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Original article

Extrapulmonary tuberculosis: epidemiology and risk factors

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ABSTRACT

Objective: To describe the epidemiology and risk factors associated with extra-pulmonary tuberculosis (EPTB).
Method: Cases of tuberculosis (TB) diagnosed from 1991 to 2008 in a Caucasian population were classified as EPTB or pulmonary TB (PTB). Of all cases, 63.7% were followed up in a specialist TB unit. A standardised protocol for data collection was used, including: gender, age, BCG vaccination, contact with PTB patient, smoking habit, alcohol abuse, diabetes mellitus, immunosuppressive drugs/steroids and HIV-status. These variables were compared between EPTB and PTB groups. Statistical analysis was based on logistic regression. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated.
Results: Among the 2,161 cases diagnosed, 1,186 were PTB and 705 EPTB. The overall TB incidence had fallen from 79.9/100,000 in 1992 to 27.1/100,000 in 2008, $P<.05$. The number of EPTB cases decreased more slowly than PTB. EPTB increased from 30.6% of cases in 1991-1996 to 37.6% in 2003-2008 (lymphatic site increased 27%), by trend test $P<.05$. At multivariate level, being female (OR 2.04; 95% CI: 1.56-2.66) and age (OR 1.02; 95% CI: 1.01-1.022) were associated with EPTB, while alcohol abuse (OR 0.33; 95% CI: 0.20-0.52), smoking habit (OR 0.45; 95%CI: 0.34-0.59), contact with PTB patients (OR 0.57; 95% CI: 0.44-0.76) and BCG vaccination (OR 0.64; 95% CI: 0.44-0.92) had a protective effect. The proportion of female gender and age of patients increased over time, whilst there was a decrease in BCG vaccinated patients.
Conclusions: Whilst there has been a reduction in the overall incidence of TB, the proportion of EPTB increased. The proportional increase in EPTB could be explained by an increase in life expectancy and the predominance of women in the population, and by a decline in BCG vaccinated patients.

Tuberculosis extrapulmonar: epidemiología y factores de riesgo

Palabras clave:
Tuberculosis
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Alcoholismo

RESUMEN

Objetivo: Conocer la epidemiología y los factores de riesgo asociados con la tuberculosis extrapulmonar (EPTB).
Método: Los casos de tuberculosis (TB) diagnosticadas entre 1991-2008 en una población caucásica fueron clasificados como EPTB o TB pulmonar (PTB). De todos los casos, 63,7% fueron seguidos en una consulta monográfica de TB. Se utilizó un protocolo estandarizado para la recogida de los datos, incluyendo: sexo, edad, vacunación con BCG, contacto con algún paciente con PTB, tabaquismo, alcoholismo, diabetes mellitus, corticoides/fármacos inmunosupresores e infección por el VIH. Se compararon las variables entre los grupos de EPTB y de PTB. El análisis estadístico se basó en un estudio de regresión logística. Se calcularon los odds ratio (OR) y sus intervalos de confianza (IC) del 95%.
Resultados: Entre 2.161 casos diagnosticados, 1.186 fueron PTB y 705 EPTB. La incidencia global de TB disminuyó desde 79.9/100.000 en 1992 hasta 27.1/100.000 en 2008, p<0,05. El número de casos de EPTB disminuyó de forma más lenta que el de PTB. La proporción de EPTB aumentó desde 30,6% de los casos en 1991-1996 hasta 37,6% en 2003-2008 (la localización ganglionar aumentó un 27%), p<0,05 en un ji al cuadrado de tendencia. En el estudio multivariante, ser mujer (OR 2,04; IC 95%: 1,56-2,66) y la edad (OR 1,02; IC 95%: 1,01-1,022) se asociaron con EPTB mientras que el alcoholismo (OR 0,33; IC 95%: 0,20-0,52),

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el tabaquismo (OR 0,45; IC 95%: 0,34-0,59), el contacto con pacientes con PTB (OR 0,57; IC 95%: 0,44-0,76) y la vacunación con BCG (OR 0,64; IC 95%: 0,44-0,92) tuvieron un efecto protector. La proporción de mujeres y la edad de los pacientes aumentaron a lo largo del tiempo, y descendió el número de pacientes vacunados con BCG.

Conclusiones: Con la reducción en la incidencia global de TB, la proporción de EPTB aumentó. El incremento proporcional de la EPTB se podría explicar por el aumento de la esperanza de vida y el predominio de la mujer en la población, y por un descenso de los pacientes vacunados con BCG.

Introduction

There has been a constant decrease in the number of cases of tuberculosis (TB) in industrialised countries due to improvements in social conditions and the availability of effective antituberculosis drugs.[1] This decrease halted between the years 1985 and 1992 due to the relaxation of prevention and control programs, the appearance of HIV infection, and the migratory movements of people from countries with a greater incidence of TB.[2,3] Although the total number of cases of TB has decreased, the reduction in cases of extra-pulmonary tuberculosis (EPTB) has been smaller, resulting in a proportionate increase in EPTB compared to pulmonary tuberculosis (PTB).[4] In the cases of TB reported in the US, for example, EPTB accounted for 15.7% of total cases in 1993, but 21% in 2006.[5] The reasons for this smaller reduction are little known and have been attributed, among others causes, to demographic changes in the susceptible population and a decreased uptake of vaccination with BCG.[6,7] There are no prospective studies that analyse other possible enhancing factors for EPTB infection.

We present a prospective research study with the following targets:

1. To describe the epidemiology of EPTB in a Caucasian population, comparing the incidence and characteristics of EPTB with those of PTB.
2. To analyse factors contributing to the increased proportion of cases of EPTB.

Method

A specialised unit for following up patients with TB was opened within our hospital in 1991, and a program for prevention and control of TB began in the North West Spanish region of Galicia in 1995. An active search of all the diagnosed cases of TB was performed from 1991 in our health area with a predominantly Caucasian population. In 1991 the population consisted of 218,749 inhabitants, with a mean age of 38.8 years (16.3% older than 64 y); 51.% women (59.9% older than 64 y); 0.29% were born outside Spain and the AIDS incidence was 6 cases per 100,000.[8,9] In 2008 the population decreased to 205,122, with mean age of 44.1 years, (22.9% older than 64 y), with a life expectancy of 77.6 years for men and 84.8 years for women; 51.8% were women, (58.6% older than 64y); 2.1% were immigrants (40.9% from European Union, 3.5% from Eastern Europe, 4.7% from Africa, 2.5% from Asia, 48.3% from Central and South America), and the AIDS incidence was 4.5 cases per 100,000.[10,11]

We analysed data collected at the time of diagnosis for all cases of TB recorded during an 18 year period (1991-2008). Cases of TB were defined by the presence of positive cultures for *M. tuberculosis* complex, histological samples showing presence of tuberculous granulomas and by clinical diagnosis with a favourable response to the antituberculous treatment. Five cases with *M. bovis* were excluded. The cases of TB were classified as either EPTB or PTB. EPTB sites encompassed pleural, lymphatic, genitourinary, bone and/or joint, meningeal, peritoneal, gastrointestinal, cutaneous and unclassified cases.[12] EPTB cases that included >1 EPTB disease site were classified according to the major site. Cases of disseminated TB and cases with concurrent EPTB-PTB were excluded from our principal analysis, because they were not distinctly classifiable as either EPTB or PTB. In order to determine the possible ramifications of this definition of EPTB, we performed a separate analysis that compared disseminated and concurrent EPTB-PTB with EPTB only and with PTB only. In addition, we performed a separate analysis in which disseminated and concurrent EPTB were added to our existing EPTB classification.

In order to respond to the first goal of the study, we performed an analysis of the evolution of the EPTB and their different locations for all cases of TB recorded during the 18 year period. A standardised protocol was used to gather data from each patient at the time of diagnosis as regards socio-demographic and clinical information, including sex, age, country of birth, previous diagnosis of TB, sites of disease, methods of diagnosis, antitubercular drugs susceptibility of *M. tuberculosis* isolates from culture-positive patients, alcohol abuse and human immunodeficiency virus (HIV) status. After obtaining informed consent, HIV testing was performed on patients suspected of having an HIV infection. HIV status was classified as HIV-infected, HIV-negative, or missing or unknown HIV status. Missing or unknown HIV status included patients having indeterminate, unknown, or missing test results, as well as patients refusing or not offered testing.

Of all diagnosed cases in the area, 1,377 (63.7%) [533 with EPTB and 661 with PTB] were prospectively followed up in the specialised TB unit opened in 1991. In order to determine the second of our objectives, we performed an analysis in these cases comparing the characteristics of EPTB patients with those of PTB, and we performed an adjusted analysis to assess the factors that appeared to be associated with the EPTB and influenced their evolution over time.

For cases followed up in the TB unit, data was gathered from each patient as regards socio-demographic and clinical characteristics, previous diagnosis of TB, drug susceptibility test results, and risk factors, including: female gender, age, Bacillus Calmette-Guerin (BCG) vaccination, history of contact with PTB patients, gastrectomy, smoking and alcohol habits, diabetes mellitus, chronic renal failure (CRF), neoplasia, use of immunosuppressive drugs/steroids, albumin level and HIV status. Individuals were considered to be BCG vaccinated if this was recorded in their vaccination records or by the presence of cutaneous scar. Immunosuppressive drugs considered were anti-TNF, chemotherapy and steroids, if more than 15 mg prednisone/day were administered during at least 2 weeks. Smoking habit was considered if the patient smoked 5 or more cigarettes/day[13] and alcohol abuse if the patient drank more than 60 g ethanol/day.[14]

This study was approved by ethics committee of our hospital. Computerised data-bases for registration of data were created. These did not allow the participants in the study to be identified, and only health professionals had access to the information, maintaining strict confidentiality.

The results of the two series were analysed using the commercially available SPSS software, version 14.0. Variables were compared between EPTB and PTB groups. Variables were also compared