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Short Communication

The inconsistent definitions used for tuberculosis in the medical literature

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ABSTRACT

In order to assess the confusion attendant with current definitions of extrapulmonary tuberculosis, pleural and miliary disease, a set of 37 papers published which analyzed disease states were assessed for how the terms adhered to official definitions of the American Thoracic Society, the World Health Organization, and the Centers for Disease Control. The findings showed uncertainties in the classification of extrapulmonary disease, a frequent inconsistency in the inclusion of pleural disease within pulmonary rather than extrapulmonary disease, and the ambivalent use of the terms pleural and disseminated tuberculosis. Further attention by editors and authors is needed in the use of tuberculosis definitions.

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Introduction

Tuberculosis (TB) remains the disease with the highest global mortality for a single infectious agent [1]. While the disease was described clinically in the nineteenth century after the cardinal discoveries of Robert Koch [2], the classification of the disease evolved over largely the twentieth century as the clinical manifestations of the disease were made evident. Most of the current classification remains anatomic, for example, pulmonary, extrapulmonary, pleural, urogenital, bone and joint, meningitis, miliary and disseminated all refer to the anatomic areas where disease is manifested. Unique aspects of TB described in the last century include, for

example, the predilection of pleural disease to affect younger patients [3] and the tendency of tuberculous meningitis to occur from the spillage of an intracerebral “Ghon complex” rather than as a manifestation of disseminated disease (a key observation made by Johns Hopkins pathologist Arnold Rich) [4].

Recently it is argued, especially among pediatricians [5] and the Russian community [6–9] that the current classification systems need modification, that the pathogenicity of disease is a reflection of the microbiologic resistance of the organism, of the immune status of the patient (it appears certain HLA factors may predispose, for example, to disseminated disease [10]) and of a variety of clinical factors which

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remain undefined. The fact that disease is more recently readily classified as “severe” or “less severe” is of use to clinicians more than to pathologists or those who study the pathogenesis of *Mycobacterium tuberculosis* (MTB) in man.

In a recent meta-analysis performed by the authors and published herein [11], it was evident that the classification systems for extrapulmonary disease traditionally used to suffer from inconsistency. There is a failure to adhere to the recommended definitions elaborated by international or national agencies such as the World Health Organization [12], the American Thoracic Society (ATS) [13], or the Centers for Disease Control and Prevention (CDC) [14]. An inconsistent usage of these definitions compromises the incorporation of much data into larger studies or meta-analyses. Other authors have argued that the terms “extrapulmonary” and “pulmonary” require clearer definitions when used in analyses [15].

In this study, a cohort of papers were analyzed for their usage of terms used to classify TB, and on the basis of these, it was determined that there is a need – if the traditional systems of classifications are still used – to advise more close attention to the adherence to these definitions.

Methods

Thirty-seven papers used for the study of extrapulmonary TB, identified by PubMed and Google Scholar searches, identified as described in an earlier study on extrapulmonary TB [11] and updated, were analyzed for specifics regarding how extrapulmonary, pulmonary, pleural and disseminated TB were defined. Data were tabulated and analyzed using STATA 11 [16]. A PubMed and Google Scholar review was done to analyze the earliest usage of the term “extrapulmonary” with TB. The official definitions for TB including extrapulmonary disease were those used by the ATS [13], the CDC [14], and WHO [12].

Results

Thirty-one (84%) of the 37 analyzed papers provided data on the numbers of pulmonary and extrapulmonary cases. The studies that inconsistently classified combined pulmonary and extrapulmonary disease as extrapulmonary [7], as both extrapulmonary and pulmonary [4] TB, or as pulmonary disease [3] were excluded from the analysis [6]; the remainder of the studies were clearly documented [11]. Pleural disease was included as extrapulmonary in 25 (68%) studies, but as pulmonary in 4 (11%) studies, and there was no criterion in the remaining 8 (22%) studies. In only 18 (49%) of the studies were disseminated or miliary disease defined. Only 14 (38%) of the series reported the number of patients with combined pulmonary and extrapulmonary disease. Among all studies, in only 4 (11%) were the combined patients analyzed as a completely separate category.

Discussion

The terms used in TB warrant a short discussion because the confusion and complexity of even such terms as “extrapulmonary” are today under debate [15]. The current usage of such

terms in studies will be discussed in light of the findings in this paper and then recommendations for future usage provided.

TB is a term derived from the Latin *tuber*, and it refers to the rounded swellings or tuberosities characteristic of radiographic findings of the disease. Its usage dates from the mid-nineteenth century with earlier terms having been consumption, phthisis, or if localized, scrofula. When Koch described in 1881 in Berlin his original findings in “Über Tuberculose” [2], it represented a new recognition of the cause and pathology of the disease, and the term “tuberculosis” appears to have taken firm root then.

The exact onset of the term extrapulmonary disease is not clear [17]. It was used in the title of a paper in 1915 in a descriptive manner [18]. This is the first mention of “extrapulmonary disease” in the United States Pub Med listings, and the second is over 35 years later [19]. Earlier citations of “extrapulmonary” disease in reference to bovine TB [20], source of coughing [21], and radiographic analysis [22] do not necessarily refer to TB and can be found through Google Scholar resources. A series describing various clinical manifestations appeared throughout the twentieth century, including urogenital TB [15,23], meningitis [24], bone and joint disease [25], miliary disease [26,27], and pleural disease [3]. All of these terms are officially considered part of extrapulmonary disease using the official definitions of WHO, ATS and CDC.

The data collected above show an inconsistency with these official definitions and confusion on the basis of current authors who collate data on extrapulmonary disease. The main points of confusion include: (1) a tendency to include pleural disease among pulmonary disease; (2) a failure to officially distinguish disseminated from other forms of disease; and (3) a tendency to lump for analyses cases of pulmonary and extrapulmonary disease. Because up to 40% of extrapulmonary disease includes pulmonary disease [28], the last of these points is readily understood.

What can be done to correct these imbalances in the definitions used?

One can also argue, as do the pediatricians and the Russian communities, that the terms currently used are at times antiquated, that “severe” and “nonsevere” might be more parsimonious and more readily used, in the manner that the classification of dengue has recently been modified [29]. Nonetheless, the various forms of disease require further analysis (in this analysis, a unique HLA-type was seen for gastrointestinal disease [30], for example, and the pathogenesis of the various forms of TB are possibly quite distinct).

The terms miliary and disseminated are also often confused. Miliary is a form derived from the presence of *milia* or millet seed and appears to have been first used in the late 17th century [31]. Which are milia and which are tubercles? The latter term was used first, and there is a tendency to think of milia as the manifestation of disseminated disease, but tubercles also disseminate, and there is a tendency also to think of tubercles as radiologic manifestations and milia as pathologic, although this is a false distinction and both can be either. Disseminated suggests disease throughout the body which can clearly be miliary or tubercular. Bacteremic disease is a term commonly used in the Republic of South Africa and suggests disseminated disease, but using blood culture positivity to diagnose TB is not done as often in the United States.

What can be done to clarify the confusion in diagnosis?

The terms miliary and disseminated remain, and it will be difficult to restrict their usage. It is recommended that authors tabulating a series of TB cases adhere to the official guideline definitions for extrapulmonary disease, that they distinguish clearly between pulmonary and extrapulmonary disease, and identify the percentage of cases which contain both forms of disease (recognizing that many may be underdiagnosed). This could most readily be done by authors of journals which publish peer-reviewed papers on TB, and an inclusion of definition criteria is recommended in the formulating of comparative standards necessary for publication.

The results of such actions by authors and editors will facilitate the study of extrapulmonary TB and provide all with a better understanding of the complex manner by which MTB appears in a select set of patients to disseminate beyond the lung and to disseminate to particular organs of the body.

Conclusion

Extrapulmonary TB is not always distinctly classified in clinical and research studies of TB. Pleural disease is not always considered extrapulmonary, as recommended in international standardized guidelines, and thus was erroneously classified in a sizable percentage (32%) of reviewed studies. The inclusion of disseminated or miliary disease was also inconsistent.

More restrictive guidelines are needed in the definitions used for TB by authors and editors (in peer-reviewed criteria). Such definitions will help produce clearer studies of pathophysiology and more valid meta-analyses. Such improved classifications should assist in the global control of TB.

Conflict of interests

The authors have no conflicts of interest.

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