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Efficacy of Mantoux Test in Detecting Latent Tubercular Infection in Nephrotic Children

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Abstract

Background: Nephrotic syndrome (NS) is the most common kidney disease in children. These children are immunocompromised and very prone to infections like tuberculosis (TB) that can flare up during treatment. Latent tuberculosis (LTB) infection is not uncommon in nephrotic children and is difficult to diagnose, particularly due to the overestimation of the Mantoux Test (MT). The study aimed to analyze the ability of Mantoux test in detecting LTBI in nephrotic children.

Methods: This cross-sectional analytic study was conducted at the Department of Pediatric Nephrology of National Institute of Kidney Disease and Urology (NIKDU), Dhaka, Bangladesh from October 2019 to March 2021. A total of 91 BCG vaccinated nephrotic children aged 1-12 year were included in this study through convenient sampling using specific inclusion and exclusion criteria. Statistical analysis was done by using SPSS 23. Qualitative data were compared by chi-square test and quantitative data were compared by t-test.

Results: Considering the QuantiFERON TB Gold Plus test as reference the MT test showed 100% sensitivity, 75.9% specificity, 28.57% positive predictive value, 100% negative predictive value, and 78.02% accuracy.

Conclusion: Latent TB must be confirmed by QFT- plus test before giving treatment of nephrotic syndrome.

Key words: Nephrotic Syndrome, Latent Tuberculosis infection, Quanti FERON-TB Gold Plus Test, Mantoux Test

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Introduction:

Nephrotic syndrome (NS) is the most common pediatric kidney disease, that is characterized by proteinuria ≥40 mg/m^2/hour, hypoalbuminemia (3gm/dl), or edema[1].

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Worldwide approximately 2-16 per 100,000 children each year become affected by NS[2]. It is estimated that, incidence of NS in Bangladeshi, Indian, and Pakistani children is higher but the actual numbers of cases and rates of the disease remain unknown[3]. In children with NS, there may be a relationship with TB infection preceding the onset of NS or develop TB during the treatment of NS with glucocorticoid and/or immunosuppressive medications[4]. It is still one of the commonest causes of morbidity in children with NS in developing countries[5]. In Bangladesh, among all forms of TB cases, childhood TB cases were 4.01%[6]. In this country, the prevalence of LTBI among children after exposure to adults with smear-positive TB, as determined by tuberculin skin test, was 41.5% and children not having household TB contacts had the prevalence of LTBI was 9.2%. [7] LTBI is a mycobacterium tuberculosis infection without evidence of clinically manifested TB or a positive immunological test result in the absence of active TB[9]. Approximately, 10% of people will develop active TB disease but conversion to active TB disease following infection depends on several factors, the most important one being the immunological status of the host[6].Children with NS are immunodeficient during the disease and are at

greater risk of infections than the general population[10]. Most young children become infected after household exposure to an adult with sputum-positive TB. Children are usually negative for sputum smear, and also less infectious. Children with MTB infection are not ill and do not have symptoms of TB disease unless the disease is active. So, before giving immunocompromised drugs, MT should be done to find out LTBI. MT is called positive while more than 10 mm, but in immunocompromised patients its positive while ≥5 mm[8]. A false positive response may be seen in people who are BCG vaccinated due to cross-reactivity of protein present with certain atypical mycobacteria. So, its specificity is poor in BCG-vaccinated people. The sensitivity of MT varies depending on the size of the cut-off from 74% at 5 mm and 40% at 15 mm [11]. When the cut-off point is counted at 5 mm, 74% of patients are test positive who are disease positive and cut-off point 15 mm, 40% patients are tested positive who are disease positive. When there is a 5 mm tuberculin skin test (TST) reading in BCG vaccinated people it has a chance of a false positive reaction but when it is 15 mm it is likely to have mycobacterial tuberculosis infection[12].The two most used methods for diagnosis of LTBI include MT and interferon-gamma release assays (IGRAs). Both tests work on the principle of cell-mediated immunity[14]. For decades, the MT was the only test available for diagnosis of latent TB, though both false positive and false negative results can be found[15]. Whereas, positive IGRAs have been significantly better than the MT 10 mm and MT 5 mm strategies in predicting the development of active TB among high-risk individuals from TB-endemic countries[16]. IGRAs showed a high diagnostic value to detect LTB in immunocompromised children when performed in addition to TST so that they could be able to distinguish positive TST results caused by atypical Mycobacterial strain[13]. Hence, this study aimed to find the ability to detect latent tuberculosis by Mantoux test in nephrotic children.

Materials & Methods:

This cross-sectional analytical study was conducted at the Department of Pediatric Nephrology of National Institute of Kidney Diseases and Urology, Dhaka, Bangladesh from October 2019 to March 2021. A total of 91 nephrotic children (1-12 years of age) who were BCG vaccinated were enrolled in this study through convenient sampling. Nephrotic children with active tuberculosis, critically ill nephrotic syndrome patients having sepsis, shock, and electrolyte imbalance were excluded from the study. All the children underwent Mantoux Test (MT), X-ray chest and Gene X-pert test, and QuantiFERON TB Gold Plus (QFT- Plus) test. Nephrotic syndrome (NS) was defined as proteinuria ≥40 mg/m2/hour, hypoalbuminemia (3gm/dl), or edema. LTBI was defined as mycobacterium tuberculosis infection without evidence of clinically manifested TB or a positive immunological test result in the absence of active TB[9]. QFT-Plus test was the reference test. ≥5 mm cut-off value of MT was considered test positive[8].All necessary information was recorded using a pre-structured data sheet. Statistical analysis was done by using SPSS 23. Qualitative data were compared by chi-square test and quantitative data were compared by t-test. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated.

Informed written consent was obtained from all parents of the participants without any influence before sample collection. The study subjects were assured of their confidentiality and freedom to withdraw from the study anytime. Ethical clearance was obtained from the institutional ethics committee.

Results:

Among studied children the majority were in the age group of 5-8 years. The mean age was 6.96(±2.64) years in the MT positive group and 6.07(±3.06) (years) in the MT negative group. [Table 1].

Table-I

Distribution of MT positive and MT negative children by age (n=91).

Age (year)	MT positive (n=28)	MT negative (n=63)
d"4	5 (17.90)	21 (33.30)
5-8	17 (60.70)	27 (42.90)
9-12	6 (21.40)	15 (23.80)
Mean ±SD	6.96±2.64	6.07±3.06

In this study, 8 (8.8%) nephrotic children had latent TB as they were positive for the QFT-Plus test. 28 (30.8%) children were MT positive and 63 (69.2%) (n=63) were MT negative.

In this study, the majority of the study population were male but regarding the MT test female children

constituted 57.10% of MT positive and 28.60% of MT negative whereas 42.90% of male were MT positive and 71.40% of male were MT negative. [Figure 1]

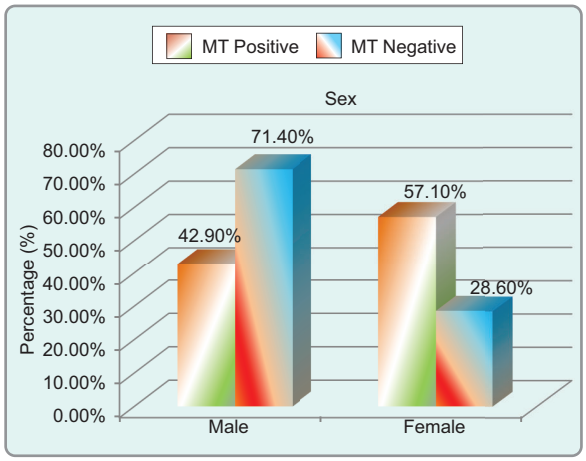

Figure 1: *Distribution of respondents by sex (n=91)*

The majority of the study participants of both MT positive (16,57.1%) and MT negative group (35, 55.6%) were urban residents. There was no statistically significant difference.

Regarding the residence (rural/urban), biochemical parameters - serum cholesterol, serum albumin, and spot protein creatinine ratio, urinary albumin, chest X-ray findings and Gene X-pert of sputum samples and the use of steroids there was no statistically significant difference between MT positive and negative group.

14% of MT positive cases had household TB contact. MT negative cases did not have such contact.

All the patients who were QFT-Plus positive tested positive for MT. There was statistically significant difference in detecting LTBI by MT and QFT-Plus test. [Table II]

Table-II

Frequencies of positive and QFT- Plus test result in the nephrotic children with positive and negative Mantoux test (MT) (n= 91)

Mantoux test	QFT-Plus test positive (n, %)	QFT-Plus test negative (n, %)	p value
Positive	8 (100)	20 (24.1)	<0.001
Negative	0	63 (75.9)	

In the study population, Mantoux test showed 100% sensitivity, 75.9% specificity, 28.57% positive predictive value, 100% negative predictive value, and 78.02% accuracy. [Figure 2]

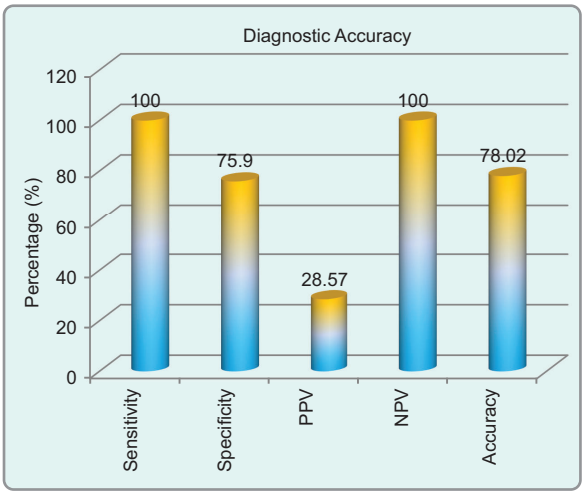

Figure 2: *Diagnostic accuracy of MT (Mantoux Test) in detecting latent TB among nephrotic children (n = 91).*

Discussion:

A total of 91 patients of nephrotic syndrome aged 1-12 year were included in this study, among them 28 (30.8%) patients were MT positive and 63 (69.2%) were MT negative. Biochemical parameters and steroid category were similar in both groups. All patients had negative Gene X-pert and normal X-ray chest. The majority of the children were in the age group of 5-8 years with an average age of 6 years. It was similar to the study done by Dossier et al. where the average age was 5.4 years.[17] Other studies done by Sarker et al. also showed male predominance.[18, 19] The children hailed from both urban and rural areas but a slight urban majority was observed. So, the demography of the study population reflects the urban bulk of people living in the capital which was quite understandable with other studies.[17,18] In a study, it was observed that infection was an important complication in children with NS, especially in developing countries.[5] The history of household contact with active TB patients was 14% in MT positive but in MT negative patients they had no H/O household contact with active TB patients which was quite relatable with the study done by Islam et al., [7]. Among 28 MT-positive children, only 8 (28.6%) were found positive for the QFT-

TB Gold Plus test while none of the MT-negative children was positive for the QFT-TB Gold Plus test. False positivity of MT occurs due to cross-reactivity with BCG (Bacilli Calmette Guerin) vaccinated people, infection by atypical mycobacteria, and error in measuring the size of induration of the skin reaction. [20] The frequency of latent TB in nephrotic syndrome was 8.8% confirmed by QFT- plus test. A study conducted by Lighter et al. observed only 23% of MT-positive children having QFT-plus test positivity and 77% of children with positive TST results had a negative QFT test, which indicated a lack of specificity of TST.[21] considering the QFT-plus test as confirmatory, the MT test showed 100% sensitivity, 75.9% specificity, 28.57% positive predictive value, 100% negative predictive value, and 78.02% accuracy. In another study conducted on 311 patients, out of them 177 (36.38%) were MT positive (≥15mm) and the sensitivity of MT was 95.86%, specificity was 95.18%, positive predictive value 91.53%, negative predictive value 97.69%. From their study, it can be concluded that the MT test had high sensitivity and specificity to the diagnosis of tuberculosis when results were ≥15mm. but in this study, MT result ≥5mm was counted as positive and had a low specifity75.9%. So, another more specific and gold standard test considering QFT-TB Gold plus test was done as a confirmatory test. [12] Another author had done a systematic review and meta-analysis on the utility of interferon-gamma release assays for the diagnosis of MTB infection in children and observed sensitivity of TST was 100%, specificity was very low, having 58%. Whereas specificity of QFT was 100%, sensitivity was 93% among the immunocompromised children and the author concluded that IGRAS showed high diagnostic value in childhood TB, when performed in addition to TST. [22]

Limitations of the Study

The study was conducted in only one hospital with small sample size. So, the results may not represent the whole community.

Conclusion:

Latent TB is not uncommon in children suffering from nephrotic syndrome and conventional MT test is not conclusive. So latent TB must be confirmed by QFT-plus test before giving corticosteroids.

Conflict-of-interest: None

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