ELSEVIER

CrossMark

Archives of Medical Research 46 (2015) 142–148

Archives of Medical Research

ORIGINAL ARTICLE

Diabetes and Other Risk Factors for Multi-drug Resistant Tuberculosis in a Mexican Population with Pulmonary Tuberculosis: Case Control Study

Alejandro Gómez-Gómez,[a,b,c] Martin Magaña-Aquino,[a,b,c] Salvador López-Meza,[d] Marcelo Aranda-Álvarez,[e] Dora E. Díaz-Ornelas,[f] María Guadalupe Hernández-Segura,[g] Miguel Ángel Salazar-Lezama,[h] Martín Castellanos-Joya,[i] and Daniel E. Noyola[j]

[a]*División de Medicina Interna, Hospital Central "Dr. Ignacio Morones Prieto", San Luis Potosí, México*
[b]*Departamento de Medicina Interna, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México*
[c]*Comité Estatal de Tuberculosis Farmacorresistente,* [d]*Programa de Atención al Adulto Mayor,* [e]*Dirección de Políticas y Calidad en Salud,*
[f]*Programa de Micobacteriosis Servicios de Salud del Estado de San Luis Potosí, San Luis Potosí, México*
[g]*Servicio de Medicina Preventiva, Hospital Central "Dr. Ignacio Morones Prieto", San Luis Potosí, México*
[h]*Asesor Nacional en Tuberculosis Farmacorresistente, Instituto Nacional de Enfermedades Respiratorias, México, D.F., México*
[i]*Dirección Programa Nacional de Tuberculosis, Secretaría de Salud, México, D.F., México*
[j]*Departmento de Microbiología, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México*

Received for publication August 22, 2014; accepted January 29, 2015 (ARCMED-D-14-00474).

Background and Aims. Multidrug resistant tuberculosis (MDR-TB) poses problems in treatment, costs and treatment outcomes. It is not known if classically described risk factors for MDR-TB in other countries are the same in Mexico and the frequency of the association between diabetes mellitus (DM) and MDR-TB in our country is not clear. We undertook this study to analyze risk factors associated with the development of MDR-TB, with emphasis on DM.

Methods. A case-control study in the state of San Luis Potosi (SLP), Mexico was carried out. All pulmonary MDR-TB patients diagnosed in the state of SLP between 1998 and 2013 (36 cases) evaluated at a state pharmacoresistant tuberculosis (TB) clinic and committee; 139 controls were randomly selected from all pulmonary non-multidrug-resistant tuberculosis (non-MDR-TB) cases identified between 2003 and 2008. Cases and controls were diagnosed and treated under programmatic conditions.

Results. Age, gender, malnutrition, being a health-care worker, HIV/AIDS status, and drug abuse were not significantly different between MDR-TB and non-MDR-TB patients. Significant differences between MDR-TB and non-MDR-TB patients were DM (47.2 vs. 28.1%; $p = 0.028$); previous anti-TB treatments (3 vs. 0, respectively; $p < 0.001$), and duration of first anti-TB treatment (8 vs. 6 months, respectively; $p < 0.001$).

Conclusions. MDR-TB and DM are associated in 47.2% of MDR TB cases (17/36) in this study. Other recognized factors were not found to be significantly different in MDR-TB compared to non-MDR-TB in this study. Cost-feasible strategies must be implemented in the treatment of DM-TB in order to prevent the selection of MDR-TB.

Key Words: MDR-TB, Diabetes, Latin America.

Introduction

Tuberculosis (TB) remains a global public health problem (1,2). Multidrug-resistant TB (MDR-TB) is defined as a *Mycobacterium tuberculosis* strain that shows resistance to two or more drugs, at least simultaneously to rifampin

Address reprint request to: Dr. Alejandro Gómez-Gómez, Internal Medicine Division, Hospital Central "Dr. Ignacio Morones Prieto", Avenida Venustiano Carranza 2395, San Luis Potosí 78210, México; E-mail: agomez.cer@prodigy.net.mx

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2015.01.006

(R) and isoniazid (H). Pulmonary infections caused by these strains are much more difficult and expensive to treat, with cure rates between 48 and 54% compared to 96% success in drug-susceptible pulmonary tuberculosis (DS-TB) (1−4).

The World Health Organization (WHO) has estimated 630,000 cases of MDR-TB worldwide (range 460,000−790,000) (1). WHO estimates that 3.7% of new TB cases and 20% of re-treatment cases are MDR-TB (1). According to the National Program for Tuberculosis Control and Prevention in Mexico, there were 18,848 new cases of tuberculosis in 2010 and 629 MDR-TB cases between the years 2010 and 2012 (5,6).

Many risk factors for the development of MDR-TB have been described but a history of multiple drug treatments is the most frequent factor (2,7−11). In Mexico, factors that have been reported in association with this condition include administration of monotherapy, treatment dropouts, long-term evolution of the disease, and multiple previous treatments (12,13). Other risk factors frequently reported in many countries (2,7−11) such as drug use, imprisonment, psychological disorders, HIV infection, and being a health-care worker have rarely been described in Mexican MDR-TB patients (6,12,13). The lack of Directly Observed Therapy Strategy (DOTS) is another risk factor in these studies; in Mexico DOTS is applied to 85−90% of DS TB patients (5). Mexico recommends a standardized treatment for all first anti-TB treatment recommended by WHO (14,15).

Diabetes mellitus (DM) has been clearly associated as a risk factor for TB; however, the prevalence of DM among TB patients varies widely (1.9−30%) in different studies. DM has also been shown to increase the risk of treatment failure (16−24). In the U.S. the frequency of DM among TB patients is higher in the Hispanic population (Mexican-Americans) than in other populations (17). The association of DM and MDR-TB is less clear and different studies have shown conflicting results with some reporting a significant association (25,26), whereas others have failed to do so (27,28); nevertheless, as DM has been associated with the number of cavities observed on chest films, delayed sputum conversion, and treatment failure (16,20,22), it is inferred to be a risk factor for MDR-TB. DM is present in 50% MDR-TB patients in Mexico (observational unpublished national data of MDR-TB patients between years 2010 and 2012; http://www.who.int/tb/mexico_tb.pdf), the highest frequency for this association described in the world. Because of the elevated frequency of DM in Mexico compared to other countries (9.2% prevalence in the general population and 9.4−26.3% in persons between ages 40 and 69 years old (29), its impact on MDR-TB may be higher compared to other countries. Due to the elevated economic cost of treatment and high transmission risk of MDR-TB it is important to define the role of DM as a risk factor for this condition because this may lead to specific policies for the follow-up of DM-TB patients in Mexico. The objective of this study was to describe risk factors associated with pulmonary MDR-TB with emphasis in DM in a Mexican cohort of pulmonary non-MDR-TB and MDR-TB patients under programmatic conditions.

Materials and Methods

As of 1998, all patients with suspected MDR-TB in the state of San Luis Potosí (SLP) (total population 2,585,518 inhabitants according to the 2010 census) are referred to a multidisciplinary group for assessment, treatment, and follow-up (State Committee for MDR-TB). For this study, data from all cases ≥18 years of age with confirmed pulmonary MDR-TB evaluated from 1998−2013 by this committee was analyzed (n = 36). Patient assessment included a careful past treatment history obtained by a standardized protocol, sputum culture for mycobacteria, polymerase chain reaction (PCR) assay for *Mycobacterium tuberculosis* complex, and drug susceptibility test for first line antituberculosis drugs. HIV and general laboratory tests are performed in all MDR-TB cases as part of the initial evaluation. Drug susceptibility testing was done by the proportion method. All strains were tested at the Laboratorio Estatal de Salud Pública, a regional certified laboratory, for susceptibility to four first-line drugs as a policy of the Mexican Ministry of Health: the medium used was modified Middle-Brook 7H9−7H10-BACTEC™ MGIT™ 960 (30,31) and tests performed were for isoniazid (0.2 μg/mL), rifampin (2.0 μg/mL), streptomycin (4.0 μg/mL) and ethambutol (5.0 μg/mL). Resistance was defined as the growth of >1% of the colonies in drug-containing media compared with the growth in a drug-free (control) medium. All patients classified as MDR-TB had a positive culture and positive PCR test for *M. tuberculosis* as well as resistance to at least isoniazid and rifampin. In addition, 60% of samples from MDR-TB cases were also processed at the Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE), a supranational laboratory for quality control that used Middlebrook 7H10- BACTEC™ MGIT™ 960 (30,31).

As a comparison group, we included information from patients treated in SLP for pulmonary TB during a 6-year period under programmatic conditions. For this group, 139 patients were randomly selected from all patients reported to the TB program in SLP between years 2003 and 2008 with sputum samples in which acid-fast bacilli were identified by Ziehl-Neelsen staining, with clinical-radiographic data compatible with the diagnosis of pulmonary TB and in whom resistance to rifampin and MDR-TB were excluded (non-MDR-TB). In Mexico it is not a standard practice to perform culture and drug susceptibility tests to all recently diagnosed cases of TB. The control population was selected from patients treated from 2003−2008