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The extrapulmonary dissemination of tuberculosis: A meta-analysis

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ABSTRACT

Background and objective: The epidemiology of the forty percent of tuberculosis patients who present with disseminated and/or extrapulmonary disease is in need of further study. Further study of such dissemination using published data from international indices may provide data which assist with control of tuberculosis.

Methods: For each clinical or epidemiologic factor studied, summary odds ratios and corresponding 95% confidence intervals were calculated showing associations between such factors and documented extrapulmonary dissemination of tuberculosis.

Results: Eighteen studies fulfilled criteria for study of the clinical factors and nine for the cytokine studies. Significant factors associated with a greater risk of extrapulmonary dissemination were female gender (summary odds ratio, 1.92 (95% confidence intervals, 1.72–2.13), *I*-squared 86.9), age under 45 (1.37, 1.18–1.60, 63.7), and as well the absence of smoking, drinking and diabetes but not HIV infection (1.10, 0.91–1.32, 80.5). Among cytokines, the macrophage receptor protein P2X7 was associated most strongly associated with extrapulmonary dissemination of tuberculosis (2.28, 0.88–5.90, 92.9).

Conclusion: Young age, female gender, and the macrophage purinergic receptor protein P2X7 were major factors associated with extrapulmonary dissemination of tuberculosis.

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Introduction

The extrapulmonary dissemination of tuberculosis (TB) is the result of pathogen, host genetic and environmental factors. The relative importance of these factors is a debatable topic. The known pathogen factors include the particular virulence of certain types, such as the Beijing strain, which is associated with extrapulmonary disease [1], as well as biologic properties of disseminating pathogens as shown by mice studies in which variants of a heparin-binding hemagglutinin are associated with an increased risk of disseminated disease [2].

Is it possible to answer questions about risk factors for extrapulmonary disease simply by referring to published data from international indices? Data provided by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) provide widely disparate values for the incidence of extrapulmonary tuberculosis [3–5]. For example, Cambodia reports that 37% of their reported (TB) cases are extrapulmonary, while China reports only 7% [4]. The overall rate is 11.6% for high-risk nations and 13.1% for all nations in this WHO report, while a CDC report for the same period lists a rate of 19% for extrapulmonary disease [3]. Age and

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sex disaggregated data, however, are not typically available as cited in the most recent WHO report [4]. The recognized fact that up to 40% of extrapulmonary cases also contain pulmonary disease complicates any analysis [6].

Host factors are also important in extrapulmonary dissemination and traditionally suggested by the fact that the human immunodeficiency virus (HIV)-infected [7,8] and patients with other immunosuppressive diseases such as systemic lupus erythematosus [9] show an increased risk of extrapulmonary dissemination when infected with *Mycobacterium tuberculosis*. The biologic basis for this host susceptibility is the subject of many studies, dating back to early NIH studies when the then-classified HLA group Bw15 ("w" for "working") was found in a small series to be associated with extrapulmonary dissemination of TB [10].

To assess the correlates which are most strongly associated with extrapulmonary dissemination of TB, meta-analyses of published series of TB were performed. This article presents the findings of these meta-analyses.

Materials and methods

Searching for studies

PubMed database and Google Scholar were searched for studies comparing extrapulmonary tuberculosis (EPTB) to pulmonary tuberculosis (PTB) controls. The search terms used were: extrapulmonary OR extrathoracic AND pulmonary AND tuberculosis within the title or abstract. Searches were limited to the English language although all languages with English translations were included. Abstracts and titles of articles were scanned for key words ("epidemiology," "demographics," "risk factors") indicating a comparative analysis. The bibliographies of the first set of articles were reviewed to locate additional articles.

Selecting studies and collecting articles and data

Studies were included if they: (a) compared data for EPTB and PTB cases; (b) were published within the last 10 years (because of the scarcity of earlier studies); and (c) provided calculated odds ratios or sufficient data for the calculation of such odds ratios. Studies were excluded if: (a) cases in which clinically both EPTB and PTB were reported as part of either group; (b) pleural TB cases were included in the PTB group (because the convention is to include them as EPTB); or (c) studies contained duplicate data from a larger study. Due to large differences in available resources and health care protocols between study sites, no studies were excluded based on method of TB confirmation. When duplicate papers using the same data were encountered, the larger study was chosen. A sample search would include the above variables, and examining the individual articles, for example, for data on gender and then collating the relevant articles.

Factors studies by meta-analysis

These meta-analyses were performed on analyzed factors present in sufficient frequency for statistical analysis. These included gender, age, HIV status, African ancestry, smoking and drinking history, the presence of diabetes, and the presence of polymorphisms in five cytokines, including interferon-gamma (γ), tumor necrosis factor-alpha (α), interleukin 10, toll-like receptor 2, and the macrophage protein P2X7.

Limitations of factors used in meta-analysis

HIV-negativity was assumed when HIV status was reported as unknown because without this restriction, few studies were usable. Smoking, diabetes and excess alcohol drinking habits were generally reported based on the authors' assessments, usually without specific definitions. Race was rarely reported with detail. In the end, only African or non-African ancestry reports were present in sufficient number or detail to justify analysis. Age was reported with diverse stratification and the most often used age for stratification (age 45, 4 studies) was used for this meta-analysis. The use of other age cutoffs did not provide sufficiently large samples for analysis.

Statistical analyses

Characteristics of patients reported in at least 2 eligible studies were analyzed using STATA software (version 11.0, College Station, TX [11] and "metan" commands [12]). Meta-analysis was performed using random effects analysis, and heterogeneity was measured using the I^2 statistic. The studies were analyzed with graphs produced with best fit lines showing the odds ratio for extrapulmonary vs. pulmonary disease given the presence of a studied demographic, trait, behavior, or polymorphism. For cytokine and molecular polymorphisms, absolute allele numbers and associated proportions were used rather than specific genotypes, and the search criteria were limited by the paucity of polymorphism articles related to dissemination of TB.

Results

From 1257 articles generated in the initial search, 27 met the inclusion criteria and 3 additional articles were found using bibliographies in the 27; among the 30 articles, 11 were excluded for combining pulmonary and extrapulmonary disease, 3 were excluded for equating pleural with pulmonary disease, 1 was excluded for duplicate data, an additional 3 were located in reviewing data, and the final 18 were suitable for inclusion in the meta-analysis. Large public health databases (CDC, WHO) did not typically contain sufficient detail regarding combined pulmonary and extrapulmonary cases and thus did not fit the inclusion criteria for the study.

The proportion of cases confirmed by culture varied by study and this proportion was often not reported. The remaining cases were confirmed by a variety of methods including microscopy, histology, and clinical decision-making.

The data analyzed on cytokines and immune polymorphisms were based on reviews of 30 recent publications, and data from 9 articles met criteria for the study.