Predictive value of QuantiFERON-TB Gold test for the risk of active tuberculosis

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Abstract. Objective: The aim of this study was to determine the predictive value of QuantiFERON-TB Gold (QFT-G) test in screening for latent tuberculosis (TB) progression to active TB in subjects with recent contact with active TB cases. Material and method: The study included 72 subjects aged over 18 who had close contact with active TB cases in the last 3 months. Subjects have been evaluated clinically and radio-graphically every six months after inclusion in the study, over a period of 2 years. Two immunological tests were used for estimation of latent TB: tuberculin skin testing and QFT-G test. Results: During follow-up (2 years), 7 subjects (10.1%) were diagnosed with active TB. Hepatitis B, type 2 diabetes, cancer, COPD, poor living conditions, positive tuberculin skin testing and QFT-G were associated with a high risk for onset of active TB in univariate analysis (p<0.05). In multivariate analysis a positive QFT-G test showed a risk of developing active TB 2 years after contact with patients with active disease, 8 times higher than a negative result (HR (hazard ratio), 8, CI95% 1.3% - 46.7%, p=0.02), while HR given by the presence of diabetes was 5 (CI95% 1% - 23.8%, p=0.03). Conclusions: QFT-G test and the presence of type 2 diabetes were independent predictors for risk of active TB.

Key Words: active tuberculosis, predictors, tuberculin skin test, QuantiFERON-TB Gold

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Introduction
Active tuberculosis (TB) prevention requires an effective screening program to identify and treat latent TB cases in high-risk populations. But latent TB (LTB) is associated with a variable risk of progression to active disease, a complex risk which is poorly understood and characterized. Patients with latent TB are an important source of new cases of active TB. Prophylaxis is effective in preventing active TB incidence. Therefore, diagnosis and treatment of latent TB as well as identifying high risk cases of active TB are particularly important issues. The highest risk of developing active TB is in the first 2-3 years after infection with Mycobacterium tuberculosis (Ferebee 1970). People with predisposing factors (environmental or intrinsic) also show an increased risk of developing active TB. WHO (World Health Organization) estimates that up to 10% of people with latent TB have a much higher risk of developing active TB. Up to 95% of TB deaths occur in poor or developing countries, which makes TB situation in our country require special attention (WHO 2013). The introduction of Interferon-Gamma Release Assays (IGRAs) 10 years ago created an alternative to Purified Protein Derivative (PPD) test. Theoretically, IGRAs have an enhanced specificity for detection of Mycobacterium tuberculosis and it was assumed that they can more accurately identify latent TB cases with high risk of progression to active disease. Studies in this direction have provided conflicting results (Diel et al 2012; Rangaka et al 2012). WHO estimates that treatment of latent TB with high risk of progression to active disease could reduce disease incidence by 64% (Abu-Raddad et al 2009). Currently, active TB preventive therapy is determined after lengthy procedures and requires careful adverse reactions monitoring. To avoid many unnecessary stages, there is a need for accurate screening tests to predict the progression of latent TB to active disease more accurately than tuberculin skin testing.

The clinical benefits of the QuantiFERON-TB Gold test (QFT-G) are relevant only if subjects identified with latent TB by the use of this test are at high risk of developing active TB, compared to subjects with negative test, and if these individuals are real candidates for prophylactic treatment.

The aim of this study was to determine the predictive value of QFT-G test in screening for latent TB progression to active TB in subjects with recent contact with active TB cases.

Material and method
The study was conducted at “Leon Daniello” Clinical Hospital of Pneumology, Cluj-Napoca, between January 2010 - January 2012. Patients were selected from the hospital units after signing the consent form for enrollment in the study.

The study included subjects aged over 18 who had close contact with active TB cases in the last 3 months. Diagnosis of active
TB was established according to the standard criteria (Ghid metodologic de implementare a programului național de control al tuberculosei 2007-2011). Subjects have been evaluated clinically and radiographically every six months after inclusion in the study, over a period of 2 years. Subjects were instructed to submit to medical examination earlier than the established date if they notice the occurrence of TB symptoms. Cases diagnosed with active TB have been noted.

Quantified variables
We gained medical history and physical examination information for each subject and noted the presence or absence of the following: age, gender, rural or urban origin, kinship of contact with persons with active TB, personal case history of active TB or suspected TB treatment, previous BCG immunization, the presence of respiratory diseases (chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, pulmonary embolism), autoimmune diseases, diabetes mellitus, psychiatric diseases, sarcoidosis, heart failure, infectious diseases, kidney disease with hemodialysis, fever, lack of appetite, fatigue, chills, night sweats, cough, hemoptysis, chest pain and dyspnea. We also noted the patients’ workplace, social status, family, any kind of substance consumption (cigarettes, alcohol, drugs), concomitant medication (corticosteroid, immunosuppressive, chemotherapy). In terms of the blood tests, we have considered results for: white blood cells count, lymphocyte count, hemoglobin count, hematocrit level. For the assessment of renal function blood values of urea and serum creatinine were also determined. We estimated creatinine clearance by glomerular filtration rate calculation using Cockcroft-Gault formula. All patients were tested for HIV, hepatitis B and C.

Radiography
X-ray examination was performed on each patient, in both left or right posteroanterior and lateral position. We determined the presence/absence of the following radiological signs: infiltrates, cavities, calcifications, fibrotic lesions, pleural effusion. Radiography was performed in the Department of Radiology at “Leon Daniello” Clinical Hospital of Pneumology, Cluj-Napoca.

Bacteriological examination
We conducted bacteriological examination for each subject: stained sputum smear for BARR and mycobacterial cultures on solid medium (Löwenstein-Jensen) and liquid medium (MB/BacT system). Interpretation of results is explained in general methodology chapter.

Immunological examination
Two tests were used for diagnosis of latent TB: tuberculin skin testing and QFT-G test. Interpretation of results was explained in a previous article (Găvriluț & Pop 2012).

Statistical analysis
Statistical analysis was performed using Medcalc software version 12.4. Normality of distribution for quantitatives variables was tested using Kolmogorov-Smirnov test. Quantitative variables were analysed with T test for independent variables or Mann-Whitney U test, whichever appropriate. For comparison of categorical data we used the chi-square test. We calculated sensibility and specificity for PPD test and QFT-G for risk of active TB. We analysed the risk for active TB using Kaplan-Meier curves and Cox regressions. We adjusted for multiple comparisons using the Bonferroni correction. The level of statistical significance was set at p lower than 0.05.

Results
Of the 72 subjects in close contact with active TB in the past 3 months, 3 patients showed the existence of active TB during the examination (bacteriological diagnosis). These subjects were excluded from the study.

Parameters such as age, height, weight, BMI, mitogen QFT-G, hemoglobin, leukocytes, bilirubin, total protein and PPD test, had a normal distribution (Kolmogorov-Smirnov test, p>0.05). QFT-G antigen values, QFT-G Nil values, erythrocytes, urea, creatinine and glucose had an abnormal distribution (Kolmogorov-Smirnov test, p<0.05).

During follow-up (2 years), 7 subjects (10.1%) were diagnosed with active TB.

Median time to onset of active TB was 8.4 ± 5.6 months. The shortest period of time from inclusion in the study group to diagnosis of active TB was 2 months, and the longest 18 months. No differences were found between patients that developed active TB and those that did not become infected regarding age, sex ratio, rural or urban origin, history of active TB, comorbidities (asthma, autoimmune diseases, heart failure) smoking, treatment with steroids or immunosuppressive drugs (p>0.05). Hepatitis B, type 2 diabetes, cancer, COPD and poor living conditions were more frequent in the group that developed active TB (p<0.05).

Pulmonary radiography detected infiltrative lesions in 2 patients (3.2%) without active TB and in none of the subjects who developed active TB (p=1). Cavitary lesions were detected in 2 patients (3.2%) with active TB, and in 2 subjects (28.5%) without active TB. This difference was statistically significant (p=0.04). Pleural effusion was not detected in any of the patients with active TB, but it was found in 3 subjects (4.8%) without active TB (p=0.01).

We found no differences between the two groups in terms of hemoglobin levels (p=0.7), leukocytes (p=0.4) and total protein levels (p=0.3). Red blood cell counts (p=0.5), lymphocytes (p=0.7), urea (p=0.6), creatinine (p=0.6) or glucose levels (p=0.1) did not differ between groups.

PPD test was positive in 4 patients (57.1%) who developed active TB and in 13 patients (20.9%) without active TB (p=0.05). The following values were determined for PPD: sensitivity 51.7% (CI95%: 18.7% - 89.5%), specificity 79% (CI95%: 66.8% - 88.3%), positive predictive value 23.5% (CI95%: 6.9% - 49.9%) and negative predictive value of 94.2% (CI95%: 84% - 98.7%) for the risk of active TB in contacts of subjects with active TB. Average size of induration of PPD test was significantly bigger in patients with active TB than in those without the disease (t-test for independent variables, p=0.007).

Logrank test (p=0.03) was applied to evaluate the predictive value of PPD test for the risk of developing active TB, taking into account the time after the enrollment in the study when the patient developed the disease. QFT-G test result was positive in 12 patients (19.3%) without active TB and in 5 patients (71.4%) with active TB (Fisher
test, p=0.008). For QFT-G we calculated a sensitivity of 71.4% (C195% 29.2% - 95.4%), specificity of 80.6% (C195% 68.6% - 89.5%), positive predictive value of 29.4% (C195% 10.4% - 55.9%) and negative predictive value of 96.1% (C195% 86.7% - 99.4%) for the risk of developing active TB 2 years after contact with a case of active TB.

Logrank test (p = 0.001) was applied to evaluate the predictive value of QFT-G test for the risk of developing active TB, taking into account the time after the enrollment in the study when the patient developed the disease.

Several predictive models were made using Cox regression in order to evaluate the independent predictive value of various parameters for the development of active TB in univariate analysis. Due to the relatively small number of subjects, multivariate analysis could not comprise simultaneously all the variables with statistical significance. In the end, we chose the two most stable predictive models, one of them considering patient age, presence of diabetes mellitus and QFT-G test, and the second including PPD test instead of QFT-G test. In the first model, QFT-G test showed a risk of developing active TB 2 years after contact with patients with active disease, 8 times higher than a negative result (HR [hazard ratio] 8, C195% 1.3% - 46.7%, p=0.02), while HR given by the presence of diabetes was 5 (C195% 1% - 23.8%, p=0.03). In the second model, PPD test showed a risk of developing active TB 2 years after contact with patients with active disease, 4.4 times higher than a negative result (HR, 4.4; C195% 1% - 20%, p=0.05). When we made the adjustments for multiple comparisons, PPD test has not retained its statistical significance.

**Discussion**

This study determined the predictive value of several clinical and biological parameters for developing active TB 2 years after the subjects had been in direct contact with subjects diagnosed with active disease. In univariate analysis several variables were associated with the risk of active TB in subjects in close contact with active TB cases. Thus, chronic hepatitis B, COPD, diabetes mellitus, neoplasms, poor living conditions, presence of cavitary lesions, positive PPD test and positive QFT-G test were associated with a greater likelihood of developing active disease. In multivariate analysis, however, only the presence of diabetes mellitus and positive QFT-G test were predictive factors for developing active TB 2 years after close contact with TB.

Positive QFT-G test results had a sensitivity of 71.4% and a specificity of 80.6% for the risk of active TB 2 years after contact with the disease. Haldar *et al* (2013) reported a sensitivity similar to that calculated in our study (70%) and a higher specificity (85.9%). Their study included a much bigger number of subjects than our research, which may explain the high specificity. Subjects with positive QFT-G test results have developed active TB 8 times more frequently than subjects with negative QFT-G test results.

PPD test failed to obtain statistically significant predictive values when using Bonferroni correction. In a meta-analysis conducted by Diel *et al* (2012) positive IGRA test results predicted active tuberculosis better than the tuberculin skin test.

European Centre for Disease Prevention and Control (ECDC) recommends IGRA assays to establish the management of cases with risk of developing active TB. Thus, for cases with positive QFT-G test results with high risk of developing active TB (immunocompromised, children, close contact and recent exposure), IGRA can be used to assess the overall risk. Healthy subjects with negative IGRA results also have a very low probability of developing active TB (European Centre for Disease Prevention and Control 2011).

Diabetes mellitus was an independent risk factor for active TB in those patients with recent contact with active disease. This is supported by several studies in literature, indicating a double problem for global health (Jeon & Murray 2008; Baker *et al* 2011; Goldhaber-Fiebert *et al* 2011).

Some limitations of the study are the small number of subjects included, the impossibility of performing some more specific tests (GeneXpert MTB/RIF) and the fact that it was a single-center study.

**Conclusion**

QFT-G test and the presence of type 2 diabetes were independent predictors for risk of active TB. PPD test did not predicted the onset of active TB.

**References**


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