INTERPRETATION OF MANTOUX TUBERCULIN SKIN TEST IN THE DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

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ABSTRACT

The aim of this study was to determine the cut-off induration size demarcating negative from positive results of the Mantoux test in a group of children with confirmed tuberculosis and to determine whether the nutritional status of children has influence on the induration size of the Mantoux test. A retrospective descriptive study was conducted based on a review of the history record of patients with diagnosed tuberculosis, under the age of 14 years. All newly registered tuberculosis cases that were treated in the period from January 2003 until December 2007 were included. Out of 420 records reviewed, 270 were included in the study. Induration sizes varied from 0 to 34 mm, with a mean of 3.41 mm. The induration distribution showed a bimodal pattern, with 49 (18.1%) patients with negative reaction (<5mm) and a second mode between 15-19 mm in 78 (28.9%) patients. Person coefficient was 0.175, showing weak positive linear correlation between the nutritional status and the Mantoux induration size. Cut-off induration, demarcating the negative from positive Mantoux reactions was 5 mm. Malnourished children were significantly more likely to have a negative Mantoux reaction.

Key words: tuberculosis, children, Mantoux, induration, nutrition.
INTRODUCTION

Tuberculosis (TB) is known from ancient times and even though is prevented and treated, it is still one of the lethal infective diseases in the world (1, 2). The disease in children easily progresses in difficult forms of TB, therefore, early diagnosis, especially in high risk groups (intra family contact with sputum smear positive adult, high prevalence surrounding and region, low access to public health service, immunosuppressive condition of the child) is essential (2, 3, 4).

The tuberculin skin test (TST), Mantoux technique, is the widest method used for demonstrating infection with Mycobacterium tuberculosis in children. In Republic of Macedonia (Macedonia) this is the only technique which is used. The reaction depends on the quality and dosage of tuberculin, the technique of application, and the biological characteristics of the tested population (5). Its application, in any group of patients usually yields a wide range of results, from a presence of reaction in un-infected children to the complete absence of a reaction in some children with confirmed TB disease (6).

Nutrition and tuberculosis are in close interrelation. Nutrition has an important role in the etiology, complications and therapy of tuberculosis (7). The importance of malnutrition for TB is that it suppresses the immune reaction towards TB antigens and gives false negative reaction to the TST (8). The percentage of negative responders on the Mantoux test varies from 40% to 61% of the children with malnutrition and TB (6, 9). A negative TST never rules out a diagnosis of TB in a child (10). Therefore, for the test to be useful in the clinical setting, an appropriate cut-off needs to be defined to demarcate positive and negative reactions.

The aim of this study was to determine the induration size of the Mantoux TST, in a group of children under the age of 14 with confirmed tuberculosis and subsequently to determine cut-off induration size demarcating negative from positive results in case of high Bacille Calmette Guerin (BCG) coverage in Republic of Macedonia (11). Another objective was to determine whether the nutritional status, expressed as weight for age z-score, in children, had influence on the induration size of the Mantoux test.

MATERIALS AND METHODS

A retrospective study was carried out on 270 children and adolescents aged 0 to 14 years, treated from TB, in the period from January 2003 until December 2007 at the “Institute for pulmonal diseases and childhood tuberculosis-Kozle” (Institute-Kozle) in Skopje, Macedonia. The Institute is a specialized pediatric hospital for treatment of children TB in the country. The number of children treated at the Institute represents the prevalence and incidence of TB in children in Macedonia (12).

The study included review of the patients’ records and patient data were filled in a specially designed questionnaire for this study. 420 history records were reviewed. Inclusion criteria for this study were: newly registered TB cases, Mantoux test result, age under 14 and weight in kilograms (kg.), noted in the history of patients. TB case was defined according to standard guidelines (2, 5, 10). Exclusion criteria were: TB contactor, suspicious TB case, TB infection and pulmonal disease other than TB. Also, patients with confirmed TB, who did not fill one of the inclusion criteria, were excluded from the study. For one patient, record for the weight did not existed and therefore this patient was not included in the analysis of the nutritional status, but was included in the other statistical analyses.
Variables taken into consideration for this study were: gender, Mantoux induration size, nutritional status (z-score) and age in months of the patient. According to the present guidance, the Mantoux technique was performed using 5 tuberculin units (TU) of tuberculin PPD-RT 23 on the left forearm (5). Results were read between 48 and 72 hours and recorded as the transverse diameter (in millimeters) of palpable induration. For purposes of diagnosis, indurations of ≥ 5 mm were interpreted as positive, regardless of the nutritional status or history of BCG vaccination. The age in months was calculated using the software: Epi info, version 3.5 from June, 2008 (Epi info 3.5). The nutritional status was calculated as the weight for age standard deviation (z-score) using the software Epi info 3.5.

The statistical analysis of the variables was basically descriptive. All data were analyzed using the SPSSS statistical software, version 16.0 (SPSS Inc, Chicago). The level of significance was set at p<0.05 for all analyses. Distribution frequencies were analyzed for each of the variables: age in months, gender, induration size and z-score. Correlation between Mantoux results and nutritional status was calculated with Pearson coefficient of correlation. The results from Mantoux test induration sizes were plotted on a frequency distribution curve in order to define a demarcation between positive and negative reactions. Induration sizes, grouped in a range of 5 mm, were plotted on a frequency distribution graph. A curve was superimposed onto the graph and the modes and antimode were identified. The antimode was taken to represent the demarcation between negative and positive results. The nutritional status of the group, presented as z-scores, was plotted on a distribution curve allowing comparison with the National Centre for Health Statistics (NCHS) and the Center for disease control (CDC) 1978 standard reference population.

The study was retrospective and did not affect the treatment of the patients.

RESULTS

Four hundred and twenty (420) history records of patients treated in the period from 2003 to 2007 at the Division for treatment of tuberculosis at the Institute-Kozle, Skopje have been reviewed. 270 of these filled the inclusion criteria and were included in this study.

One hundred and forty five-145 (53.7%) patients were male and 125 (46.3%) female. The ratio male/ female was 1.16:1 for the males. The age distribution of the patients is presented in Figure 1.
Patients ranged from 1 month to 165 months (14 years), with average of 75 months (6 years and 3 months), (SD = ± 4.208). The median value was 77.5 months. The mode was between 12-23 months (41 patients), and on the second place where patients between 84-95 months (28 patients).
Figure 2 presents the distribution frequency of the Mantoux induration sizes. The Mantoux results among patients ranged from 0 to 34 mm, with mean of 14.6 mm. 49 (18.1%) patients had not-detectible reaction, with transverse induration size of < 5 mm. In 221 (81.9%) patients a positive reaction was recorded, with induration size of ≥ 5 mm. The distribution curve showed bi-modal form, with a primary mode at 0 mm and a second mode between 15-19 mm. The antimode between the two modes was between 5-9 mm. From this frequency distribution it could be concluded that the point of 5 mm demarcates the negative from the positive reactions.
The weight for age (z-score) distribution frequency ranged in the interval from -3.63 to +4.68, with median of -0.46. The mean value of the weight for age z-score was -0.4016 with SD=1.4282. 33 (12.26%) from the patients had < -2.00, while 236 (87.73%) patients had weight for age z-score > -2.00. Figure 3 presents that the weight for age z-score nutritional status of the patients does not show normal distribution frequency, but there is movement of the average value of the weight for age z-score for -0.4016 to the left, in relation to the 0.00 on the abscissa (x-scale) from the coordination system. This shows malnutrition in 12.26% of the study patients.

The Pearson-coefficient of correlation of 0.175 for the Mantoux results and nutritional status of the patients (weight for age z-score) showed weak positive correlation between these two variables.

The linear regression of correlation between the Mantoux reaction and the nutritional status of the patients had $r^2=0.031$; B constant=0.193; β-coefficient=0.175 with p=0.004. Confidence Interval (CI) was in the limits between 0.062-0.323 (95% CI) and showed positive partial correlation between these two variables, more precisely by moving the z-score of the nutritional status towards the negative scores (malnutrition), the results of the Mantoux test in mm were moving towards the negative scores also.
DISCUSSION

The report of the WHO (10) that most common age when children present with TB is between 1 and 4 years, was confirmed also in our study. The most common age of TB manifestation in children in Macedonia was between the age of 1-2 years, that was the same as the age reported by African studies (6) and lower than South American studies (13) that reported slightly greater frequency of the disease in the 11 to 15 year age group.

Concerning the gender distribution, the current series of 270 TB cases in children, provided data similar to that from the WHO and from other studies of TB in children that show no effect of gender on predominance of TB (6, 12, 13, 14).

The interpretation of tuberculin test in children vaccinated with BCG is of major importance in our population due to the high vaccination coverage (95-97%) in the country (11). In Macedonia, there is a continuous BCG vaccination policy beginning from 1948 when the BCG vaccination became obligatory (12). There is no specific agreement on the influence of the BCG vaccine in interpretation of the Mantoux results. The reaction of the TST test in vaccinated person, depends on the potency of the vaccine, the time passed from the moment of vaccination (it is the strongest in the first years after immunization), as well as from the prevalence of the TB in the area where such person live. Since, those data are not known usually; arbitrary the diameters of 10 mm and 15 mm are used as upper limits (2, 13, 15). Therefore, the 10 mm and 15 mm cut-offs, are not general criteria for differentiation of the postvaccinial reaction from the reaction as a result of an infection with Mycobacterium tuberculosis (9). Furthermore, different populations and regions have different cut-off values for the TST (16, 17).

Most guidelines recommend the cut-off to be determined according to the risk factors and not the BCG status of the child. An induration of ≥5 mm is considered positive in children in high-risk situations such as: close contact with a diagnosed or suspected TB case, clinical evidence of disease, radiologic changes consistent with TB, children receiving immunosuppressive therapy and immunodeficiency; in all other children ≥10 mm diameter of induration is considered positive (6, 18, 19, 20). According to Jakovski (5), in Macedonia induration size of <5mm should be considered as a negative reaction, reactions ≥5mm as positive and tuberculin hyper reactions should be induration sizes ≥15mm.

In order to determine the cut-off values for our study group, Mantoux induration size, distribution size was performed. The technique of induration distribution analysis is more often applied to community surveys seeking to estimate the prevalence of TB infection in populations. It is recognized that when applied to patient groups, the distribution is similar to that obtained in populations with allow rate of false-positives (i.e. the test is highly specific). In both cases the results usually show a bi-modal distribution with a clear anti-mode demarcating positive from negative reactions. If such a distinct anti-mode is present it may be used as a rational cut-off for that particular group (6, 20).

Results from this group of patients showed the expected bi-modal distribution with a large proportion having no or mild reactions induration size of <5 mm and the test having stronger, positive reactions ranging from 5 mm to 34 mm. The anti-mode was at 5 mm indicating that this would be a reasonable cut-off for this patient group. This result was the same as obtained by Kiwanuka (6) in his study and justifies the general recommendations of the WHO on the interpretation of the TST Mantoux test (20).

Tuberculin testing was of great significance in this study and it produced a positive reaction (≥ 5mm) in the majority of cases (81.92%); this result was similar with the findings of
Franco et al. where 86.52% of the children with TB were considered positive (≥ 5mm) (13); and much higher compared to the results obtained by Kiwanuka (6) where only 48% of the patients had induration ≥ 5mm. Our study showed 18.1% patients with not-detectible Mantoux reaction (< 5mm); in South American children with TB 13.5% (13); 25% reported by the American Thoracic Society (2) and up to 52% in African children (6). This high false-negative rate appears to be due to poor nutrition and general health, overwhelming acute illness, or immunosuppression (2).

Since malnutrition and TB are very often common for certain regions, the negative TST could lead to misdiagnosis of TB infection in such populations (8). However, a great majority of children in the community suffer from mild to moderate degrees of malnutrition, and an assessment of the TST status of the latter groups is of greater importance from the public health stands point (21). In two surveys conducted in Macedonia, between years 1982-1991 and 1992-1996, malnutrition was observed in 43.8% and 48.1% of the children with TB, respectively (12). In our study period 2003-2007, malnourishment (z-score <-2) was observed in 12.26% of the patients with TB, which was lower than the 63% underweight children (z-score <-2) with TB from a recent study by Kiwanuka (6). Taking into consideration the strong association between poverty, malnutrition and TB, these results show improvement of the socio-economic situation in Macedonia.

The nutritional status in children with TB, in our study, was not directly linearly related to the size of reaction to tuberculin (r=0.175, r²=0.031); the results were similar to the results obtained by Kiwanuka (r=0.27, r²=0.07) (6); and Ganapathy & Chakraborty (r=0.3) (22) which studied the influence on nutrition in a healthy child population. However, as in other studies, underweight children (z-score <-2) in this study were significantly more likely to have a negative Mantoux test (6, 24, 25).

Limitations of this study were the retrospective nature, with some loss of information in the medical records; this characteristic rendered the true evaluation of the nutritional status in children in relation to the calculation of the body mass index (weight and height for age). Weight for age (z-score) was the parameter used for evaluation of the nutritional status in patients.

CONCLUSIONS

In conclusion, there is no gender effect on the predominance of TB in the child population. The BCG vaccination policy in Macedonia and the BCG status of the child should not be a consideration in the interpretation of the Mantoux test. The strongly reactor tuberculin test results in children with TB show that the Mantoux technique is still the most useful tool for diagnosis of TB in children and the ≥5mm induration size should be considered as a cut-off point for demarcating the positive from negative cases. The Mantoux test in children with malnutrition is often negative and should be read by health providers with carefulness.

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