

Latent tuberculosis infection (LTBI): a real host defence or a permanent threat?

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SUMMARY

Screening of latent infection by *Mycobacterium tuberculosis* (LTBI) and treatment of positive subjects is the key point in the prevention of TB; such a strategy should be performed mainly among individuals with risk of progression. Progression from LTBI to active TB is highest both in recent contacts of patients with active TB, and in immunocompromised subjects. Therefore, LTBI could either be considered a permanent host

defence or, seen from the opposite point of view, it could represent a long-lasting threat if the efficiency of the immune system declines over a lifetime. Interferon gamma release assays (IGRAs) show better sensitivity and specificity than the Mantoux test.

Keywords: active tuberculosis, latent tuberculosis infection, interferon gamma release assays.

INTRODUCTION

Tuberculosis (TB) is a disease caused by a germ called *Mycobacterium tuberculosis* (MTB) that is spread from person to person through the air. Persons inhaling air containing these droplet nuclei may become infected.

The infection does not determine TB disease as ever. As a result, two TB-related conditions exist: latent TB infection (LTBI) and TB disease. A person with latent TB infection is described as following:

- Usually has a skin test or blood test result indicating TB infection.
- Has a normal chest X-ray and a negative sputum test.
- Has TB bacteria in his/her body that are alive, but inactive.
- Does not feel sick.

- Cannot spread TB bacteria to others.
- Needs treatment for latent TB infection to prevent TB disease; however, if exposed and infected by a person with multidrug-resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB), preventive treatment may not be an option.

About 5 to 10% of infected persons will develop TB disease at some time in their lives (reinfection), mostly within the first two years of infection. The risk of developing TB disease is considerably higher for persons whose immune systems are weak.

Since almost one third of the world population is infected by MTB, LTBI is the source of most future TB disease so that the strategies to eliminate TB in industrialized countries hinge on diagnosis and treatment of LTBI.

O'Connor in the far 1940 stated: "... is it better to have a positive or negative tuberculin test? Show me the student who has not asked this question. I might add, show me the physician who can give an unequivocal answer ..." [1].

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■ IMMUNOLOGY

Still today, we do not understand neither what constitutes a protective immune response to TB in the lung nor the extent to which the phenotype of antigen-specific CD4⁺ T cells contributes to this protective response. Another potential confounder is that MTB is able to manipulate both the innate and acquired immune response of the host so that the result can be an effective CD4⁺ T cell response limiting the disease but it can also promote the development of progressively destructive lesions in the lung [2].

A plausible working model is that MTB initiates recruitment of permissive phagocytes into the lung, limiting the recruitment of T cells capable of redirecting the permissive phagocytes to a bactericidal state, resulting in a permissive environment wherein the bacterium can grow without significant barriers.

Cellular immune responses to *Mycobacterium tuberculosis* progress in two stages. First, initial innate immunity involves the direct production of cytokines, such as tumor necrosis factor (TNF), interleukin-12 (IL-12) and others, by infected macrophages activated via toll-like and other pattern receptors [3].

Later, such mechanisms are amplified by adaptive responses of pathogen-specific T lymphocytes recruited to the site of infection, leading to the production of interferon gamma (IFN γ), useful both to amplify the immunological response and to activate intracellular antibacterial mechanisms [4]. Therefore, the early macrophage-T-cell interactions result in inhibition of mycobacterial growth, and lead to the formation of granuloma.

The tubercle bacilli enter the body via the respiratory route. The bacilli spread from the site of initial infection in the lung through the lymphatics or through the blood to other parts of the body. LTBI is the result of inhalation of MTB, if bacterial load is high and/or immune host defense is not adequate. Infection develops in 40-90% of subjects exposed to even isolated contact. Within a couple of years from the contact, infection can cause overt disease in 5-10% of infected subjects, remaining latent in 90-95%, owing to capacity of immune system of limiting MTB growth. After the first two years from the contact, LTBI can become active, causing overt disease in 0.1-0.5% of

infected subjects per year. This is the lifetime year risk for tuberculosis.

From a first point of view, we can consider LTBI a permanent threat. Risk factors for progression of infection to active tuberculosis (reinfection) are:

- human immunodeficiency virus (HIV) infection;
- infants and children aged <5 years and persons aged >75 years;
- immunosuppressive therapy such as tumor necrosis factor-alpha (TNF- α) antagonists, systemic corticosteroids equivalent to ≥ 15 mg of prednisone per day, or immune suppressive drug therapy following organ transplantation;
- recent infection with *M. tuberculosis* (within the past 2 years);
- history of untreated or inadequately treated active tuberculosis (including persons with fibrotic changes on chest radiograph consistent with prior active tuberculosis);
- silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck, or lung;
- gastrectomy or jejunioileal bypass;
- weight <90% of their ideal body weight;
- cigarette smokers and drugs or alcohol abuse
- populations defined locally as having an increased incidence of active tuberculosis, possibly including medically underserved or low-income populations.

In particular tobacco smoking and chronic obstructive pulmonary disease (COPD) are very common and important risk factors that cause increased susceptibility to chronic subclinical infections, aberrant inflammatory response, and altered oxidant-antioxidant balance [5, 6].

It is now recognized that TNF mAbs represent a high risk for reactivation of LTBI, which, if untreated, produces Tb reactivation rates many times more than in the general population [7]. Most of that risk is concentrated in the first few months of anti-TNF treatment, suggesting that the subsequent decline of incidence of TB cases could be due to depletion of "reactivable" LTBI [8].

From the opposite point of view, Andrews et al. studied two prospective cohorts of persons exposed to patients with infectious tuberculosis, to estimate the incidence of tuberculosis among individuals with latent tuberculosis infection (LTBI group) and without latent tuberculosis (uninfected). Individuals with latent tuberculosis had 79%

lower risk of progressive tuberculosis after reinfection than uninfected individuals. What comes from such a study could lead to the conclusion that LTBI could represent a permanent defense [9].

■ DIAGNOSIS

Nowadays, the gold standard test to diagnose latent tubercular infection is still Mantoux test, which is more than 100 years old and presents some limitations:

- measures a single antigen;
- can induce a boosting effect;
- it's necessary a second visit;
- there is an inter-operator variability;
- result comes out in 48-72 h.

In the last ten years, interferon gamma release assays (IGRA) tests have shown a higher sensitivity and specificity than tuberculin test (9-13). IGRAs advantages are numerous:

- are an *in vitro* test;
- measure multiple antigens, particularly those related to cell mediated immune response to different polypeptides, as ESAT-6, CFP-10, TB7.7;
- do not induce boosting effect;
- it's not necessary a second visit;
- no (or minimal) inter-operator variability;
- result in 24 h;
- recently, Quantiferon Gold® plus seems to measure additional peptides in which there are epitopes recognized by CD8 T-lymphocytes, potentially contributing to identify active tuberculosis more than latent infection, recent exposure more than ancient one, infection even in immunocompromised subjects (HIV) or in children under 5 yrs.

Considering such advantages, as a whole, IGRA tests are very useful in order to detect LTBI, more than Mantoux test, but do not perform to monitor treatment both of latent infection, and of active disease [10].

■ CONCLUSIONS

In conclusion, LTBI can be considered both a defense mechanism and a threat potentially danger-

ous for the subject: the cut-off between the two possibilities has to be identified in the integrity of immune system. LTBI *per se* is undoubtedly a protective entity, representing the complex strategy of host, set up in response to tubercular infection, finalized to contain the spread of bacilli. At any phase of life, the effectiveness of host defense can decrease, owing to chronic disease, cancers, advanced age, immunosuppressive drugs or immunocompromising disease, to such a level, that residual, low-viable *M. tuberculosis* strains can escape granulomas and disseminate the whole organism, overcoming also other innate immune defenses, like NK cells, a strong protection, like in several pulmonary disease [14, 15].

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