Coinfection by HIV-1 and Human Lymphotropic Virus Type 1 in Brazilian Children Is Strongly Associated With a Shorter Survival Time

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Abstract: Coinfection by HIV-1 and human lymphotropic virus type 1 is a frequent finding in South America, the Caribbean and Africa, and its prevalence varies from 4% to 16% according to the available reports. Although the impact of coinfection on HIV disease is still controversial, there is evidence supporting the contention that it can affect the natural history of both infections. No information is available on coinfection in children. In a nested case–control study, we evaluated 35 coinfected children matched by age, gender, and time of diagnosis to HIV monoinfected control subjects. At the first evaluation, coinfected children were more likely to present any signs and symptoms of disease ($P < 0.001$) than monoinfected ones despite having significantly higher $CD4^+$ cells count (1429 ± 608 vs 928 ± 768 cells/mm^3; $P = 0.003$). The proportion of deaths was higher (80%) for coinfected children than for HIV-1-infected ones (20%; relative risk, 2.1; 95% confidence interval, 1.4–3.1; $P = 0.01$). Survival was also significantly shorter for coinfected children ($P = 0.001$). Coinfection by HIV-1 and human lymphotropic vírus type 1 in Brazilian children was strongly associated with higher mortality and shorter survival time despite coinfected patients having a higher baseline $CD4^+$ cells count.

Key Words: HIV-1, HTLV-1, coinfection, survival, children

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INTRODUCTION

Human lymphotropic virus type 1 (HTLV-1) and HIV-1 are human retroviruses with some common characteristics. These agents share the same routes of transmission, are tropic for CD4+ T lymphocytes, and are found in some common geographic areas of the world.[1–4] In consequence, coinfection by HIV-1 and HTLV-1 is frequently detected in regions where they are prevalent.[5,6] On the other hand, they have distinct biologic behavior; although HIV-1 is highly cytopathic and cause clinical disease in almost all infected individuals, HTLV-1 induces lymphocyte proliferation and causes clinically relevant diseases in a minority of infected patients.[4] In addition, although HIV-1 promotes severe immunodeficiency over time, HTLV-1 infection is characterized by a strong immune response to the virus, which can cause a progressive neurologic disease.[7,8]

Although simultaneous infection by these viruses is a relatively common finding, the clinical resultants of coinfection are not completely understood. Most available data suggest that HIV-1 increases the risk of HTLV-1-related neurologic disease in coinfected patients, but the impact of HTLV-1 infection on HIV disease is less clear. Some previous work detected a shorter survival time for coinfected patients in comparison with HIV singly infected ones as well as a strong association of coinfection and severe forms of scabies.[9] However, other studies conducted in North American patients did not find any difference for clinical outcomes between coinfected and singly infected subjects.[10] The wide variation in methodology of the available studies and the retrospective design of most of them did not allow us to clearly define the real impact of HTLV-1 coinfection on HIV disease.

All published papers on HIV-1 and HTLV-1 coinfection were focused on adult patients. As far as we know, no report on the effects of coinfection in a pediatric population is available. It is important to note that most clinicians who treat HIV are not familiar with HTLV infection and vice versa. In addition, pediatricians are usually unaware of the potential role of HTLV infection as a cause of clinical problems in children. This can lead to a low degree of suspicion for such problems in coinfected patients. To describe the characteristics and outcomes of HIV-1/HTLV-1 coinfection in children, we conducted a review in all cases diagnosed in our clinics.

METHODS

Study Design

This is a nested case–control within the cohort of children followed in the institution; coinfected children (cases) were matched by age, gender, and closest date of HIV infection diagnosis with singly infected ones (only HIV-1 infection).

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Patients and Setting

All children attending the AIDS outpatient clinic of the Federal University of Bahia Hospital (HUPES) from 1988 through 2004 had their medical charts reviewed. Demographic data, mean $CD4^+$ cells count, opportunistic infections, or other diseases associated with HTLV infection (including infectious dermatitis, tropical spastic paraparesis, parotiditis, lymphoma, persistent diarrhea, and oral candidiasis), date of death, and serology for HIV-1 and HTLV-1 were recorded. Potential infection exposures for both HIV and HTLV were also extracted from patient charts, including blood or blood products transfusion and breastfeeding. The likely route of the mother's infection (for both agents) was also recorded.

Laboratory Tests

HIV-1 and HTLV-1 infections were diagnosed by enzyme immunoassays and confirmed by Western blot (HTLV-1 and HIV-1) or molecular methods (HIV-1). Because this was a retrospective study, different tests and manufacturers were used for serologic diagnosis during the 16-year review. Because we introduced the routine screening for HTLV infection only in 1995, those children under follow-up before that year had a retrospective diagnosis of HTLV infection (serology performed in stored samples if the patient was already dead).

Statistical Analysis

The comparison of categorical variable frequencies were performed by chi-square test. To compare the $CD4^+$ cells count mean (normal distribution), Student *t* test was used. Children's survival was estimated by Kaplan-Maier test, and the difference in survival time between groups was calculated by log-rank (Mantel-Cox). For the analyses between groups, demographic characteristics, $CD4^+$ cell count, and frequency of clinical events were compared and presented as odds ratios and 95% confidence intervals.

The study was approved by the institutional ethics research board.

RESULTS

All 74 children and adolescents included in the study were born in Bahia, Brazil. Eighty-two percent of the children were racially mixed or black. Thirty-five coinfected children were matched to 39 who were monoinfected. Table 1 summarizes the characteristics of the two groups at the moment of diagnosis.

Most (94.3%) of these coinfected children were infected by both viruses from mother-to-child transmission. There were only two exceptions: one child was born to HIV-negative parents but received a blood transfusion in 1995. The second one was born to a HIV-positive mother and breastfed by a HIV-negative women but positive for HTLV infection (cross breastfeeding). The main risk factor for the mother's coinfection was sexual exposure (36 women [48.7%]) followed by intravenous drug use (24–32.4%). Only 18.9% of these women did not know the potential infection route. The proportion of women who breastfed was similar for mono-infected and coinfected patients (68.6% and 75.0%, respectively, $P = 0.76$), but it was not possible to estimate its duration. The children's age at the time of diagnosis varied from 2 to 16 years.

Any opportunistic disease, signs, or symptoms at the first medical visit were significantly more frequent among coinfected children (88.6%) than in monoinfected ones (44.7%, $P < 0.001$). In addition, we also observed a significantly higher $CD4^+$ cell count for coinfected children (1429 ± 608 vs 928 ± 768 cells//mm^3; $P = 0.003$) at that time point. During the period of follow-up, the proportion of deaths was higher for coinfected cases (34.3%) than for monoinfected (7.7%; odds ratio, 6.3; 95% confidence interval, 1.6–24.6; $P = 0.01$). After diagnosis, coinfected children's survival time differed significantly between groups ($P = 0.003$). Figure 1 shows a survival curve for evaluated children according to their serologic status. Mean baseline $CD4^+$ cell count was similar for coinfected children who died during follow-up (1049 ± 605 cells/mm^3) and for HIV-monoinfected ones (1302 ± 761 cells/mm^3, $P = 0.4$).

DISCUSSION

In our study, children coinfected by HIV-1 and HTLV-1 had a higher mortality rate, a shorter survival, and a higher likelihood of having clinical symptoms at the first medical visit. In addition, we detected a higher mean $CD4^+$ cells count among coinfected in comparison with singly infected children. These findings are similar to those observed in adult patients and suggest the observed higher $CD4^+$ cell count may mislead pediatricians in choosing the optimal moment to start anti-retroviral therapy or prophylaxis against opportunistic

TABLE 1. Characteristics of Monoinfected (HIV) and Coinfected (HIV-HTLV) Children at the Moment of Diagnosis in Bahia, Brazil, 2010

Characteristics	HIV (N = 39)	HIV/HTLVI/II (N = 35)	OR	(95% CI)	*P*
Male gender	18 (46.2%)	17 (46.6%)	1.1	(0.4–2.7)	1.0
History of breastfeeding	24 (75.0%)	24 (68.6%)	0.7	(0.2–2.1)	0.75
Any clinical symptoms*	17 (35.4%)	31 (64.6%)	9.6	(2.8–32.5)	<0.001
Mortality	3 (7.7%)	12 (34.3%)	6.3	(1.6–24.6)	0.01
$CD4^+$ (cells/mm^3)	1429.3 ± 608.3	928.3 ± 768.2			0.003

*Opportunistic disease (including infectious dermatitis, Tropical Spastic paraparesis [STP], parotiditis, lymphoma, persistent diarrhea, and/or oral candidiasis).
HTLV, human T-cell lymphotropic virus; OR, odds ratio; CI, confidence interval.

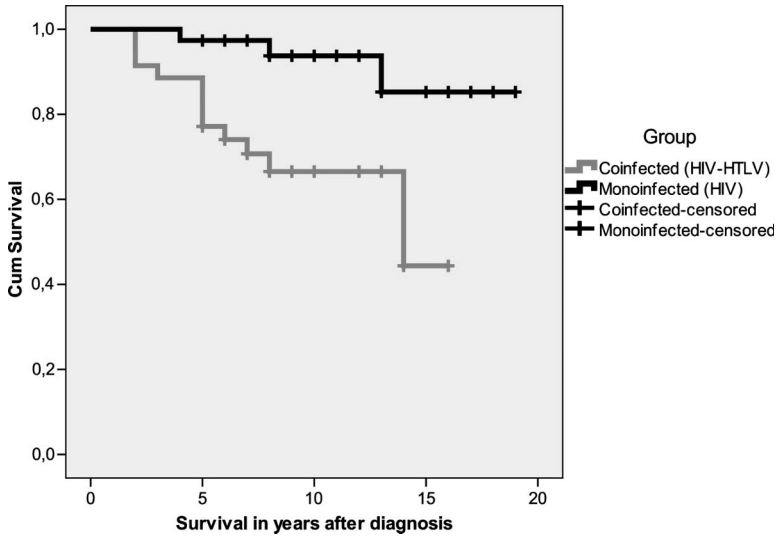

FIGURE 1. Survival curve of a cohort of HIV-1 or HIV-1–HTLV-1-infected children matched by age, gender, and date of diagnosis in Bahia, Brazil, 2010. HTLV-1, human lymphotropic virus type I.

infections.[11] It is interesting to note that such apparent better immune status, as indicated by $CD4^+$ cell count at the first visit, was not translated into a better clinical condition, because most of the coinfected children were symptomatic at the moment of diagnosis regardless of their $CD4^+$ cell count. Unfortunately, the small numbers of patients and the variability in time of laboratory evaluation did not allow us to compare the slope of decline in $CD4^+$ cells over time for both groups.

The AIDS epidemic has significantly changed in Brazil in the last two decades. According to data from the Brazilian Ministry of Health, there is an increasing number of women among the HIV-1-infected population and also a progressive spread of HIV-1 infection to small cities, where information on prevention is still scarce and women are even more vulnerable to contamination.[12] This new picture can increase the rates of mother-to-child-transmission for both HIV-1 and HTLV-1. In Bahia, we have detected rates of coinfection by these agents in adult patients as high as 15% in the past, but a recent estimate suggests coinfection affects approximately 8% of adult patients and 7% of children. Preliminary studies have detected an extremely high rate of mother-to-child transmission for both viruses.[13]

There is some evidence suggesting that HIV-1–HTLV-1 coinfection can negatively affect the natural history of both infections.[14–17] In a previous work, we detected a shorter survival time among adults coinfected patients, but the reasons for such finding were not clear.[16] Other authors were not able to find any evidence of a deleterious interaction by both agents, but the wide variation of design for the available studies does not permit any definitive comparison on such issue.

One common finding in all studies is the higher $CD4^+$ cell count observed in coinfected patients, but it does not seem to provide any additional protection against opportunistic infection. These patients frequently present with severe opportunistic infection despite the high $CD4^+$ cell count. This suggests the increment in such cell populations is artificial, and they probably are dysfunctional. However, because $CD4^+$ cell count is still the most used surrogate marker to define the moment of starting therapy and prophylaxis, the higher counts found in coinfected patients probably lead physicians to underestimate their immunodeficiency intensity and to delay introduction of therapy as we observed in adults.[18] This could explain the higher mortality rate we found for coinfected patients. The similar $CD4^+$ cells count for patients who died during follow-up, regardless of their serologic status for HTLV infection, reinforces this hypothesis.

We cannot discard other potentially important resultants of double infection. We have some laboratory evidence suggesting coinfection can modulate the viral expression and cytokines production.[19–22] However, the scarce evidence from in vivo studies suggest the immune response in coinfected patients is driven by HTLV-1, which causes a Th1 type shift with an increase in interleukin-1, gamma-interferon, and a decrease in interleukin-10 and interleukin-4.[23] Thus, the available data are not enough to completely explain what the real impact of coinfection is on clinical evolution of adults and children.

The main limitations of this study are its small sample size and the potential biases introduced by a case–control study. However, we have no previous information on coinfection in the pediatric population, and it would be very hard to establish a prospective cohort of coinfected children as a result of the scarce number of coinfected patients within this age range and the long follow-up time required to answer these questions.

We believe serologic screening for HTLV-1 in HIV-1-infected children should be routinely performed in areas where HTLV-1 circulates. This would make it possible to detect coinfection earlier in the course of disease and could help to prevent additional morbidity and/or mortality for this population. In addition, antiretroviral treatment should be started for coinfected patients, regardless of the $CD4^+$ cell count, to minimize such problems.

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