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Why disease due to *Mycobacterium tuberculosis* is less common than expected in HIV-positive patients in Edinburgh

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By December 1993, only five cases of tuberculosis were observed in the 1030 HIV-positive patients in Edinburgh, U.K., although, on the basis of historical tuberculin skin test data, between four and eight new cases of tuberculosis were expected per year. Of 310 HIV-positive patients, none of the 19 (6·1%) who were tuberculin skin test positive had developed tuberculosis after 87 months (average) of follow-up. It is suggested that new or re-infection is a more common cause of tuberculosis in HIV-positive patients than reactivation. Restriction fragment length polymorphism typing of *Mycobacterium tuberculosis* strains could confirm this hypothesis and support currently suggested additional infection control procedures.

Introduction

Edinburgh has recently experienced an epidemic of HIV infection (1). By December 1993, 1030 cases of HIV infection had been notified, with 60% of these among intravenous drug abusers (2). Only five cases of tuberculosis (TB) complicating HIV infection had been reported in these 1030 cases up to December 1993, in comparison with rates of TB infection in AIDS cases in Europe ranging from 4·7% in Italy to 46% in Portugal (3). In the only study performed to date, tuberculosis is reported to complicate HIV infection in those dually infected with *Mycobacterium tuberculosis* and HIV at the rate of 10% per annum (4). Therefore, this study seeks (1) to determine the outcome in HIV-positive patients known to have been tuberculin skin test positive when tested at the age of 13 years as part of the schools BCG vaccination programme and (2) on the basis of similar historical skin test data appropriate to the age groups of the HIV-positive patients, to predict the total number of cases of tuberculosis expected per annum in this population. The clinical features of the five cases of tuberculosis are also described.

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Methods

Chest clinic records of skin test and BCG vaccination status were checked for matches of name and date of birth for the 523 HIV-positive patients identified in Edinburgh by 1991. Lothian Health Board records for the birth cohorts of the years 1969, 1974 and 1979 were checked for the number of natural tuberculin skin test positive reactors determined for each cohort at the age of 13 years during the schools BCG programme.

Results

TUBERCULIN POSITIVITY IN HIV-POSITIVE PATIENTS

Three hundred and ten of 523 HIV-positive patients had matches of name and date of birth on the check of school skin test and BCG vaccination records. Of these 310 patients, 243 had Heaf skin tests grade 0 or 1 and had received BCG; 46 patients had defaulted (of whom, interestingly, 43 became intravenous drug users); four patients had not been given BCG for various reasons, one had calcified primary TB on the chest radiograph and one had previously treated TB; and 17 patients had not been given BCG because they were natural positive reactors, i.e. Heaf tests grade 2–4 without previous BCG. Therefore, there were 19 individuals with previous tuberculous infection (one previously treated) identified by skin testing or chest radiography who

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were subsequently found to be HIV-positive. After post-HIV diagnosis follow-up for 87 months on average (range 24–123 months), none of these patients had developed TB although, on the basis of a rate of 10% TB yr^{-1} in the dually infected, 1·8 cases per annum (13 cases over the average 7-yr period of follow-up) would have been expected (4). The most recent CD_4 counts for these 19 individuals show that four patients had counts of <500 mm^{-3}, seven patients had counts of 500–1000 mm^{-3} and eight patients had counts of >1000 mm^{-3}.

PREDICTIONS OF DUAL INFECTION BASED ON HISTORICAL SKIN TEST DATA

In 1993, the mean age of the HIV-positive population was 33·9 ± 7·4 (SD) years. The majority of this population was included in this study after consideration of the tuberculin skin test status at the age of 13 years of the birth cohorts of 1969, 1974 and 1979, when the percentage of natural tuberculin skin test positive reactors (Heaf test grades 2–4 without previous BCG) ranged from 4·2–7·7%. Assuming that these figures apply to those subsequently becoming HIV-positive, then 4–8 cases of TB yr^{-1} would be expected from the 1993 population of 1000+ HIV-positive patients and 2–4 cases yr^{-1} from the 500+ HIV-positive patients who had been identified by 1991 on the basis of a rate of 10% TB yr^{-1} in the dually infected (4). These expected figures compare with the observation of a cumulative total of only five cases of tuberculosis in the HIV-positive population.

THE FIVE CASES OF TUBERCULOSIS

Five male, HIV-positive patients aged 25–29 years presented between 1988–1993 with fevers, sweating and malaise without new respiratory symptoms and were found to have TB. Four patients were intravenous drug users and one was homosexual. Chest radiography was normal in three of these patients, showed a pleural effusion in one patient and showed basal lung shadowing in the other. One patient had one sputum specimen which was smear positive for *M. tuberculosis*; three patients were sputum culture positive and the organism was isolated from the blood or marrow in four cases, from urine in two cases, from lymphatic tissue in two cases and from pleural fluid in one patient. The organisms were fully sensitive and a good response was seen to rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by triple therapy with rifampicin, isoniazid and ethambutol for a total of 18 months.

Two patients had had documented BCG confirmed by the presence of a scar; three patients had no history of BCG and no scar. The CD_4 count was over 100 mm^{-3} (range 100–200) in four patients and 10 mm^{-3} in the fifth.

Discussion

Edinburgh (population about $0·6 \times 10^6$) has experienced a fall in TB notifications from 182 yr^{-1} in 1980 to 56 yr^{-1} in 1993 of which only 26% had smear positive pulmonary, and therefore infectious, disease (5). The low number of infectious cases of TB, combined with continuing stringent public health measures of TB control (6) renders the likelihood of transmission of TB, even to the immunocompromised, very low.

Tuberculosis developing in the HIV-positive patients would therefore be expected to be more commonly due to reactivation of pre-existing tuberculous infection.

The mean age of the Edinburgh HIV-positive population is relatively low at 33·9 ± 7·4 (SD) years, and the rate of pre-existing tuberculous infection determined by consulting historical skin test records from the schools BCG vaccination programme is therefore also low at between 4–8%. Even with this low rate of pre-existing TB infection, and therefore dual infection in the HIV-positive patients, the observed number of TB cases in the HIV population of this study is much lower than would be expected from the observed rate of development of TB of 10% yr^{-1} in dually infected patients in North America (4). If the North American cases were due, as claimed, to reactivation disease and the same rate of reactivation applied to the dually infected HIV population in Edinburgh, then between 4–8 cases of TB yr^{-1} would have resulted rather than the observed total of five cases of TB. The absence of tuberculous disease in the 18 known tuberculin positive HIV patients (followed up on average for 7 yr) supports this hypothesis although it is possible that TB may yet develop in individuals in this group.

This leads to the suggestion that the 10% yr^{-1} rate of development of TB in the North American report on dual infection (4) does not represent, as claimed, development of TB due to reactivation. Instead, it is suggested that TB developing in the dually infected is more often due to new or re-infection with TB as has been well described recently in homeless men in Australia (7) and in patients with advanced HIV-infection in North America (8). Such re-infection would be unlikely to occur in a low-prevalence area like Edinburgh.

The hypothesis that TB in the HIV infected is more likely to be due to re-infection rather than

reactivation as is currently believed, is amenable to testing in dually infected HIV-positive populations by the application of currently available Restriction fragment length polymorphism techniques of typing *M. tuberculosis* (9). Support from such testing for the re-infection hypothesis would lend added weight to the additional control measures currently being proposed in relation to TB in HIV-positive patients (10).

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