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Performance of Tuberculin Skin Tests and Interferon-γ Release Assays in Children Younger Than 5 years

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ABSTRACT

Background : Available data to assess the optimal diagnostic approach in infants and pre-school children at risk of tuberculosis (TB) are limited.

Methods: We conducted a prospective observational study in children younger than 5 years undergoing assessment with both tuberculin skin tests (TST) and QuantiFERON-TB Gold In-Tube® (QFT-GIT) assays at two tertiary TB Units in Barcelona, Spain.

Results: 383 children were included. One of 304 participants considered uninfected developed active TB during follow-up (median [IQR]: 47 [30;48] months), compared with none of 40 participants with latent TB infection (follow-up since completion of anti-TB treatment: 42 [32;45] months). Overall test agreement between TST and QFT-GIT was moderate (κ=0.551), but very good in children screened after TB contact (κ=0.801) and in BCG-unvaccinated children (κ=0.816). Discordant results (16.8%, all TST+/QFT-GIT negative) were mainly observed in new-entrant screening and in BCG-vaccinated children. Children with indeterminate QFT-GIT results were on average younger than those with determinate results (median age: 12 versus 30 months; p<0.001). The sensitivity of TSTs and QFT-GIT assays in children with confirmed active TB was 100% (95%CI: 79.4-100%) and 93.7% (95%CI: 69.8-99.8%), respectively. In patients with latent TB infection or active TB there was no correlation between age and antigen-stimulated interferon-gamma responses (r=-0.044, p=0.714).

Conclusions: In young BCG-unvaccinated children with recent TB contact a dual testing strategy using TST and QFT-GIT in parallel may not be necessary. However, TST+/QFT-GIT negative discordance is common, and it remains uncertain if this constellation indicates TB infection or not. In active TB, QFT-GIT assays do not perform better than TSTs.

Introduction

Children younger than 5 years infected with *Mycobacterium tuberculosis* (MTB) are at greater risk of progression to active tuberculosis (TB) and developing severe and disseminated forms of TB than are adults. In infants the rate of progression is up to 40-50% in the first 2 years after primary infection.[1-3]

In the absence of a gold standard, the diagnosis of latent tuberculosis infection (LTBI) in infants and toddlers remains challenging, because of the limitations of current immune-based diagnostic tests, the *in vivo* tuberculin skin test (TST) and *ex vivo* interferon-gamma (IFN-γ) release assays (IGRAs).[4,5] Moreover, the non-specific clinical presentation of active TB and the comparatively low diagnostic yield of microbiological investigations in this age group commonly result in delays in establishing the diagnosis of active TB.[2,6]

Commercially available IGRAs detect circulating T-cells that produce IFN-γ in response to stimulation with MTB-specific antigens that are absent from all Bacillus Calmette-Guérin (BCG) vaccine strains and from most non-tuberculous mycobacteria (NTM).[3,7] Both TSTs and IGRAs indicate host sensitization to mycobacterial antigens by detecting cell-mediated immune responses, which are critical in preventing progression to active TB.[8] The physiological immaturity of the immune system of infants and toddlers not only results in a reduced ability to contain MTB infection (i.e., prevent progression),[9] but may also result in impaired diagnostic accuracy of TSTs and IGRAs.[10,11]

In many industrialized countries IGRAs have largely replaced TSTs as the main TB screening tool in adults.[12-14] The existing evidence regarding the optimal diagnostic approach for children younger than 5 years at risk of LTBI is limited. Recent U.S., Canadian and European guidelines recommend the preferential use of TSTs irrespective

of BCG vaccination status in this age group, and consider IGRAs as a complementary tool to improve sensitivity and specificity.[3,10,12-14] The Spanish Society of Pediatric Infectious Diseases also recommends using TSTs as the first line investigation in children younger than 5 years after TB contact.[15] In those with a negative TST result, performing an IGRA test is recommended. In patients with a positive TST result, IGRA testing is considered unnecessary unless there is a history of prior BCG vaccination. Recent shortages of purified protein derivative (the test substance used for TSTs) have led to changes in TB screening practices, increasing the need for more robust data on IGRAs in young children.[16]

The aim of this study was to evaluate the performance of TSTs and QuantiFERON-TB Gold In-Tube (QFT-GIT) assays in the diagnostic evaluation of LTBI and active TB in previously healthy children younger than 5 years.

Materials and methods

Study population

We performed a prospective observational study of children younger than 5 years at risk of TB undergoing assessment at one of two tertiary Pediatric TB Units, the Drassanes-Vall d'Hebrón (DVH) Unit in Barcelona City or the Hospital Sant Joan de Déu (SJD) in Regió Sanitària Barcelona Sud. Both units are located in Catalonia, Spain and are jointly covering a population of more than 2,9 million inhabitants, of which 15.8% are younger than 15 years.[17] In Catalonia, the incidence of TB gradually decreased from 21.6/100,000 in 2004 to 16.6/100,000 in 2014. In 2014 the TB incidence in children aged 0 to 4 years was 12.4/100,000.[17] BCG vaccination is not part of the routine immunization program in Catalonia.

Children were eligible for participation if they were assessed for LTBI (either in the context of contact tracing or as part of new entrant screening) or were investigated for