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Influence of HIV Infection on Spectrum of Extrapulmonary Tuberculosis

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Abstract

Introduction: Co-infection with human immunodeficiency virus (HIV) has changed both the clinical presentation and the outcome of tuberculosis (TB) dramatically in the last few decades.

Material and methods: We have analyzed a cohort of 190 consecutive patients with extrapulmonary tuberculosis (EPTB) with and without HIV-co-infection. All patients were diagnosed in the Novosibirsk anti-TB dispensary from January 2015 – December 2016.

Results: Of the 190 EPTB patients 117 (61.6%) were HIV co-infected and 73 patients (38.4%) were HIV-negative. Among 117 HIV-infected EPTB patients CNS involvement was diagnosed in 73 (62.4%), while among non-HIV-infected patients TB CNS was found in 6 (8.2%) only. On the contrary, urogenital TB (UGTB) was more common in immunocompetent patients (21/ 28.8%) while among HIV- infected patients UGTB was diagnosed in 3 patients only (2.5%). Bone and joint TB (BJTB) was found in 24 non-HIV-infected patients (32.9%) while among HIV-infected EPTB patients BJTB was diagnosed in 14 (12.0%). Peripheral lymph node (LN) TB was found in 13 HIV-infected patients (11.1%) and in 16 immunocompetent patients (21.9%).

Conclusions: TB CNS developed eightfold more often in HIV-infected patients, while UGTB was diagnosed tenfold more often in immunocompetent patients. BJTB prevalence was about three times higher among immunocompetent patients than among HIV-infected patients. LN TB was also seen more often in immunocompetent patients. Other forms of EPTB were non-depending on HIV infection.

Keywords: Extrapulmonary tuberculosis; Epidemiology; Co-infection HIV/tuberculosis; Urogenital tuberculosis; Lymph node tuberculosis; Bone and joint tuberculosis; Central nervous system tuberculosis; HIV infection

Introduction

From year to year the number of patients with tuberculosis (TB) is increasing worldwide [1]. The epidemiology of pulmonary TB is well documented, but the true incidence and prevalence of extrapulmonary TB (EPTB) is poorly known and probably underestimated [2,3]. Co-infection with human immunodeficiency virus (HIV) has changed both the clinical presentation and the outcome of TB dramatically during the last few decades [4,5]. Worldwide, it is estimated that 14.8% of all new TB cases in adults are attributable to HIV infection [6].

The risk of developing TB is estimated to be between 26 and 31 times greater in people living with HIV than among those without HIV infection. In 2015, 10.4 million new (incident) TB cases were registered worldwide, and of them 1.2 million (11%) were co-infected with HIV [7]. A recent study showed that TB patients older than 35 years had lower risk of HIV infection than younger patients as well as pulmonary TB patients with positive smear. Otherwise EPTB patients with positive smear had bigger risk of HIV infection than patients with negative smear [8]. Data from UK and Ireland show that TB rates in HIV infected children were higher than those reported in the general pediatric population [9]. Likewise, the rise and fall of TB incidence in Malawi between 1985 and 2014 was strongly associated with HIV infection [10]. TB is responsible for more than a quarter of deaths in people living with HIV. TB has recently surpassed HIV as the primary infectious disease killer worldwide, but the two diseases continue to display a lethal synergy [11]. The probability of death in people living with HIV who default TB treatment is approximately four times greater than in those who do not default treatment. Approximately 10% of people living with HIV and latent TB will develop active TB infection each year. This is an argument for active screening for TB among people living with HIV [4]. The early mortality among HIV-positive adults remains high and TB is the leading cause of death in this group [12,13]. Disseminated. HIV infection is associated with higher rates of disseminated and extrapulmonary diseases [5,11]. The main risk factor for EPTB rates as whole is the presence. of HIV infection [14]. Extrapulmonary involvement is seen in more than 50% of patients with concurrent HIV and TB. Due to diagnostic difficulties, extrapulmonary disease is often recognized too late in both HIV-positive and HIV-negative cases [15]. Urogenital TB (UGTB) can imitate various other urological diseases, especially in HIV co-infected patients [16]. Although a systematic review has shown frequent association between HIV and EPTB, there is high heterogeneity of the

analyzed studies and a need for prospective cohort studies to assess the true risk of EPTB in the HIV infected patient population [17]. The aim of the present study was to analyze the rate of HIV-infection among patients with EPTB in a TB endemic region.

Material and Methods

Patients

In this open retrospective cohort study 190 consecutive patients with isolated EPTB were enrolled. All were out-patients which were diagnosed at the Novosibirsk anti-TB dispensary from January 2015 – December 2016. The inclusion criterion was diagnosis of EPTB in any localization and in any combination. Patients were stratified according to evidence of HIV-infection. Diagnosis of pulmonary TB in active stage was the only criterion for exclusion. No patients were left out during the selection process. The diagnosis of EPTB was based on identification of M. tuberculosis (Mtb) by microscopy or culture, by provocative test, immunological tests, tuberculin test, histological findings, X-ray changes, and specific history (close contact to TB infection etc). Pulmonary TB was excluded by x-ray examination. The diagnosis of HIV-infection was based on blood test with enzyme immunoassay.

Data analyses

Data were retrieved from outpatient notes and entered into Excel where they were analyzed. No estimations of sample size were made. Statistical analyses were performed using Statistica 8 (StatSoft Inc., USA). The Fisher exact test was used to compare spectrums of TB localization in HIV infected and non-HIV infected patients. Statistical significance was set at $p<0.05$.

Ethical approval

The study was approved by the local ethics committee of the Novosibirsk Research Institute for Tuberculosis. Informed consents were not required as this was a retrospective, epidemiological.

Results

During the two years study period (2015-2016) 190 consecutive new patients with isolated EPTB were diagnosed in the Novosibirsk region. TB of the central nervous system (TB CNS) was the most common form followed by TB of bones and joints (BJTB). Among all cohorts there were 79 patients with TB CNS (41.6%) and 38 patients with BJTB (20.0%). Lymph node (LN) TB were the third most common form and was found in 29 patients (15.3%). UGTB was diagnosed in 24 patients (12.6%). Among them 21 patients (87.5%) had urological TB and two patients (12.5%) had female genital TB. Other forms included abdominal TB, skin TB, saliva gland TB, TB tonsillitis and mammary TB. All patients had isolated EPTB only. Pulmonary TB was excluded by X-ray examination. Of the 190 patients with EPTB 117 (61.6%) were HIV co-infected and 73 patients (38.4%) were HIV-negative.

Spectrum of EPTB according to HIV-status

Among 117 HIV-infected EPTB patients CNS involvement was diagnosed in 73 (62.4%), while among non-HIV-infected patients TB CNS was found in 6 (8.2%) only. On the contrary UGTB (TB of kidney and both male and female genitals) was more common in immunocompetent patients. This form of EPTB was diagnosed in 3 HIV- infected patients only (2.5%), while among non-HIV-infected patients UGTB was diagnosed in 21 (28.8%). BJTB was much rarer among HIV-infected than among immunocompetent patients.

Localization	HIV- negative		HIV-infected		Total		P
	n	%	n	%	n	%	
TB CNS	6	8,2	73	62.4	79	41.6	<0.0001
Urological TB (kidney + Male genital TB)	18	24.7	3	2.5	21	11	<0.0001
Female genital TB	3	4.1	0	0	3	1.6	0.0553
Urogenital TB as whole	21	28.8	3	2.5	24	12.6	<0.0001
Bone and joint TB	24	32.9	14	12	38	20	0.0005
Peripheral lymph nodes TB	16	21.9	13	11.1	29	15.3	0.0366
Others	6	8.2	14	12	20	10.5	0.2865
Total	**73**	**100**	**117**	**100**	**190**	**100**	

Table 1: Influence of HIV-infection on the spectrum EPTB.

This form of EPTB was found in 14 HIV-infected EPTB patients (12.0%) and in 24 non-HIV-infected patients (32.9%). Peripheral LN TB was found in 13 HIV-infected patients (11.1%) and in 16 immunocompetent patients (21.9%). The rates of most EPTB forms were highly statistically significant depending on HIV-co-infection (Table 1).

Discussion

The epidemiology and spectrum of EPTB varies and depends on numerous factors such as the epidemic situation of TB in a region; the epidemic situation on HIV infection; the level of poverty; the number of migrants and even on the classification EPTB adopted in the region. In our study of 190 EPTB patients the number of patients who were immunocompromised due to HIV-infection was twice as high as the

number of HIV-negative patients. The spectrum of EPTB differed significantly according to HIV status. TB CNS was diagnosed eight times more frequently in HIV-infected patients than in immunocompetent patients. Peripheral LN TB was also found more often in HIV-infected patients than in immunocompetent patients. BJTB was significantly less common among HIV-infected than among immunocompetent patients. Our findings underline the importance of including co-infections with HIV in epidemiological reports on TB. Interestingly, UGTB was less often diagnosed in HIV-co-infected patients than in immunocompetent patients. We believe this is a sign that sexual contact is not the common way of acquiring HIV-co-infection in UGTB patients.We are not aware of other comparative studies of the spectrum of EPTB depending on HIV status. It has been shown however, that the prevalence of HIV infection among EPTB suspected patients was 14.1%, and 32.4% in two series of GeneXpert-confirmed EPTB cases in Etiopia [18]. Diagnostic uncertainty is a problem in the work-up of patients suspected of having EPTB. Urine PCR for Mtb showed the same sensitivity in HIV-positive and HIV-negative UGTB patients [19]. A new technique for Mtb-specific identification of peptide fragments and rapid quantification of their serum concentrations was reported recently [20]. The sensitivity of this method for EPTB was 92.3% in HIV-negative and 75.0% in HIV-positive patients, and the specificity was 87.1-100% in both groups20. The detection of mycobacterial lipoarabinomannan (LAM) antigen in urine has emerged as a potential point-of-care test for TB [21,22]. Urinary-LAM testing appears to be a rapid, low-cost, diagnostic test for HIV-associated TB [21,22]. However, a review of 12 studies showed that LAM has low sensitivity to detect TB in adults living with HIV whether the test is used for diagnosis or screening [23]. Therefore, these new methods are not yet recommended for routine practice. The BACTEC MGIT 960 system which is a fully automated and non-radiometric culture system has been recommended for faster mycobacterial isolation from clinical specimens [24]. The culture is monitored with the oxygen-quenching fluorescent sensor technology every 60 minutes, which provides a satisfactory performance in a short laboratory turnaround time when compared with conventional methods. In our experience BACTEC has higher efficiency for the identification Mtb in urine and ejaculate [24]. A weakness of this study is its retrospective nature and the fact that no sample size estimations were made. To some extent this is counterbalanced by the fact that no patients were excluded. The study is a comprehensive single center series from an endemic TB area.

Conclusions

In our series almost two third of patients with EPTB were HIV co-infected. The spectrum of EPTB forms was significantly different among patients with and without HIV. TB CNS was eight times more frequent in HIV-infected patients, while BJTB, LN TB, and UGTB were diagnosed more often in immunocompetent patients. Although EPTB is less frequent than Pulmonary TB and is a secondary target for national TB control programs, the significance of EPTB has increased worldwide during the HIV epidemic and we therefore recommend registering also the spectrum of EPTB. Our findings demonstrate that surveillance of EPTB should also comprise HIV co-infections.

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