vertical transmission of HTLV-I, indicates the importance of this route infection among us.
Through prenatal screening for HTLV-I and the refraining from breast-feeding a reduction of ~ 80% of vertical transmission has been observed in Japan. We suggest that in Brazil serologic screening for HTLV-I infection must be done for selected groups in the prenatal care: pregnant women from endemic areas, Japanese immigrants or Japanese descendents, intravenous drug users (IDU) or women whose partners are IDU, human immunodeficiency virus carriers, pregnant women with promiscuous sexual behavior and pregnant women that have received blood transfusions in areas where blood donors screening is not performed. There are in the literature few reports demonstrating the vertical transmission of HTLV-II.
KEYWORDS: Viral vertical transmission; Breast-feeding transmission; HTLV-I transmission HTLV-II transmission; Adult T-cell leukemia/lymphoma; Infective dermatitis.

HTLV-I

Epidemiological studies

The human T-cell lymphotropic virus (HTLV) type I was first isolated in a T-lymphoblastoid

cell line established from a patient with cutaneous lymphoma in 1980[49] and its clear association with human disease was demonstrated in the following years[24]. This virus is endemic in Southwestern and Northern Japan, Africa, Australia, Alaska, South America and the Caribbean islands[63]. Hyperendemic areas, ie, those where seroprevalence is higher than 15% in the normal population age 40 and older, have been reported in some Japanese islan as well as in Melanesia[47]. Surveys performed in several Brazilian cities among blood donors showed the following prevalence rates: Manaus and Florianópolis 0.08%, Recife and Rio de Janeiro 0.33%, São Paulo 0.4%, and Salvador 1.35%. In these studies no case of HTLV-II infection was detected[15, 17]. A prevalence study among Japanese immigrants from Okinawa and their descendents living in São Paulo and Campo Grande (Brazil) revealed that 10% of them presented antibodies to HTLV-I[34].

Studies in Salvador-Bahia revealed a frequency of HTLVI/II infection among healthy individuals and patients with the acquired immunodeficiency syndrome (AIDS) of respective 1.8% and 22.7%[44]. More recently, evaluations discriminating between types I and II of the virus showed a prevalence rate of 25.5% of HTLV-I among injecting drug users (IDU).[4] It is important to emphasize that unlike findings in the United States and Europe, in Bahia as wel as in São Paulo, HTLV-I infection is more prevalent than HTLV-II among IDU[4, 6].

No evaluation of vertical transmission of HTLV-I has been made in South America so far. However studies of prevalence of infection among pregnant women have been performed. Evaluating 1,024 pregnant women in Salvador (Bahia), SANTOS et al. (1995)[51] found a prevalence rate of 0.88% of HTLV-I/II seropositive mothers. In a study that is in progress ir prenatal care unit BITTENCOURT et al. (data not published) observed 0.72% of HTLV-I seropositive women in contrast to only 0.02% of HTLV-II seropositive mothers. They screened 5,000 pregnant women.

The infection can be transmitted through sexual contact, blood transfusion, vertically (from carrier mothers to their children), and through needle sharing among drug users[13]. Sexual transmission is considered to occur primarily from male to female. The rate of HTLV-I transmission from infected males to females is considered to be 60.8% whereas transmissio from infected females to males occurs only rarely (rate of 0.4%)[29]. Another possible means horizontal transmission among us may be through breast-feeding by wet-nurses.

Associated diseases

The major interest in preventing HTLV-I infection is because the carriers may develop an agressive form of adult-T cell leukemia/lymphoma (ATLL) and a chronic neurologic disease, the HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). In Nagasaki (Japan) 60 new cases of ATLL are registered each year and they account for ~ 0.5% of total deaths in this area[22]. A recent study including only patients from Bahia demonstrated that 7.3% of the non-Hodgkin lymphomas/lymphocytic leukemias and 33.3% of the T-cell lymphomas are associated with HTLV-I[9]. Another previous study referred that 20% of the T-cell lymphomas diagnosed in Rio de Janeiro were HTLV-I positive[50]. The estimate life risk fo an HTLV-I carrier to develop ATLL corresponds to ~ 5%[63]. Conventional chemotherapy is nc curative in HTLV-I associated lymphomas, and relapses occur quickly and frequently. The median survival from diagnosis in the acute form of disease is only 11 months[13]. It is important to emphasize that to date, most cases of ATLL have been considered to result fror vertical transmission[58], notwithstanding this disease is rarely reported in childhood[10, 40].

In contrast to HAM/TSP, ATLL have been rarely reported following HTLV-I infection by blood transfusion[47]. HAM/TSP is characterized by progressive and permanent lower-extremity weakness, spasticity, hyperreflexia, sensory disturbances, and urinary incontinence. Less tha 1% of HTLV-I infected individuals develop HAM/TSP[30]. Twenty-seven per cent to 35% of the myelopathies diagnosed in Salvador, Bahia, represent examples of HAM/TSP, but in these

studies no discrimination was done between HTLV types I and II. An important aspect is tha this pathology occurs predominantly in the female gender in a proportion that varies betwee 72% to 94%[5, 42]. The literature stresses the fact that association of ATTL and HAM/TSP is exceptional [47], however we have observed 20% of this association among 25 cases of HTLV- + cutaneous T-cell lymphoma in Salvador-Bahia. It is possible that in Bahia vertical transmission also plays some role in the development of HAM/TSP.

HTLV-I infection has been considered to be an indirect cause of or a contributing factor in some other diseases, such as chronic lung diseases, opportunistic lung infections, cancers, monoclonal gammopathy, chronic renal failure, strongyloidiasis, dermatomycoses, HTLV-I-associated lymphadenitis, uveitis, chronic arthropathy, polymyositis, folliculitis decalvans, and infective dermatitis[7, 36, 58]. The association of HTLV-I infection with these diseases is considered to be due, to some extent, to the immunodeficiency induced by the virus[58].

Besides ATLL, infective dermatitis is another disease generally associated with vertical transmission. It manifests itself as a chronic eczema associated with a refractory non-virulen *Staphyloccus aureus* or beta-hemolytic *Streptococcus* infection of the skin and nasal vestibules. This entity was first described in 1966 by SWEET[56] in Jamaican children. Later, i Jamaica, LAGRENADE et al. (1990)[36] linked this disease to HTLV-I infection. None of 14 children described by these last authors has received blood transfusions, therefore transmission of infection has presumably occurred vertically. All mothers tested so far have been seropositive and some of them have died of ATLL[36, 38]. The average age of disease onset is two years. In Brazil a case of infective dermatitis was reported in Rio de Janeiro[38] and recently in Salvador, Bahia, we have observed four cases. Two of them were sibling children breast-fed for more than two years, whose mother was also seropositive. In two children the disease began during the first two months of life (data not published). Infective dermatitis has also been described in Nagasaki (Japan), Colombia, Trinidad and Tobago, and Barbados[11, 55, 64]. Less frequently this entity has occurred in adulthood. There are some reports in the literature of cases of infective dermatitis associated or evolving into ATLL[19, 3 64].

Transmission by breast-feeding

This route of vertical infection has been proved by virological, experimental and epidemiological arguments and constitutes the major means of contamination. Cells rather than free virions in the breast milk are responsible for the HTLV-I transmission[23]. Large amounts of HTLV-I infected cells have been identified in breast milk of carrier mothers and marmosets can be infected with fresh breast milk samples from these mothers[33, 63]. In Nagasaki city retrospective studies indicate that vertical transmission was linked to breast-feeding. Serological surveys of children born to carrier mothers found carrier state rates varying from 15.4% to 25% [35, 54]. Conversely VILLE et al. (1991)[67] in Africa studying 45 HTLV-I seropositive pregnant women did not find vertical transmission in spite of the fact th all the children were breast-fed during three months. It is necessary to point out that these infants were investigated serologically and until one year of age, thus some of them can represent seronegative carriers.

Other means of vertical transmission

Three point three percent to 12.8% of children that have been bottle fed are seropositive for HTLV-I thus an alternative pathway of vertical infection may exist[2, 25, 28, 57]. However the prevalence of infection among formula-fed children are less than that observed among breas fed subjects. HIRATA et al. (1992)[25] found that 13% of bottle-fed children born to carrier mothers are infected by HTLV-I, whereas the prevalence of infection among breast-fed children was 18.6%. Another study observed transmission in only 3.3% of bottle-fed babies whereas HTLV-I infection was detected in 77% of breast-fed babies[2]. The mechanism of vertical transmission in the bottle-fed infants remains to be established, however the most

probable routes of infection are transplacental or contamination in the birth canal.

In order to investigate the possibility of transplacental infection several studies using differe methods, addressed the question of whether cord blood lymphocytes of carrier mothers are infected by HTLV-I. SATOW et al. (1991)[53] detected viral antigen in cultured cord-blood lymphocytes of 7.1% of carrier mothers, contrasting with negative results obtained by other authors using the same method[26, 46, 51]. Many studies demonstrated through polymerase chain reaction (PCR) the presence of infected mononuclear cells in cord blood lymphocytes c carrier mothers[26,46,51]. SAITO et al. (1990)[51] detected provirus in cord blood mononuclear cells of three neonates among 40 children born to HTLV-I carrier mothers and these three babies remained HTLV-I sequence positive in follow-up studies. However when these babies were examined by a conventional technique for detection of HTLV-I-associated-antigen on peripheral mononuclear cells, all 40 neonates were HTLV-I-associated-antigen negative. The aforementioned data indicate that the frequency of the diagnosis of vertical transmission relies on the sensibility of the method used for diagnosis.

The presence of HTLV-I in cord blood lymphocytes indicates transplacental passage of these infected cells, however it is not always an evidence of fetal infection. The outcome of fetal o infant infection depends on the protective fetal immunity and on the protection given by the transplacentally acquired maternal antibodies. KATAMINE et al. (1994)[32] followed seven children whose cord blood was positive for HTLV-I proviral DNA up to 24-48 months after birth and none showed serological evidence of HTLV-I infection. The authors concluded that detection of HTLV-I in cord blood is not a hallmark for intrauterine infection. However in the study of KATAMINE et al. (1994) it is not possible to discard the possibility of a late seroconversion.

Infection of the fetal part of the placenta constitutes another strong evidence of the transplacental via of infection. There is in the literature only one report about HTLV-I infecti of the placenta. Fujino et al. (1992)[14] studying trophoblastic cells cultured from nine placentas of HTLV-I positive mothers, by immunocytochemistry and PCR, detected the virus 22% of them.

No fetal autopsy of carrier mothers was ever reported. TOHYAMA et al. (1992)[62] described a case of congenital hydrocephalus clinically diagnosed at 36 weeks of gestation by ultrasonography, that they considered to represent a case of congenital HTLV-I infection. Th assumption was based in the fact that screening of serum and cerebrospinal fluid for microrganisms that may cause hydrocephalus (toxoplasma, rubella virus, cytomegalovirus, and herpes simplex virus) was negative. However hydrocephalus may also have a non-inflammatory origin.

Mechanisms of transplacental transmission of HTLV-I

Considering that some bottle-fed children from HTLV-I carriers are infected other means of vertical transmission besides breast-feeding may exist. As previously mentioned, infected lymphocytes have been observed in the umbilical cord blood and HTLV-I has been detected syncytiotrofoblastic cells of the human placenta. These findings indicate that the transplacental route can be the alternative via of vertical transmission.

In the placenta the fetal blood circulates through an immense capillary network present in th villi. The villi are lined by the syncytiotrophoblast (ST) that forms a continuous epithelium i direct contact with the maternal blood present in the intervillous space. Thus this epithelium separates the fetal structures of the placenta from the maternal blood flowing through these spaces. The cytotrophoblast layer is immediatly beneath the syncytiotrophoblast and consist of stem cells from which the ST is derived. The cytotrophoblastic cells are prominent and form a complete layer in early pregnancy but become flattened after the fourth month of gestation. In the mature terminal villus of the term placenta the circulation interface consists of just ST, a fused basal lamina and an endotelial layer (the vasculo-syncytial membranes).

In order to gain access to the fetal circulation, infectious virus or infected maternal cells mu move from the maternal blood present in the intervillous space and traverse the trophoblast and its basal lamina as well the basement membrane and endothelial cells composing the fetal villous capillaries. An intervening phase of infection of the stromal macrophages (Hofbauer cells) may occur before virus moves across fetal capillary cells[8]. However the init pathogenic event involved in transplacental transmission of a virus depends on whether it exists in a cell-free state or it is carried in maternal peripheral blood cells[8]. In spite of the fact that previous studies have suggested that for infection by HTLV-I to occur a direct cell-t cell contact is required[10], several other investigators have observed infection of target cells by cell-free HTLV-I[60].

Infection of the fetus must involve several steps that includes 1) attachment to and passage through the ST by cell-free or cell-associated viruses, 2) passage through the villous stroma or directly through the fused basement membranes of the trophoblast and endothelium and migration through the villous endothelial cell layer into the fetal circulation[1]. Concerning the step attachment, little is known about the expression of receptors for microrganisms by the ST cells and nothing is known regarding to HTLV-I[1, 8]. If maternal viremia is cell-associated infectious virus may enter the trophoblast by cell-to-cell spread, or intact infected maternal blood cells may cross the trophoblast. However virus that enters the ST layer may or may nc replicate at this site before spreading into stromal cells of the villus or into the endothelial cells of the fetal capillaries. Dissemination of infectious virus may occur by direct release from endothelial cells into the fetal circulation. Intact maternal lymphocytes have been detected in the fetal circulation, but migration of these cells across the trophoblast, and through the fetal capillary endothelium into the fetal circulation, seems to be a rare event. Fetal infection by this mechanism could depend on the number of virus-infected cells in the maternal blood[8].

Besides CD4 T lymphocytes, other cells can be infected by HTLV-I, such as macrophages, endothelial cells, fibroblasts and ST cells [60]. ST cells exhibit restricted permissiveness for HTLV-I. Human ST cells may become persistently but essentialy non-productively infected with this virus[61]. However dual infection of ST cells with HTLV-I and human cytomegaloviru (HCMV) can induce simultaneous replication of both viruses. Furthermore permissive replication cycle of HTLV-I is induced by coinfection with Epstein-Barr virus (EBV)[61]. The coinfection with these last viruses induces secretion of tumor necrosis factor-ß (TNF-ß) and transforming growth factor-ß1 (TGF-ß1), but infection with either virus alone did not lead tc secretion of these cytokines. Besides, infection of ST cells with EBV, but not HTLV-I induces interleukin-2 (IL-2) and IL-6 secretion. Augmented secretion of these last cytokines occurs i coinfected cells with both viruses. Based in these experimental observations, TÓTH et al. (1997) [61] suggest that activation of HTLV-I gene expression by EBV in coinfected ST may represent a mechanism for transplacental transmission of HTLV-I.

Risk factors for vertical transmission

The rate of vertical transmission is directly related to the time of breast-feeding[12, 25, 48]. It significantly higher (27%) among breast-fed children for over three months than that of tho breast-fed for under three months (5%)[12]. Besides duration of breast-feeding, mother-to-child transmission of HTLV-I is also associated with older age of the mother, maternal antigenemia, and higher HTLV-I antibody titers, in particular to a certain immunogenic porti of the gp46 envelope glycoprotein[21, 53, 67]. Forty per cent of children born from antigen-positive mothers were carriers, contrasting to only 8% of carrier children born from antigen-negative mothers[54].

Diagnosis of vertical transmission

The most reliable diagnosis method for HTLV-I infection is serology. Notwithstanding this method is not ideal for detection of vertically transmitted infection early in life. First becaus

of the persistence of maternal antibodies in the infants during the first months of life and second due to a late seroconversion in HTLV-I infected babies.

Maternal antibodies titers decrease continuously after birth but at the age of 6 months detectable amount of maternal antibodies still remain in ~ 20% children. Rarely these antibodies still persist at the age of 12 months[23].

There is much controversy about the time of seroconversion of the infected children. According to some authors most children seroconvert by the age of 3 years or later [35, 43] while others believe that seroconversion occurs earlier. HINO et al. (1997) [23], considering that the majority of children seroconvert by the age of 12 months, recommend the age of 18 months as the ideal for diagnosis of vertically acquired HTLV-I infection. ANDO et al. (1993) refer that some HTLV-I carriers may remain antibody negative for long periods after infection[3]. Contrasting with these observations, UEDA et al. (1993)[65] fail to prove the possibility of prolonged viral latency.

Taking into account what was said above it is necessary to employ more sensitive technique such as PCR, in order to identify the silent carriers especially the bottle-fed infants of carrier mothers[28]. In a study of 27 children born to HTLV-I-seropositive and PCR positive mothers, only 7% of infected children were detected by serology contrasting to a rate of 28% using PCR. The seronegativity associated with PCR positivity may be due to a long latency period of HTLV-I[43].

Prevention of vertical transmission

Prevention in endemic areas relies on screening pregnant women for HTLV-I antibodies and advising seropositive women to refrain from breast-feeding. In Nagasaki, a prefecture wide intervention using this strategy blocked ~ 80% of HTLV-I vertical transmission[22, 23].

Another point to take into consideration is that HTLV-I infection may be transmitted verticall from seronegative carrier mothers that seroconvert later[22]. In these cases the women are infected by sexual intercourse or blood transfusion. For this reason HINO et al. (1996)[22] recommend that doctors should refrain as much as possible from using blood transfusion to young females in endemic areas where blood donors screening is not performed.

We have already cited that the prevalence of HTLV-I infection among pregnant women in Salvador is around 0.8%, that HTLV-I+ lymphomas represent 30% of T-lymphomas and that cases of infective dermatitis have been detected in Salvador. All these diseases are related to vertical transmission. These findings emphasize the importance of vertical transmission and demonstrates that it constitutes a public health problem that must be more widely investigated in order to evaluate its significance in Brazil.

We suggest that Brazilian obstetricians should be aware of this problem and include serolog screening for HTLV-I infection in the prenatal care for selected groups: pregnant women fro areas of higher prevalence rates, Japanese immigrants or Japanese descendents, intravenous drug users (IDU) or women whose partners are IDU, human immunodeficiency virus carriers women with sexual promiscuous behavior and women who have received blood transfusions in areas where blood donors screening is not performed. Considering that the HTLV-I carrier mothers generally detected belong to a low socio-economic class, it is necessary to provide an alternative nutritional supply and pediatric assistance for the babies, when asking the mothers to refrain from breast-feeding. Another strategy could be to recommend short-term breast-feeding, although this measure is not as effective as refraining from breast-feeding.

HTLV-II

HTLV-II was the second human retrovirus discovered. It was isolated in 1982 from an adult

with hairy-cell leukemia and it is closely related to HTLV-I, both viruses sharing 66% of thei genomic sequences. They present extensive serologic cross-reactivity and for their differentiation it is necessary to perform a Western blot test which enables discrimination between the two viral types or PCR[66]. HTLV-II is transmitted by sharing contamined needles sexual contact, and blood transfusion. No disorders have as yet been consistently associatec with HTLV-II infection in spite of the fact that there have been isolated reports describing association of this virus with certain lymphoproliferative disorders and HAM/TSP[18].

The infection is endemic among native American populations of North and South America. A serologic survey among Brazilian Amerindians revealed prevalence rates varying from 24% t 38%[41]. The virus also infects as many as 20% of injecting drug users in the United States[66] Furthermore, over half of HTLV-I/II seropositive blood-donors in the United States are infected by HTLV-II[66]. As above referred the prevalence rate of HTLV-II infection among intravenous drug users in Brazil is lower than that of HTLV-I. In São Paulo and Bahia the prevalence rates of HTLV-II infection correspond to 11.1% and 8.8%, respectively[4, 6].

In spite of the fact that HTLV-II provirus has been found in the breast-milk of infected mothers[20], no case of infection of bottle-fed or breast-fed children born to these mothers ha been detected until 1995[16, 31]. Recently three HTLV-II-seropositive children were reported, diagnosed at 2 , 3 and 8 years of age, all of them born of carrier mothers[38, 66]. These children did not receive blood transfusions and one of them was bottle-fed. The authors concluded that HTLV-II may be transmitted through breast-feeding. In the bottle-fed child th infection may have occurred congenitally or through contamination in the birth canal.

RESUMO

Transmissão vertical do HTLV-I /II - Revisão

A transmissão vertical do *virus linfotrópico para células T humanas tipo* I (HTLV-I) ocorre principalmente através a amamentação. Como um pequeno percentual de filhos de portadora alimentados artificialmente é soropositivo, devem existir outras vias de transmissão vertical.

A taxa de prevalência de transmissão vertical no Japão varia de 15% a 25%. No Brasil, aind não existe nenhuma avaliação desta forma de transmissão, no entanto, sabe-se que em Salvador-Bahia 0, 7% a 0, 9% das gestantes de classe socio-econômica baixa são portadora deste virus. Além disto, em Salvador, já foram detectados vários casos de linfoma/leucemia de células T do adulto e quatro casos de dermatite infectiva, condições que são diretamente ligadas à transmissão vertical do HTLV-I, demonstrando assim a importância desta via de transmissão entre nós.

Através de seleção sorológica de gestantes no prenatal e evitando a amamentação nas soropositivas, conseguiu-se no Japão redução de ~ 80% da transmissão vertical deste virus É necessário que no Brasil os órgãos de Saúde Pública comecem a fazer estudos no sentido de se certificar da magnitude deste problema. Sugerimos que em nosso país seja feita avaliação sorológica pré-natal em grupos selecionados, tais como: gestantes provenientes d áreas endêmicas, imigrantes japonesas ou descendentes de japoneses, usuárias de drogas injetáveis (UDI) ou gestantes cujos parceiros sejam UDI, portadoras do virus da imunodeficiência adquirida, gestantes com comportamento sexual promíscuo e aquelas que tenham recebido transfusão sanguínea.

Já se documentou a transmissão vertical do HTLV-II.

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