Human T-Cell Lymphotropic Virus Type 1 (HTLV-1) and HTLV-1–Associated Myelopathy/Tropical Spastic Paraparesis

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(See the Major Article by Tanajura et al on pages 49–56.)

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The human T-cell lymphotropic virus type 1 (HTLV-1) is an oncogenic retrovirus that is transmitted from mother to child, particularly through prolonged breastfeeding; between sexual partners through unprotected intercourse; and from donors to recipients through transfusion and transplantation. Thirty-five years after its discovery, screening for HTLV-1 infection is at best patchy and mostly nonexistent. There are 2 main reasons for this: first, the most recent estimate of the prevalence of HTLV-1 is 5–10 million persons worldwide, with the important caveat that 86% of the global population is data poor in this regard [1]; second, there is a perception that disease related to this virus, which has coexisted with humankind for 60 000 years, is uncommon. Whether this reputation is justified requires up-to-date and reliable sero- and clinical epidemiology.

The lifetime risk, among carriers, of adult-T-cell leukemia/lymphoma is 2%–6% regardless of the region of study. However, for HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), more varied risks are reported with strong hints that, apart from the route of infection, ethnicity and human leukocyte antigen (HLA) types impact significantly on risk. Furthermore, HTLV-1 has been associated with a range of other inflammatory manifestations affecting many organs but particularly eyes, lungs, and thyroid and with increased susceptibility to a number of infections, most notably *Strongyloides stercoralis* hyperinfestation syndrome. (Given the high mortality of this latter condition, it is our policy to screen all HTLV-1 carriers who have resided in endemic areas for *S. stercoralis).* These diseases are much less well recognized even than HAM/TSP, with no data on incidence or prevalence among carriers. How, then, are we to judge the global disease burden of HTLV-1 infection?

In this edition of *Clinical Infectious Diseases*, Tanajura et al report on a longitudinal study of 414 HTLV-1–infected individuals in Brazil [2]. There are a number of striking findings. First, among study participants not previously diagnosed with HAM/TSP, 18.4% had, at baseline assessment, symptoms, signs, and investigations consistent with a definite diagnosis of HAM/TSP. Second, an additional 21%, again at baseline, had possible or probable HAM/TSP on the basis of having either 1 motor sign consistent with HAM/TSP or a neurogenic bladder (probable) or a clinical diagnosis of HAM/TSP without exclusion of other possible diagnoses (possible). Third, during up to 8 years of follow-up, 5 subjects (all from the probable HAM/TSP category) were diagnosed with definite HAM, an incidence of 1.5%. Finally, very high incidences of a range of neurological symptoms were documented, particularly sensory, including upper limb, even though the median per-person follow-up was only 2 years.

These findings are notable because they differ by an order of magnitude from most previous reports. Using data from the mid-1980s, Kaplan et al estimated a 0.25% lifetime risk of HAM in HTLV-1–infected Japanese individuals, based on an average of 24.3 new cases reported per year among approximately 794 800 seropositive individuals (3/100 000 cases per annum) [3]. These data have undoubtedly affected some public health decisions outside Japan.

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However, in the Caribbean, Murphy et al diagnosed myelopathy in 0.5% of HTLV-1 carriers in a case-control study [4], whereas Maloney et al estimated the lifetime risk of HAM/TSP at 1.9% with an age-standardized annual incidence of 17.3 per 100 000 infected males and 24.7 per 100 000 infected females [5]. In the United States, Murphy et al diagnosed myelopathy in 2.4% (4/166) newly diagnosed HTLV-1–infected blood donors [6]; importantly, this study included matched uninfected controls. Although there is an extensive literature on the influence of HLA types on risk of disease associated with HTLV-1 infection, especially through impact on proviral load, and further evidence of ethnic differences based on rates of HAM/TSP according to tribe in a small study from Zaire [7], the cross-sectional prevalence reported from Brazil suggests a lifetime risk in this population 10-fold higher than previously reported. Is this due to genetics or environment or selection bias?

The risk of HAM/TSP has been strongly associated with proviral load and, in particular, with a cutoff of 1 HTLV-1 DNA copy per 100 peripheral blood mononuclear cells (a proviral load of 1%) [8]. The Miyazaki Cohort Study followed almost 2000 persons, among whom 27% were HTLV-1 infected, in a decade-long study and reported paraesthesia, polyuria, and nocturia to be twice as common among those infected with HTLV-1. However, finding no association with HTLV-1 proviral load or strength of antibody response, they concluded that HTLV-1 per se was not causatively associated [9]. Similarly, Tanajura et al found no association with the frequency of sensory, bladder, or even motor symptoms and HTLV-1 proviral load even though up to 30% of the study participants developed such symptoms during follow-up. They did find, however, that carriers with HTLV-1 proviral loads of >5% were more likely to have demonstrated deterioration in expanded disability status score. Also at baseline, subjects diagnosed with HAM/TSP had higher median HTLV-1 proviral load (14.8%) than those who were initially asymptomatic (2.5%), with the probable/possible HAM/TSP subset intermediate at 4%. It seems, therefore, that the proviral load in this cohort may be higher than in other cohorts that cite a median of 1% for asymptomatic carriers. Even so, this does not fully account for the exceptionally high prevalence and incidence of definite HAM/TSP as assuming a lifetime risk of HAM/TSP of up to 3%, even subjects with proviral loads >1% have only a 6% lifetime risk.

Because only 59% of the cohort was identified through screening, with 32% self-referred and the remainder identified by the neurology service or by having HTLV-1 in the family, further breakdown of the data from the blood donors only would be more comparable with other studies and potentially contribute to understanding the role, if any, of selection bias. In particular, the high rate of sensory symptoms of the upper limbs are difficult to explain from previous reports of HAM/TSP and raise various possibilities, including overreporting by study participants and the presence of additional factors or alternative etiologies.

It is difficult to comment on the contribution of environment (clinic and community), but there is now an urgent need to test these findings in a new study with HTLV-1–uninfected matched controls. If confirmed, at least in some infected communities, the disease burden of HTLV-1 is considerably higher than previously reported, and this should stimulate broader and more effective prevention programs and greater interest and financial support for research into the treatment of HAM/TSP.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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