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The tuberculosis spectrum: Translating basic research into pediatric clinical practice

Buonsenso Danilo [a], Sali Michela [b], Focarelli Benedetta [a], Onesimo Roberta [a], Palucci Ivana [b], Delogu Giovanni [b,*], Valentini Piero [a]

[a] Department of Pediatrics, Università Cattolica del Sacro Cuore, Rome, Italy
[b] Institute of Microbiology, Università Cattolica del Sacro Cuore, Rome, Italy

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ABSTRACT

Recent studies suggest that the classical dichotomous classification of "active" and "latent" tuberculosis (TB) is no longer acceptable since "TB infection" encompasses a wide spectrum of conditions ranging from asymptomatic to lethal disease. In an attempt to address these issues from a pediatric clinical perspective, we describe two children with microbiologically confirmed TB but lacking any clinical and radiological evidence of disease. These two cases highlight the hypothesis that TB cannot be divided in two simple categories, but it covers a wide spectrum of manifestations ranging from asymptomatic to lethal TB. The implications of these results in the context of the new TB spectrum and the related clinical issues are discussed.

Introduction

The Paediatric Tuberculosis Network European Trials group (PTBNET) has recently defined latent tuberculosis infection (LTBI) as 'a positive immunological test result (either tuberculin skin test (TST) or interferon-gamma release assay (IGRA)) in the absence of active tuberculosis (TB)' [1]. As stated by the PTBNET, the proposed definition has a number of limitations, particularly in light of recent advances in TB pathogenesis.

In an attempt to address these issues from a clinical perspective, we describe two children with microbiologically confirmed TB but lacking any clinical nor radiological evidence of the disease. We also discuss the new theory of the TB spectrum in the context of the pediatric population, where the distinction between active and latent TB may be particularly challenging even in healthy children.

The hypothesis/theory

There is a growing understanding that the simple dichotomous classification of adult TB as "active" or "latent" is no longer acceptable and "TB infection" encompasses a wide spectrum of conditions, ranging from asymptomatic to lethal disease [2]. The lack of a clear edge between infection and disease is a major challenge for the clinician who face the problem to translate this new scenario into routine clinical practice, mainly affecting therapeutic decisions. Our hypothesis is that this new concept of TB spectrum should be applied in the pediatric population, too.

Evaluation of the hypothesis/idea

In the last few years, a large body of evidences led to the establishment of a new concept of TB infection, which is better represented by a continuous spectrum of conditions, spanning from quiescent infection, active infection and clinical disease [2]. Such TB spectrum of conditions is the results of the interaction between the host immune responses and the bacilli which establish a dynamic equilibrium that can be maintained for the lifetime. Interestingly, it has been shown that different lesions, representative of the entire spectrum, can be simultaneously detected in a single TB patient [2]. Similar observations were made in a non-human primate model of TB, where low-dose aerogenic infection of Mtb resulted in some monkeys developing active disease, others with latent infection and another group that did not fit this classical distinction [3]. This latter group of monkeys, termed *percolators*, did not show any clinical sign of disease (as latent animals), but differed from latently infected animals for the occasional shedding of bacteria in bronchoalveolar lavage and the microscopic histopathological features at necropsy, which were more consistent with active disease than latent infection [3]. A similar spectrum of conditions is likely to occur in young children since

* Corresponding author at: Institute of Microbiology, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, 00168 Rome, Italy. Tel.: +39 063015 4964; fax: +39 063051152.
E-mail address: gdelogu@rm.unicatt.it (D. Giovanni).

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they can present with subclinical TB, with active bacterial replication in host tissues, as indicated by positive microbiological tests in liquid fluid (gastric aspirates), but in absence of any overt sign or symptom of disease. The understanding of this new theory of the TB spectrum may, therefore, have practical clinical consequences, mainly on guiding the best microbiological treatment for every single child.

Empirical data

Case 1

A 2.5 year-old boy (Cs1) was brought to our attention because his nanny was diagnosed with smear-positive active TB at the beginning of April 2013. From November 2012 to January 2013 he had close and prolonged contact with his nanny and from February to April only occasional contact.

Cs1 underwent TST (30 mm induration), QuantiFERON-TB Gold in Tube (QFT) (Interferon-γ > 10 UI/ml) and a negative anteroposterior and laterolateral chest X-ray (evaluated by our referent expert in thoracic radiology and pediatric TB). The boy was healthy, no signs or symptoms suggestive of TB nor any other disease were observed. Growth was normal for age.

A diagnosis of LTBI could have been made; nevertheless, due to the close contact and the fact that another child who used to stay with the nanny was diagnosed with active TB, we decided to perform three gastric aspirates, that scored positive for acid fast bacilli staining and presence of *Mycobacterium tuberculosis* (Mtb) genomic DNA; the Mtb bacillus was also isolated in culture. Chest CT scan was performed and left hylar adenopathy with atelectsis of the lingular lobe was detected. Anti-TB therapy was started.

Case 2

A 2.5 year-old boy (Cs2) was brought to our attention because his father was diagnosed with microbiologically confirmed, sputum-smear-positive, active TB.

Cs2 underwent TST (60 mm of induration with central ulceration), QFT (IFN-γ > 10 UI/ml) and a negative anteroposterior and laterolateral chest X-ray (evaluated by our referent expert in thoracic radiologic and pediatric TB). The boy was healthy, no signs or symptoms suggestive of TB nor any other disease were detected. Growth was normal for age.

To exclude active TB, three gastric aspirates were performed that were positive for Mtb genome but were negative for acid fast staining and culture for Mtb. Chest CT scan was performed and right hilar adenopathy with a small abnormal nodule in the lower lobe of the right lung were observed. Anti-TB therapy was started.

Consequences of the hypothesis and discussion

We have presented two unusual cases of microbiologically confirmed TB in asymptomatic young children with negative chest X-ray. According to current guidelines, both children would have been considered latently infected and treated with isoniazid preventive therapy (IPT) [1], yet in both cases the detection of Mtb in gastric aspirates was an indication of active disease. This is a clear example of the challenging task of clearly defining the two classical conditions of TB infection (latent and active), which in turn raise the question on whether and when a full microbiological analysis on children potentially defined as LTBI must be conducted in order to establish proper anti-TB therapy.

The two cases presented may represent subclinical TB, with active bacterial replication in host tissues, as shedding in liquid fluid (gastric aspirates) indicates, in absence of any overt sign or symptom of disease. While it is not possible to predict the outcome of this subclinical form of TB, bacilli shedding may be seen as an indication of the (potential) inability of the host immune response to control bacilli replication in vivo and as such suggestive of an increased risk of developing active disease.

In this context, administration of the proper anti-TB regimen is important to prevent active disease. IPT is known to be very effective in preventing development of active disease in latently infected subjects [4], despite the fact that isoniazid is active only against replicating bacilli [5], which are thought to account for only a small portion of the Mtb population in latently infected subjects [6]. Indeed, the >six months treatment with isoniazid is necessary to deplete the population of metabolically active bacilli (scouts), which are continuously replenished by the reservoir of dormant Mtb [6,7]. Recent data obtained in the monkey model of TB indicate that the mutation rate of Mtb is similar during latent infection, active disease and reactivation [8], underscoring the risk of developing and selecting Mtb resistant strains in the course of monotherapy as during IPT in LTBI subjects [8].

It remains to be determined whether the beneficial effects associated with monotherapy (IPT), such as the reduced risk of developing side effects as a results of the multi-drugs regimens, are counterbalanced by the increased risk of developing drug resistance in this group of children showing subclinical TB. The dilemma for clinicians who routinely deal with these situations is whether such cases deserve more aggressive treatment than chemoprophylaxis with IPT. The approach to this problem might also differ between developing and developed communities and should take into account the age of the children, since the youngest children might elicit a more aggressive response than older children where disease following infection is much less frequent. In any case, distinguishing quiescent TB from latent/subclinical TB or asymptomatic disease would be of the greatest importance to guide the therapeutic choice.

The introduction of the IGRAs as biomarkers of TB infection offered the opportunity to identify immunological correlates of disease and infection. Some studies suggested that secretion of high amounts of IFN-γ in response to the RD1 antigens used in IGRAs correlated with an increased risk of developing active disease [9]. Interestingly, the two children included in this study had a high IFN-γ response following stimulation with the Mtb antigen in the QFT assay. However, there is a general consensus that these assays do not have a prognostic value for TB disease. The identification of new biomarkers of TB capable of identifying Mtb-infected children with subclinical disease or more likely to develop active disease [10], would provide a powerful tool that will guide clinicians to the implementation of proper therapy.

In conclusion, the two clinical cases presented highlight that the distinction between active and latent TB may be particularly difficult to achieve in healthy children. These findings are in line with the new concept of TB spectrum that is emerging in the last years as a results of several studies in preclinical animal models of infection and in humans [2]. In the last few years, we observed several cases of TB infection and disease in children encompassing the entire spectrum of conditions, ranging from asymptomatic to lethal TB (Fig. 1). The simple linear association between bacterial load in host tissues and severity of the disease may not fully represent the complexity of the host–pathogen interaction that drives to tissue damage and clinical manifestations. New biomarkers of TB infection and disease, capable of distinguishing the different clinical conditions, will certainly provide new tools to properly manage children with TB.

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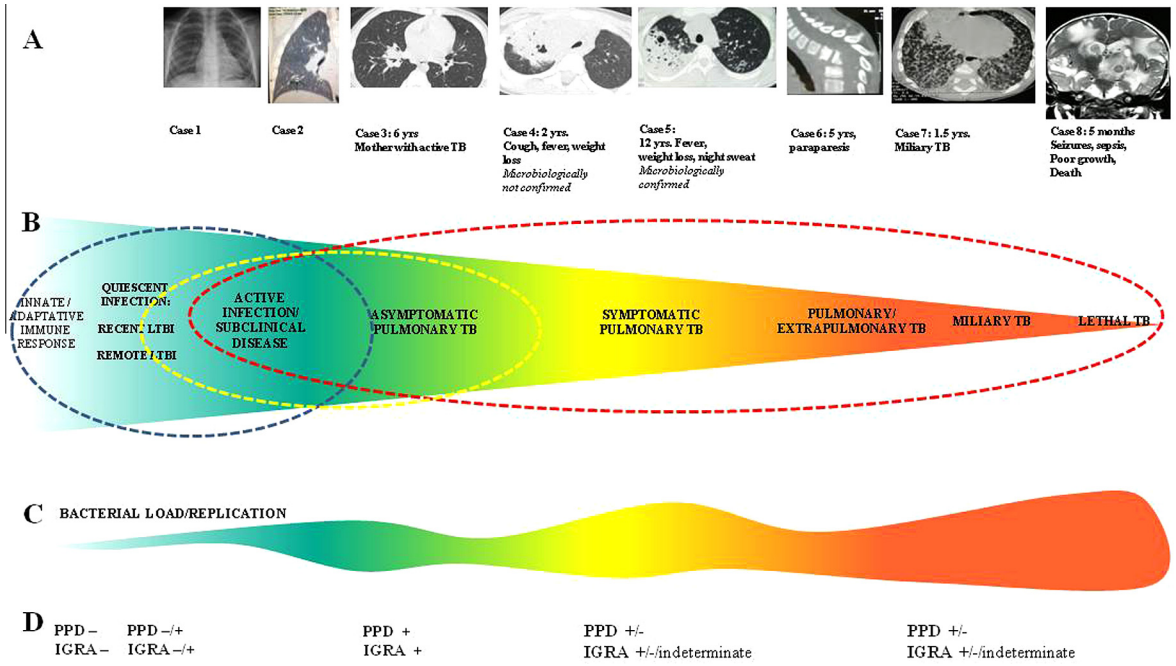

Fig. 1. The TB spectrum in children. (A) List of clinical cases of TB in children observed in our experience and heat map (B) representing the corresponding stages of TB infection and encompassing the entire spectrum of clinical conditions (adapted from Ref. [2]). TB may present as a wide range of manifestations, ranging from active infection/subclinical disease (cases 1 and 2) to lethal disease (lethal disseminated TB with massive cerebral involvement, case 8), passing through asymptomatic pulmonary TB (case 3), symptomatic pulmonary TB (with different bacterial loads and lung involvement, cases 4 and 5), extrapulmonary TB (case 6) and miliary TB (case 7). As highlighted by colored circles (B), distinction between the different stages may be challenging with implications for the patients clinical management. (C) Classically, it has been proposed that the severity of clinical TB is proportional to the bacterial burden in host tissues [2]. However, virulence of a particular strain and the features of host immune response may equally contribute to determine disease severity. (D) In this context, immunological markers of TB infection, as TST or IGRAs, can only partially describe this complexity and new biomarkers of infection are needed to provide a more accurate representation of the different stages of clinical TB in children. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Competing interests

None to declare.

Authors' contributions

D.B., P.V. and G.D. have made substantial contributions to conception, design, analysis and interpretation of data; B.F. and R.O. have made substantial contributions to acquisition and analysis of data and to the clinical management of the data. M.S. have made substantial contributions to analysis of data and performed all the microbiological analysis with G.D. All authors have given final approval of the version to be published.

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