Review of screening for Human T-cell lymphotropic virus in (HTLV-1) pregnancy

1. Process

A literature search was carried out by Paula Coles, information scientist, to find citations for HTLV-1 and-11 published since the last policy review in 2003.
The search was carried out on publications from January 2003 until the end of March 2011.

Sources searched were Medline (OvidSP), Embase, PsychINFO, Cinahi, Web of Science and the Cochrane Library. Websites of UK organisations such as the HPA were also searched for information. A total of 4075 references were retrieved and 2281 potentially relevant references remained after removal of duplicate references. The titles and abstracts of these 2281 publications were scanned for relevance to screening for HTLV-1 and HTLV-11 in pregnancy, focussing on the following:

- **The condition**- prevalence in pregnancy and in the general population, mother-to-child transmission and long term natural history
- **The test**
- **The treatment**- prevention of mother-to-child transmission
- **The screening programme**

473 references were deemed to be relevant and included.

A simple search (HTLV) was carried out for ongoing trials in the metaRegister of Controlled Trials: http:/www.controlled-trials.com/mrct/ of the 99 results retrieved, none met the criteria for inclusion.

2. Summary of and rationale for previous reviews conclusions

The last policy review (screening brief) was done in 2003 and it was concluded that screening for HTLV-1 in pregnancy should not be introduced as:

- Prevalence of HTLV-1 in UK is very low with most cases identified in black Caribbean women and those from West and Central Africa
- Risk of mother-to-child transmission is low when breast feeding is not prolonged (more than 6 months)
- Little reduction by formula feeding
- No treatment is available
- Most infected women remain asymptomatic and the lifetime risk of HTLV-1 disease is low; 1-5% for leukaemia and 0.25-3% for myelopathy and tropical paraparesis
- The negative impact of a maternal diagnosis of HTLV on the women and her families' quality of life must not be underestimated.

3. Summary of literature published since previous review

1. The condition

Human T-cell lymphotropic virus-1 (HTLV-1) was the first human retrovirus to be discovered, in 1980 (1). Shortly afterwards, in 1982, HTLV-2 was identified (2). HTLV-1 infection is life-long and most infected individuals remain asymptomatic. However, after a long latent period a small but significant proportion of individuals infected with HTLV-1 develop serious neurological and lymphoproliferative disease (3). The association of HTLV-11 with a specific human disease has not been so well characterised although mother-to-child transmission of HTLV-2 appears to occur in a similar pattern to HTLV-1 (4).

Information on the epidemiology of HTLV- infection in the general population, as well as its natural history and clinical outcomes, remains limited. Its distribution is extremely variable with most cases of HTLV-1 reported from Southern Japan, the Caribbean basin, South America, pockets in West and Central Africa with isolated foci in other areas(5). In contrast, the prevalence of HTLV-11 is highest in Native American populations, some African populations and among injecting drug users[5].

Both HTLV-1 and 11 can be acquired from contaminated blood products through blood transfusion or injecting drug use, through sexual transmission, particularly from male to female, or as a result of mother-to-child transmission through prolonged breast feeding (6). Intravenous transmission, mainly through blood transfusion is the most efficient mode for transmission and is associated with a higher risk of neurological sequelae (3).

1.1. Is HTLV an Important Public Health Problem?

Population prevalence

Information on the prevalence of HTLV-1 and 11 is based on the study of various defined populations such as blood donors, hospital populations, injecting drug users and pregnant women, each with considerable potential for bias. A systematic review based on published reports on the incidence and prevalence of HTLV-1 infection in the general population estimated the prevalence of HTLV-1 in Japan, Latin America and the Caribbean Islands but data from Africa, Asia, Europe and North America was very limited (7). Where infection was detected the highest prevalence was reported in Japan 36.40% and the lowest in Latin America 0.24-1.00%. Few data were available from general populations to inform the epidemiology of HTLV infections globally so that estimates of the public health impact and changing epidemiology are limited. Regional differences and standardisation of laboratory assays together with poorly specific assays in the earlier studies may have accounted for the significant differences noted in this review. In Europe HTLV-1 infection is uncommon in the general population but is reported in specific populations such as intravenous drug users, sex workers and immigrants from endemic areas. Prevalence declines in subsequent generations migrating from endemic areas

Prevalence in pregnancy

Most data on prevalence of HTLV-1 and-2 in Europe are based on low risk blood donors or high risk injecting drug users and there is a paucity of information on its prevalence in pregnant women. In a study of 234,078 pregnant women in Belgium, France, Germany, Italy, Portugal, Spain and the UK anti HTLV-1/11 antibodies were detected and confirmed in 96 pregnant women, 4.4 per 10,000. 73 had antibodies to HTLV-1, 17 to HTLV-11 and 6 could not be typed. The rates ranged from 0.7/10,000 in Germany to 11.5/10.000 in France (8). In a large seroprevalence study carried out in London in 1999 to determine the prevalence of HTLV infection in pregnant women the overall prevalence was 0.31 per 1,000 (see table below) (9). This was based on the unlinked anonymous testing of 126,000 newborn blood samples 67of whom had confirmed HTLV antibodies, type 1. The presence of antibodies in the newborn indicates maternal infection as maternal antibodies cross the placenta and are present in the infant's circulation. These results are comparable to results from smaller studies. The presence of HTLV was highest among women born in the Caribbean, 17 per 1,000 and lowest in the white mothers

HTLV seroprevalence in mothers delivering live births in London

- Overall prevalence 0.31 per 1000
- Prevalence in mothers born in the Caribbean -17 per 1000
- Prevalence in mothers born in West and Central Africa -3.2 per 1000
- Prevalence in black Caribbean mothers born in UK - 6.8 per 1000
- Prevalence in remaining mothers -0.06 – 0.12 per 1000

1.3 Mother-to-child transmission

Although maternal-to-fetal transmission is debated, transmission of infection to the infant through breast feeding has been confirmed (10). Based on a Japanese study estimated rates of transmission are reported to be around 2.7% in formula fed infants, 5% in infants breast fed for 3 months and about 20% in those in whom breast feeding is prolonged. . However a more recent review of Japanese data on mother-to-child transmission through breast feeding concluded that children with long term breast feeding were more likely to acquire infection than short –term breast fed infants although some studies showed no difference between artificial feeds and short term breastfeeding (11). After acquisition of infection from breast feeding there appears not to be any further transmission until puberty (12) .

1.4. Is the natural history of the condition understood?

Although transmission from mother- to- infant has been documented, as evidenced by seroconversion, no serious illness in the neonate secondary to breast feeding has been reported and in most infants infection is not associated with adverse events. Most carriers remain asymptomatic throughout life but a small proportion, around 5-10% of infected individuals, present with severe disease after a long latent period (6). This includes adult T-cell leukaemia/lymphoma (ATL), a rapidly progressing lymphoproliferative malignancy of mature T cells, as well as HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a slowly

progressive disease of the nervous system. HTLV-1 is also associated with uveitis and other inflammatory disorders (5,13,14).

The natural history of HTLV-1 infection is difficult to clarify since only a small proportion of infected individuals develop serious disease and this presents after a long latent period. There are reported differences in risk levels of HAM/TSP in different populations. Most cohorts of infected individuals being followed up are adults detected through blood donor screening and there is a paucity of information on the outcome for asymptomatic infants. Most information on long term sequelae is based on patients presenting with symptoms. There are no clear surrogate biological markers for disease progression although reported risk factors include high maternal proviral load and antibody titre, increased maternal age, maternal HTLV-1 disease and a history of blood transfusion (1),(15)..

To determine the natural history cohorts of infected individuals detected through blood donor screening are being followed up long term in the UK and elsewhere. As disease typically manifests later in life, and due to the long latent period, there is a paucity of information on the true risk of long term sequelae in children with vertically acquired infection. An estimated 1.5% of infants with infection will develop ATL, with an average latency of 30 years [21], while the life time risk of developing HAM/TSP is lower and in the order of 0.25-3% (16;17).

2. Treatment of HTLV infection

There is no treatment.

3. Prevention

In the UK and in other developed countries blood donors are screened for HTLV-1 and-11 to avoid the risk of transmission through contaminated blood. Prevention of sexual transmission through safe sex and the approaches taken to avoid transmission through injecting drug use are similar to those advocated for the prevention of HIV.

No vaccine is available.

4. Screening test

Screening for HTLV-1/11 is well established as blood donors are routinely screened to avoid contamination of the blood supplies. The diagnosis is made by detecting the presence of HTLV-1/11 antibodies by Elisa and Western blot analysis. Two sequential EIA tests with inconclusive results are confirmed by Western blot

Given the small risk of progression to disease the outlook is good for most infected individuals. However, in a follow up of women identified to be infected through blood screening the majority reported specific concerns about future progression to HTLV-related disease and fear of transmitting the infection to others (18;19)). There was also a higher rate of depression in HTLV-1 infected individuals.

In a Japanese study mothers who were identified as HTLV-1 infected in pregnancy, and their families, experienced stigma which was even greater that reported for women identified with HIV (20).

5. Conclusion

There is no new evidence to demonstrate that a screening programme for HTLV-1 or-11 in the UK would be effective in reducing mortality and morbidity. The benefits shown in the early Japanese studies suggest that there has been a decline in the prevalence of HTLV-1 in pregnancy since the introduction of screening but this cannot be directly attributed to decline in breast feeding rates among women screened positive and could be explained, in part, by improved diagnostic screening tests and the ability to distinction more clearly between HTLV-1and-11 infection

Screening for HTLV-1 and -2 in the UK is not recommended;

- Prevalence of infection in the UK is low and restricted to specific subgroups
- Risk of mother-to-child transmission through breastfeeding is low, unless breastfeeding is prolonged beyond 6 months.
- Most infected infants remain asymptomatic and the life time risk of subsequent serious disease appears to be low.
- There is no treatment and the only approach to prevention is the avoidance of breastfeeding, particularly prolonged breast feeding.
- The potential for harm cannot be underestimated. Women with HTLV infection will be identified, there is no treatment, and most will not develop HTLV related disease in later life. This situation may cause significant anxiety and stress to the women and their families

References

(1) Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 1982 March;79(6):2031-5.

(2) Manns A, Blattner WA. The epidemiology of the human T-cell lymphotrophic virus type I and type II: etiologic role in human disease. Transfusion 1991 January;31(1):67-75.

(3) Verdonck K, Gonzalez E, Van DS, Vandamme AM, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis 2007 April;7(4):266-81.

(4) Lowis GW, Sheremata WA, Minagar A. Epidemiologic features of HTLV-II: serologic and molecular evidence. Ann Epidemiol 2002 January;12(1):46-66.

(5) Araujo AQ, Silva MT. The HTLV-1 neurological complex. Lancet Neurol 2006 December;5(12):1068-76.

(6) Barmak K, Harhaj E, Grant C, Alefantis T, Wigdahl B. Human T cell leukemia virus type I-induced disease: pathways to cancer and neurodegeneration. Virology 2003 March 30;308(1):1-12.

(7) Hlela C, Shepperd S, Khumalo NP, Taylor GP. The prevalence of human T-cell lymphotropic virus type 1 in the general population is unknown. AIDS Rev 2009 October;11(4):205-14.

(8) Taylor GP, Bodeus M, Courtois F, Pauli G, Del MA, Machuca A et al. The seroepidemiology of human T-lymphotropic viruses: types I and II in Europe: a prospective study of pregnant women. J Acquir Immune Defic Syndr 2005 January 1;38(1):104-9.

(9) Ades AE, Parker S, Walker J, Edginton M, Taylor GP, Weber JN. Human T cell leukaemia/lymphoma virus infection in pregnant women in the United Kingdom: population study. BMJ 2000 June 3;320(7248):1497-501.

(10) Mylonas I, Bruning A, Kainer F, Friese K. HTLV infection and its implication in gynaecology and obstetrics. Arch Gynecol Obstet 2010 November;282(5):493-501.

(11) Oku K YNNT. HTLV-1 transmission via breastfeeding from mother to chid-Areview of the literature in Japan. Breastfeeding Medicine 2009;4(4):240.

(12) Ando Y, Matsumoto Y, Nakano S, Saito K, Kakimoto K, Tanigawa T et al. Long-term follow up study of vertical HTLV-I infection in children breast-fed by seropositive mothers. J Infect 2003 April;46(3):177-9.

(13) Nicot C. Current views in HTLV-I-associated adult T-cell leukemia/lymphoma. Am J Hematol 2005 March;78(3):232-9.

(14) Goncalves DU, Proietti FA, Ribas JG, Araujo MG, Pinheiro SR, Guedes AC et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev 2010 July;23(3):577-89.

(15) Li HC, Biggar RJ, Miley WJ, Maloney EM, Cranston B, Hanchard B et al. Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I. J Infect Dis 2004 October 1;190(7):1275-8.

(16) Kaplan JE, Osame M, Kubota H, Igata A, Nishitani H, Maeda Y et al. The risk of development of HTLV-I-associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. J Acquir Immune Defic Syndr 1990;3(11):1096-101.

(17) Murphy EL, Fridey J, Smith JW, Engstrom J, Sacher RA, Miller K et al. HTLV-associated myelopathy in a cohort of HTLV-I and HTLV-II-infected

blood donors. The REDS investigators. Neurology 1997 February;48(2):315-20.

(18) Devita D MEKZ. living with HTLV: Insights from a prospective cohort. AIDS Research and Human Retroviruses 25[11], 1209. 2009.

(19) Guiltinan AM, Murphy EL, Horton JA, Nass CC, McEntire RL, Watanabe K. Psychological distress in blood donors notified of HTLV-I/II infection. Retrovirus Epidemiology Donor Study. Transfusion 1998 November;38(11-12):1056-62.

(20) Oni T, Djossou F, Joubert M, Heraud JM. Awareness of mother-to-child transmission of human T-cell lymphotropic virus (HTLV) type I through breastfeeding in a small group of HTLV-positive women in Maripasoula and Papaichton, French Guiana. Trans R Soc Trop Med Hyg 2006 August;100(8):715-8.