Prevalence of Tuberculosis among Filipino Juvenile Idiopathic Arthritis Patients in a Tertiary Care

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ABSTRACT

Background. The administration of tumor necrosis factor-alpha (TNF-α) antagonists poses a risk of reactivation of latent tuberculosis among patients with Juvenile Idiopathic Arthritis (JIA). The Mantoux skin test is the currently available and most commonly used screening test for latent tuberculosis (TB) infection.

Objective. To determine the prevalence of tuberculosis among Filipino children with JIA.

Study design. Descriptive, cross-sectional study

Methods. Twenty-eight children with JIA were studied. Mantoux skin testing using PPD 5 TU was performed and skin reaction measured after 48 to 72 hours. A negative PPD was defined as an induration of <5 mm.

Results. Of the 28 patients included in the study, 10 (35.7%: 95% CI: 20.6-54.2) had positive Mantoux skin tests – 7 had latent tuberculous infections, and 3 had active TB disease.

Conclusion. The prevalence of tuberculosis among JIA patients was estimated at 36% and could be as high as 54%. The Philippine Rheumatology Association (PRA) guidelines for the screening and treatment of latent TB infection should be enforced to decrease the likelihood of its reactivation prior to use of biologic agents.

Key Words: juvenile idiopathic arthritis, tuberculosis, Mantoux test, prevalence, latent tuberculosis.

Introduction

Patients with Juvenile Idiopathic Arthritis (JIA) are at an increased risk for the development of TB primarily because of altered cell-mediated immunity. This is especially important among patients in the Philippines where the National Prevalence Survey undertaken by the Tropical Disease Foundation in 1997 showed a 42% overall prevalence rate of active pulmonary TB in urban and rural communities combined, and 16.1% in children aged 5-9 years.[1,2] This risk is further confirmed by the WHO Global TB Report of 2010 which showed that the Philippines has the ninth highest burden of tuberculosis in the world. The country lists tuberculosis as the sixth leading cause of morbidity and mortality with an estimated all cases prevalence of 293/100,000 (0.29%).[3]

Among JIA patients, the risk of TB is magnified as they have abnormalities in the immune system that activate inflammatory processes. Juvenile idiopathic arthritis is characterized by the production of auto-antibodies, immune complexes and complement. T-cell and humoral abnormalities activate the inflammatory cascade, resulting in widespread inflammation in the joints and synovial fluid; as well as in extraarticular organs (e.g., eyes, liver, lymph nodes).[4] In addition, there is an association between the chemotherapeutic agents used in rheumatic diseases and an increased risk of TB infection. These agents include disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, anti-malarials, and leflunomide; corticosteroids; cytotoxic combinations; and newer biologic DMARDs in the form of tumor necrosis factor-alpha (TNF-α) antagonists.[5-9]

Recent studies that monitored the adverse events related to the use of TNF-α antagonists among patients with rheumatologic disease showed an increased risk of reactivation of latent tuberculosis infection, further escalating active TB rates.[10,11] Strategies are thus advocated to screen for and treat latent TB infection prior to treatment with TNF-α antagonists.[12] The Philippine Rheumatology Association has formulated national guidelines for screening patients for tuberculosis prior to the administration of biologic therapy[13] to identify patients at increased risk of developing tuberculosis.

Early detection of TB infection and institution of appropriate chemoprophylaxis and treatment decrease the risk of spread of transmission and progression to active disease with its associated morbidity and mortality.[14] The Mantoux skin test, with its sensitivity of 87% and specificity of 80%,[15] is the currently available and most commonly used

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screening test for latent tuberculosis infection in the Philippines.[16] However, there are no local studies using the Mantoux test in determining the prevalence of tuberculosis among Filipino children with JIA.

Methods

This was a descriptive, cross-sectional study conducted at the pediatric rheumatology clinic of a tertiary hospital. Twenty-eight patients with juvenile idiopathic arthritis who gave assent and whose parents/guardians gave written informed consent were included. A baseline interview and physical examination was performed to gather demographic and clinical data. This included the age, sex, prior TB infection and treatment, history of TB exposure, history of BCG vaccination, symptoms of TB infection, presence or absence of a BCG scar, duration of illness, concomitant medications and disease activity. Active JIA disease was defined as having active synovitis and/or active extra-articular features requiring drug therapy, or manifesting with increasing number of joint involvement irrespective of drug therapy. Inactive disease was defined as having no evidence of active synovitis; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR and/or CRP; and no disease activity as measured by physician global assessment.[17,18]

Tuberculin skin test: Mantoux skin testing was performed using 5 TU PPD. The skin reaction was read after 48 to 72 hours. A negative PPD was defined as an induration of <5 mm, while a positive PPD was defined as an induration of ≥5 mm for patients with juvenile idiopathic arthritis, who were considered a high-risk group because of their immunocompromised state and the medical treatments they receive.[16] The gathered data was encoded in case report form.

For subjects positive for Mantoux test, further history, chest radiograph and appropriate laboratory examinations were performed to rule out active tuberculosis. Patients with latent tuberculous infection were started on isoniazid or rifampicin, and combination therapy for those with active TB disease.[14,16] All personal and clinical data gathered were kept confidential.

Definition of terms

Latent tuberculous infection (LTBI) was defined as infection with *M. tuberculosis* in a person with a positive Mantoux test result but no clinical or chest x-ray findings of TB disease or whose chest x-ray showed evidence of healed infection. Evidence of healed infection included granulomas or calcifications in the lungs, hilar lymph nodes or both.[19]

Active tuberculosis disease in children was diagnosed when 3 out of the 5 following criteria were fulfilled: (1) exposure to an adult or adolescent with active tuberculosis disease; (2) positive Mantoux tuberculin test; (3) signs and symptoms suggestive of tuberculosis (history of recent weight loss or failure to gain weight, cough and/or wheezing for >2 weeks, and prolonged unexplained fever of >2 weeks); (4) abnormal chest radiograph suggestive of tuberculosis; and (5) laboratory findings suggestive of tuberculosis (histological, cytological, biochemical, immunological and/or molecular).[19]

Statistical Analysis: The prevalence of tuberculosis (including latent tuberculous infection and active TB disease) among JIA patients was estimated at 95% confidence level using adjusted Wald method. A child was considered positive for latent tuberculosis if he/she had a positive tuberculin skin test. Active TB disease, on the other hand, was defined as a positive tuberculin test with chest radiograph and/or microbiologic studies confirming active disease.

Results

Mantoux skin testing was performed in 28 Filipino children with JIA. Their demographic data and baseline clinical characteristics are summarized in Table 1. The mean age was 9.7 +/- 3.5 years. The youngest was 2 and the oldest was 17.5. Forty-three percent were males. There was history of BCG vaccination in all patients, with BCG scar noted in 89.3%. There was TB exposure in 8 and history of treatment with anti-Koch's in 9 patients. Of those who received treatment, 5 were treated for pulmonary TB, 3 for symptoms of prolonged fever and weight loss with no chest x-ray and microbiologic findings suggestive of tuberculosis at the time that JIA was not yet considered, and 1 for 2 months for possible TB arthritis but eventually ruled out.

Table 1. Demographic and clinical characteristics of JIA patients (n=28)

Demographic Features	
Age	
Mean, years	12.3
Range, years	2 - 17.5
Male: Female	3:4
Disease duration	
Mean, years	3.4
Range, years	0.2 - 10
Clinical characteristics	**Number of patients (%)**
BCG vaccination	28 (100)
BCG scar	25 (89.3)
TB exposure	8 (28.6)
History of TB treatment	9 (32.1)
JIA patients with active disease	22 (78.6)
Methotrexate use	12 (42.8)

In these patients with JIA, the mean disease duration was 3.4 years and 22 had active disease. Methotrexate, a disease-modifying anti-rheumatic drug, was used by a total of 12 patients in a mean dose 7.4 (range, 4.3 to 10) mg/BSA/week for a mean duration of 9.6 (range, 0.8 to 72) months. It was used alone in 5 (17.9%) patients and in combination with naproxen in 7 (25%).

Ten of the 28 patients (35.7%) had positive PPD skin test (95% CI, 20.6% to 54.2%). On further investigation (Table 2), 7 had latent tuberculosis, and 3 with active pulmonary tuberculosis.

Table 2. Tuberculous infection among JIA patients

	Number of patients	Percentage	95% CI
Latent TB	7	25	-
Active TB	3	10.7	-
Total	10	35.7	20.6 – 54.2

Discussion

In the Filipino pediatric population, the problem of TB infection in urban poor settlements is worse with a prevalence rate of 39% compared with the national survey prevalence of 16.1%.[2,20] Among immunocompromised patients, studies show that tuberculous infection has a prevalence rate of 45% among children with acute leukemia,[21] 56% among those with type I diabetes mellitus,[22] and 46.2% among children with idiopathic nephrotic syndrome.[23] The results of this study showed that juvenile idiopathic arthritis patients had a comparable rate at 35.7%. This can even go as high as 54%.

Among the subjects who had negative PPD, 8 out of 18 were on methotrexate. While those with positive PPD, 4 out of 10 were on methotrexate. Approximately the same proportion of patients in both groups had history of methotrexate use. To the knowledge of the authors at the time of this study, there is no published evidence indicating that methotrexate use increases the risk of TB infection in JIA. Our patients on methotrexate can be further monitored for possible susceptibility to mycobacterial infections.

There is still a subset of JIA patients who do not respond to conventional therapies. Treatment of refractory cases has emerged as a problem among rheumatologists. Studies reveal that the pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-α), which correlates with disease activity, is found to be elevated in the blood and synovial fluid of children with juvenile idiopathic arthritis.[24] TNF-α has then become a target of newer biologic DMARDs.

In our country, TNF antagonists are available in the form of etanercept and infliximab. Anti-TNF agents inhibit the ability of macrophages to phagocytose and kill *Mycobacterium*. Granuloma formation, which decreases the risk of TB dissemination in the host by walling off the mycobacteria, is also inhibited.[25] The protective mechanism of the TNF-α is suppressed. These findings have prompted the Philippine Rheumatology Association (PRA) to form a task force to develop practice guidelines for TB screening prior to the administration of biologic agents.[13] The guidelines emphasize the need to screen the patient and all household and close contacts using the Mantoux test for latent TB and chest radiograph for active TB. All cases of active and latent TB should be treated appropriately. It is recommended that biologic therapy be initiated after the full course of anti-TB therapy in patients with active TB, or at least 4 weeks after starting TB prophylaxis in patients with latent TB. Furthermore, candidate patients exposed to household contacts with TB, regardless of tuberculin skin test result, should be given TB prophylaxis prior to commencing biologic therapy.

The high proportion of JIA patients with latent TB in our study further highlights the need to screen our patients and to treat them properly to decrease the risk of progression and spread of the disease.

Conclusion and Recommendation

There is a 35.7% prevalence rate (95% CI, 20.6% to 54.2%) of tuberculous infection among pediatric patients with juvenile idiopathic arthritis based on the Mantoux skin test.

Pediatric JIA patients are a high risk group for developing TB infection. They will greatly benefit if treated appropriately once detected. The Philippine guidelines for the screening of tuberculosis prior to the use of biologic agents among patients with rheumatologic diseases should be enforced to decrease the likelihood of reactivation of latent tuberculosis.

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