Journal of Clinical Virology 45 (2009) 135–138

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Age and gender specific prevalence of HTLV-1

Nobuoki Eshima[a], Osuke Iwata[b,c,*], Sachiko Iwata[b,c], Minoru Tabata[d], Yasunori Higuchi[e], Toyojiro Matsuishi[b,c], Shigeru Karukaya[c]

[a] Department of Biostatistics, Faculty of Medicine, Oita University, Oita 879-5593, Japan
[b] Center for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Kurume 830-0011, Japan
[c] Institute for Child Health, Department of Pediatrics, Kurume University School of Medicine, Kurume 830-0011, Japan
[d] Department of Applied Mathematics, Faculty of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan
[e] Research Center for Applied Medical Engineering, Oita University, Oita 879-5593, Japan

ARTICLE INFO

Article history:
Received 10 December 2008
Received in revised form 18 March 2009
Accepted 18 March 2009

Keywords:
HTLV-1
Adult T-cell Lymphoma
Vertical transmission
Seroprevalence
Gender

ABSTRACT

Background: The seroprevalence of Human T-cell Leukemia Virus Type 1 (HTLV-1) is female predominant despite the higher incidence of Adult T-cell Leukemia (ATL) in males. If the mother-to-child transmission of HTLV-1 is more common for male infants than in female infants, longer exposure to the virus for males may explain the paradoxically higher incidence of ATL.
Objectives: To test the hypothesis that the seroprevalence of HTLV-1 is male predominant during adolescence.
Study design: The presence of HTLV-1 antibody in 272,043 blood samples donated to a regional blood bank in an HTLV-1 high-endemic region was assessed.
Results: The entire population of female donors had a significantly higher seroprevalence compared to males (2.05% and 1.80%, respectively, $p < 0.0001$). However, compared with male donors, the carrier rate for female donors was lower for the youngest subgroup (16–19 years, $p = 0.0011$); was similar for the next two age subgroups (20–29 years and 30–39 years); and was significantly higher for the last two age subgroups (40–49 years and over 50–64 years, both $p < 0.0001$). In general, older age subgroups led to higher seroprevalence in both genders.
Conclusions: HTLV-1 infection is more common for males until after age 20, when male to female sexual transmission becomes likely. This suggests that mother-to-child transmission is more common for males.

1. Background

Human T-cell Leukaemia Virus Type 1 (HTLV-1) is a retrovirus which is highly endemic in Saharan Africa, South America, Caribbean Islands, Aboriginal Australia and Japan.[1] The carrier rate in Japan is ~1%, but seroprevalence of up to 10% has been reported in southern islands, such as Kyushu and Okinawa.[2] HTLV-1 causes Adult T-cell Leukaemia (ATL) and myelopathy/tropical paraparesis resulting in a significantly shorter average lifetime for carriers.[3]

Transmission of HTLV-1 occurs mainly by breastfeeding and sexual interactions.[4,5] Following the successful campaign started in the late 1980s, for exclusive bottle-feeding by HTLV-1 carrier mothers, the transmission rate during infancy has significantly fallen in Kyushu and Okinawa.[2] While the probability of mother-to-child vertical infection is considered to be non-gender-specific, sexual transmission mainly occurs from males to females,[6] which explains why females overall have a higher carrier rate than males.[2] Despite this the incidence and mortality of ATL are higher for Japanese males compared with females.[3,7] As the development of ATL is related to the length of the period after seroconversion,[2] we hypothesised that male carriers are exposed longer to the virus prior to the diagnosis of ATL because of male-dominant mother-to-child transmission of HTLV-1.

2. Objectives

The aim of this study was to test the hypothesis that the seroprevalence of HTLV-1 is paradoxically male dominant during adolescence.

3. Study design

The presence of HTLV-1 antibody in 272,043 blood samples from volunteers (16–64 years old) who donated their blood to a regional blood bank between April 1995 and March 1999 was retrospectively assessed. These bloods were screened for HTLV-1 antibody using three methods: indirect immunofluorescence; enzyme-

* Corresponding author at: Center for Developmental & Cognitive Neuroscience, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Tel.: +81 942 31 7565; fax: +81 942 38 1792.
E-mail address: o.iwata@orbix.uk.net (O. Iwata).

1386-6532/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jcv.2009.03.012

linked immunosorbent assay; and gelatin particle agglutination. The study period was chosen because only immunofluorescence was used before 1995, and more recent samples were not included to avoid the bias of the exclusive bottle-feeding campaign for HTLV-1 carrier mothers that began in the late 1980s.[8]

The seroprevalence of HTLV-1 was analyzed using binary logistic models respectively over five age bands of $G_{16–19}$ ($16 \leq$ age at donation < 20 years old), $G_{20–29}$ ($20 \leq < 30$), $G_{30–39}$ ($30 \leq < 40$), $G_{40–49}$ ($40 \leq < 50$) and $G_{50–64}$ ($50 \leq < 65$) with gender and study epochs (year at donation: 1995, 1996, 1997 and 1998) as independent variables. The age at donation was not included within the model because the seroprevalence in each age band within our study is not likely to reflect the natural age-related change because of potential biases (see Section 5 for detail). Instead the prevalence of HTLV-1 between different age subgroups was compared independently of other factors using the chi-square test. The statistical significance was corrected for the multiple comparisons over five age band categories using the Bonferroni's correction.

4. Results

No temporal change in the HTLV-1 prevalence rate was observed during four study years (data not shown). Overall females showed significantly higher HTLV-1 seroprevalence compared to males (2.05% and 1.80%, respectively, $p < 0.0001$). For $G_{16–19,}$ seroprevalence was higher for male donors (0.90%) compared to female donors (0.56%) ($p = 0.0011$, Table 1). For the next two age bands of $G_{20–29}$ and $G_{30–39}$, the seroprevalence was not significantly different between genders, whereas female dominant seroprevalence was observed for the age bands of $G_{40–49}$ and $G_{50–64}$ (both $p < 0.0001$, Table 1).

For female donors overall, the older age subgroups had significantly higher HTLV-1 seroprevalence compared with younger subgroups in all pair-wise comparisons ($p < 0.0001$) except between $G_{16–19}$ and $G_{20–29}$ (Table 1). This trend was also observed for male donors, where $G_{16–19}$ and $G_{20–29}$ were not significantly different and all other pair-wise comparisons showed significantly higher seroprevalence for older subgroups ($p = 0.0087$ between $G_{20–29}$ and $G_{30–39}$, and $p < 0.0001$ for all other pair-wise comparisons, Table 1).

5. Discussion

HTLV-1 seroprevalence was male dominant among Japanese adolescents in contrast to the female dominance that was observed after the age of 40. This suggests that mother-to-child transmission of HTLV-1 might be more common for males.

5.1. Limitations and biases

Our study was an observational study of the blood donors, who have been utilised for surveillance of viral infections.[9,10] However the donation does not occur "at random" from the natural cohort, but is biased by multiple known and unidentified factors. Some specific demographics (e.g. elderly people and house wives with young children) may affect the donation rate, as shown by the marked drop in female donors after the age of 30 in our study population. Some donors would be seropositive for hepatitis-B virus (HBV), hepatitis-C virus (HCV), human immunodeficiency virus (HIV) or HTLV-1 at medical checks (e.g. pregnancy and surgical operation), and would not be eligible for donation. However during the window of this study, the blood bank did not notify donors about the result of the blood screening tests to discourage "the donation for free blood tests".[11]

The influence of multiple donations within the same study year may also influence seroprevalence because the denominator in our study was the number of blood donations rather than blood donors. However volunteers who made multiple donations within a study year had an equal risk of acquiring HTLV-1 infection during the interval between donations as one-time donors. Such a procedure is statistically regarded as "sampling with replacement", where the influence of multiple donations are limited unless donations are mainly made by a small fraction of donors. Although no published data are available for the pattern of repeated donations, according to the website of Japanese Ministry of Health, Labour and Welfare (information in Japanese available at www.mhlw.go.jp/wp/seisaku/jigyou/), in 2001, the fraction of donors with multiple donations per year was ~25% and the average frequency of donation was ~1.6 per donor: this rate was similar between high-school students, college students and other elder populations.

Apart from sampling biases, certain medical, social and cultural trends, such as sexual practices and breastfeeding strategies (e.g. elective formula-feeding campaign),[8] may affect the HTLV-1 prevalence in specific age bands. Therefore any difference between age subgroups may not directly reflect the temporal change in prevalence within a cohort. Although the youngest donors in our study population were born at least 10 years earlier than the commencement of the campaign, we observed a significant alteration in the prevalence between different age subgroups presumably, due to reduced breastfeeding for younger subgroups.[2] Regional breastfeeding practices may also affect the transmission rate. A study based on over 50,000 Japanese infants reported a higher rate for exclusive breastfeeding at 6 months of age for female infants compared to male infants (21.5% and 20.6% respectively),[12] which may contribute to a subtle increase of the HTLV-1 vertical transmission for females.

Thus, although our study demonstrates the dynamic alteration of gender-specific HTLV-1 prevalence based on a large sample size, potential biases should be considered in interpreting the findings.

5.2. Transmission of HTLV-1 and gender-specific predominance

HTLV-1 is mainly transmitted via breastfeeding, sexual interaction and contact with carrier's blood, the last of which is rare in our population owing to the donor blood screening, relatively uncommon illegal drug injection in Japan,[6,13] and strict exclusion policy of blood donors with such a history. As reported in most previous studies,[2,6] we observed a female dominant prevalence of HTLV-1 over the entire population, which has been explained by the more efficient sexual transmission in the direction of male to female compared with the other way.[14] In contrast, the carrier rate was male dominant in the youngest subgroup. Given that the integrated individual risk of HTLV-1 acquisition is age-dependent,[15] HTLV-1 prevalence for $G_{16–19}$ would be best explained by a higher risk of vertical transmission for males compared with females. Our preliminary analyses for adolescent blood donors in the same region, but

Table 1
Dependence of HTLV-1 seroprevalence on gender and age.

Age	Male	Female	*p*-values (male vs. female)
16–19	14149 (0.90%)	19620 (0.56%)	0.0011
20–29	41967 (0.70%)	38604 (0.72%)	ns
30–39	40364 (1.22%)*	18025 (1.47%)**	ns
40–49	42504 (2.16%)*	15699 (3.39%)*	<0.0001
50–64	27828 (2.82%)*	13238 (4.47%)*	<0.0001

Values were shown as total number (carrier rate in percent).
p-values were corrected for multiple comparisons.
* $p < 0.0001$ in comparison with other age subgroups in the same gender.
** $p = 0.0087$ in comparison with 20–29 years (female) and $p < 0.0001$ with other female subgroups.

with different sampling years of 1989, 1999 and 2007, support the current finding with similar male to female carrier ratios of ~1.6[16] (data unpublished for 2007).

Previous studies in children and adolescents suggested non-gender-specific seroprevalence of HTLV-1[15,17] presumably because of the inclusion of sexually active subjects (10–19 years old)[15] or the lack of the study power (based on six seropositive subjects within 179 volunteers).[17] Few studies specifically addressed the influence of the gender to the risk of HTLV-1 vertical transmission. A study conducted in French Guyana reported a higher mother-to-child transmission rate for female infants compared with male infants.[18] However, this was based on only 21 vertically transmitted cases (6 boys and 15 girls), resulting in a limited statistical significance close to the threshold. Further studies are required to assess the actual mother-to-child transmission rate enrolling a large number of young children.

5.3. Potential mechanism of paradoxical male predominance of HTLV-1 infection during adolescence

Although the detailed mechanism of the age- and gender-dependent HTLV-1 prevalence is unknown, gender-specific differences in viral transmission and seroconversion has been widely recognised.[2,6,19–21] Mother-to-child transmission of HBV and HCV mainly occurs at delivery but rarely via breastfeeding,[22] whereas for HIV, intra-uterine infection and transmission via breast milk are both important. Conflicting reports exist on mother-to-child transmission of HBV and HCV. However, a study conducted on ~1800 infants born to HCV-infected mothers demonstrated twice as much vertical transmission to females as males.[23] For HIV, intra-uterine infection is reported to be female dominant,[24–28] whereas post-natal infection is more common for males.[29,30] One might speculate that the gender-specific risk of transmission varies according to the transmission route. Preliminary evidence in male subjects compared with female subjects suggests a higher prevalence of orally/enterally acquired infections, such as enterovirus 71,[31,32] enteric adenovirus,[33,34] and rotavirus,[34] resulting in a higher incidence of diarrhoea[35] and hand, foot and mouth disease.[31,32] Several studies did not find these gender-specific differences.[36,37] Of special note, a study in Australia based on over 1800 blood samples demonstrated male dominant seropositivity of poliovirus in younger age groups; an opposite trend was seen in the adult age groups.[38] This result is interesting especially as the injection of inactivated polio vaccine in 2000 children resulted in non-gender-specific seroconversion.[39] As our current study was not designed or powered to explain the gender-specific prevalence of HTLV-1 and other viruses, further studies are required to link the findings in different viruses and conditions.

5.4. Clinical implications and conclusions

Our findings add robust evidence to support the gender- and age-specific susceptibility to the viral infection, and may in part explain the high paradoxical incidence of ATL in Japanese males despite overall lower carrier rate of HTLV-1 compared to females. Further investigation is essential to test whether the same phenomenon is observed in regions and populations where the risk of ATL is either gender-non-specific or female dominant.[40,41] For optimal control of this viral infection, understanding the transmission route and the local defence mechanisms is essential. Future investigation may address multiple factors such as the gender, age, types of virus and other environmental factors to establish a "tailored" prevention protocol for HTLV-1.

Conflict of interest

Authors have no competing interests to declare. This study was conducted with the approval of the local ethical committee.

Acknowledgment

This work was funded by the Open Research Center Grant, Japanese Ministry of Education, Culture, Sports, Science & Technology.

References

1. 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;**7**(4):266–81.
2. Tajima K. The 4th nation-wide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. *Int J Cancer* 1990;**45**(2):237–43.
3. Arisawa K, Sobue T, Yoshimi I, et al. Human T-lymphotropic virus type-I infection, survival and cancer risk in southwestern Japan: a prospective cohort study. *Cancer Causes Control* 2003;**14**(9):889–96.
4. Mueller N, Okayama A, Stuver S, Tachibana N. Findings from the Miyazaki Cohort Study. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;**13**(Suppl 1):S2–7.
5. Wiktor SZ, Pate EJ, Murphy EL, et al. Mother-to-child transmission of human T-cell lymphotropic virus type I (HTLV-I) in Jamaica: association with antibodies to envelope glycoprotein (gp46) epitopes. *J Acquir Immune Defic Syndr* 1993;**6**(10):1162–7.
6. Seydel J, Kramer A. Transmission and population dynamics of HTLV-I infection. *Int J Cancer* 1996;**66**(2):197–200.
7. Hisada M, Okayama A, Spiegelman D, Mueller NE, Stuver SO. Sex-specific mortality from adult T-cell leukemia among carriers of human T-lymphotropic virus type I. *Int J Cancer* 2001;**91**(4):497–9.
8. Hino S, Katamine S, Miyata H, Tsuji Y, Yamabe T, Miyamoto T. Primary prevention of HTLV-1 in Japan. *Leukemia* 1997;**11**(Suppl 3):57–9.
9. Mangano AM, Remesar M, del PA, Sen L. Human T lymphotropic virus types I and II proviral sequences in Argentinian blood donors with indeterminate Western blot patterns. *J Med Virol* 2004;**74**(2):323–7.
10. Wang B, Schreiber GB, Glynn SA, et al. Does prevalence of transfusion-transmissible viral infection reflect corresponding incidence in United States blood donors? *Transfusion* 2005;**45**(7):1089–96.
11. Tadokoro K. The new Japanese blood law: its impact on blood safety and usage. *Dev Biol (Basel)* 2007;**127**:161–8.
12. Kaneko A, Kaneita Y, Yokoyama E, et al. Factors associated with exclusive breast-feeding in Japan: for activities to support child-rearing with breast-feeding. *J Epidemiol* 2006;**16**(2):57–63.
13. Degenhardt L, Chiu WT, Sampson N, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. *PLoS Med* 2008;**5**(7):e141.
14. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-I infection and associated diseases. *Oncogene* 2005;**24**(39):6058–68.
15. Murphy EL, Figueroa JP, Gibbs WN, et al. Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica. I. Demographic determinants. *Am J Epidemiol* 1991;**133**(11):1114–24.
16. Eshima N, Tabata M, Okada T, Karukaya S. Population dynamics of HTLV-I infection: a discrete-time mathematical epidemic model approach. *Math Med Biol* 2003;**20**(1):29–45.
17. Morofuji-Hirata M, Kajiyama W, Nakashima K, Noguchi A, Hayashi J, Kashiwagi S. Prevalence of antibody to human T-cell lymphotropic virus type I in Okinawa, Japan, after an interval of 9 years. *Am J Epidemiol* 1993;**137**(1):43–8.
18. Ureta-Vidal A, ngelin-Duclos C, Tortevoye P, et al. Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: implication of high antiviral antibody titer and high proviral load in carrier mothers. *Int J Cancer* 1999;**82**(6):832–6.
19. Hsieh YC, Frink M, Choudhry MA, Bland KI, Chaudry IH. Metabolic modulators following trauma sepsis: sex hormones. *Crit Care Med* 2007;**35**(9 Suppl):S621–9.
20. Lagerquist MK, Erlandsson MC, Islander U, Svensson L, Holmdahl R, Carlsten H. 17Beta-estradiol expands IgA-producing B cells in mice deficient for the mu chain. *Scand J Immunol* 2008;**67**(1):12–7.
21. Lu FX, Ma Z, Moser S, Evans TG, Miller CJ. Effects of ovarian steroids on immunoglobulin-secreting cell function in healthy women. *Clin Diagn Lab Immunol* 2003;**10**(5):944–9.
22. Hahne S, Ramsay M, Balogun K, Edmunds WJ, Mortimer P. Incidence and routes of transmission of hepatitis B virus in England and Wales, 1995–2000: implications for immunisation policy. *J Clin Virol* 2004;**29**(4):211–20.
23. European Paediatric Hepatitis C Virus Network. A significant sex – but not elective cesarean section – effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis* 2005;**192**(11):1872–9.
24. Taha TE, Nour S, Kumwenda NI, et al. Gender differences in perinatal HIV acquisition among African infants. *Pediatrics* 2005;**115**(2):e167–72.

25. Thorne C, Newell ML. Are girls more at risk of intrauterine-acquired HIV infection than boys? *AIDS* 2004;**18**(2):344–7.
26. Barbaro G, Di LG, Grisorio B, Barbarini G. Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS Investigators. *AIDS Res Hum Retrov* 1998;**14**(12):1071–7.
27. Starc TJ, Lipshultz SE, Easley KA, et al. Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: the prospective P2C2 HIV study. *J Pediatr* 2002;**141**(3):327–34.
28. Currie PF, Jacob AJ, Foreman AR, Elton RA, Brettle RP, Boon NA. Heart muscle disease related to HIV infection: prognostic implications. *BMJ* 1994;**309**(6969):1605–7.
29. Coutsoudis A, Dabis F, Fawzi W, et al. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 2004;**189**(12):2154–66.
30. Neumann T, Woiwoid T, Neumann A, et al. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients. Part I. Differences due to the acquisition of HIV-infection. *Eur J Med Res* 2003;**8**(6):229–35.
31. Shah VA, Chong CY, Chan KP, Ng W, Ling AE. Clinical characteristics of an outbreak of hand, foot and mouth disease in Singapore. *Ann Acad Med Singapore* 2003;**32**(3):381–7.
32. Chen KT, Lee TC, Chang HL, Yu MC, Tang LH. Human enterovirus 71 disease: clinical features, epidemiology, virology, and management. *Open Epidemiol J* 2008;**1**(1):10–6.
33. Aminu M, Ahmad AA, Umoh JU, de Beer MC, Esona MD, Steele AD. Adenovirus infection in children with diarrhea disease in Northwestern Nigeria. *Ann Afr Med* 2007;**6**(4):168–73.
34. Jarecki-Khan K, Tzipori SR, Unicomb LE. Enteric adenovirus infection among infants with diarrhea in rural Bangladesh. *J Clin Microbiol* 1993;**31**(3):484–9.
35. Staat MA, Morrow AL, Reves RR, Bartlett AV, Pickering LK. Diarrhea in children newly enrolled in day-care centers in Houston. *Pediatr Infect Dis J* 1991;**10**(4):282–6.
36. Mota-Hernandez F, Calva JJ, Gutierrez-Camacho C, et al. Rotavirus diarrhea severity is related to the VP4 type in Mexican children. *J Clin Microbiol* 2003;**41**(7):3158–62.
37. Waters V, Ford-Jones EL, Petric M, Fearon M, Corey P, Moineddein R. Etiology of community-acquired pediatric viral diarrhea: a prospective longitudinal study in hospitals, emergency departments, pediatric practices and child care centers during the winter rotavirus outbreak, 1997 to 1998. The Pediatric Rotavirus Epidemiology Study for Immunization Study Group. *Pediatr Infect Dis J* 2000;**19**(9):843–8.
38. Gidding HF, Backhouse JL, Gilbert GL, Burgess MA. National serosurvey of poliovirus immunity in Australia, 1996–99. *Aust N Z J Public Health* 2005;**29**(1):48–52.
39. Diedrich S, Schreier E. The German Health Interview and Examination Survey for Children and Adolescents (KiGGS): state of immunity against poliomyelitis in German children. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007;**50**(5–6):771–4.
40. Murphy EL, Hanchard B, Figueroa JP, et al. Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. *Int J Cancer* 1989;**43**(2):250–3.
41. Tosswill JH, Taylor GP, Tedder RS, Mortimer PP. HTLV-I/II associated disease in England and Wales, 1993–7: retrospective review of serology requests. *BMJ* 2000;**320**(7235):611–2.