

Clinical characteristics of tuberculosis in children in the north of Taiwan

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Tuberculosis (TB) in children is an endemic and sometimes life-threatening disease in Taiwan. This study analyzed the clinical characteristics of a total of 112 children with TB managed in a referral children's hospital in the north of Taiwan between 1998 and 2002. The diagnosis of TB was made by either a positive result of culture, acid-fast stain, histopathology, or polymerase chain reaction (PCR). Tuberculin skin test was positive (indurations ≥ 10 mm) in 73% of 63 patients tested. The male-to-female ratio was 0.93 (54/58), and the mean age was 10.7 years. Thirty one percent of children were younger than 6 years of age, 12% were 6 to 12 years old, and 57% were older than 12 years. Fifty percent (50/100) of these children had household members with TB; 29.2% (31/106) were aboriginal; 93% had received Bacille Calmette-Guérin (BCG) vaccine. Isolated pulmonary TB was diagnosed in 65 cases (58%), extrapulmonary TB in 25 (22%), and combined intra- and extrapulmonary TB in 22 (20%). Fever was not a presenting symptom in 30.4% of children, was low grade ($<38.5^{\circ}\text{C}$) in 23.2% and was high grade ($\geq 38.5^{\circ}\text{C}$) in 46.4%. The mean duration of fever was 13.9 days. Patients with combined intra- and extrapulmonary TB had a significantly longer hospital stay ($p < 0.001$), a higher peak body temperature ($p < 0.001$), and a longer duration of fever ($p = 0.024$). Patients with extrapulmonary TB had a significantly lower incidence of fever ($p = 0.001$), a lower segment count ($p = 0.007$) and a lower serum C-reactive protein level ($p = 0.019$). Ventriculoperitoneal shunt insertion was performed in 8 of 12 cases with central nervous system involvement. Among 21 cases of TB osteomyelitis, tibia (33%) and spine (33%) were the most common sites of involvement. The overall mortality rate was 3.6% (4/112). Extrapulmonary TB and combined intra- and extrapulmonary TB were more commonly seen in children with a younger age and in those who had not received BCG vaccination. This study found that household members with TB history and aboriginal ethnicity were strongly associated with TB in Taiwanese children. Multidrug-resistant TB was uncommon in children born before the year 2003.

Key words: BCG vaccine, ethnology, risk factors, tuberculin test, tuberculosis

According to data from the World Health Organization (WHO), about 2 billion people are currently infected with *Mycobacterium tuberculosis* (one-third of the world population). Each year, there are approximately 9 million new cases of tuberculosis (TB) worldwide, and 3 million deaths from the disease. TB is a more serious problem in developing countries, which account for 95% of worldwide TB cases, and 99% of worldwide TB mortality [1].

Taiwan is a country located in northeastern Asia with a relatively high prevalence of TB. Since the 1960s, the

mortality rate and prevalence of TB have declined, subsequent to mass vaccination with Bacille Calmette-Guérin (BCG) and the introduction of effective antituberculous drugs. TB has not been on the list of the leading causes of death in Taiwan since 1985. However, the incidence of TB in Taiwan remains high, particularly in aboriginal people [2]. According to a report from the Center for Disease Control (CDC) of Taiwan in 2002, the incidence and mortality rate of TB was 74.6 and 5.68 per 100,000 population, respectively [3].

The incidence of TB in children is a marker of the recent transmission in the population, and levels of drug resistance in children are indicators of patterns of resistance currently being transmitted. In addition, disease patterns are different in children compared with those in adults. One-third of children infected with

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M. tuberculosis will develop symptomatic disease, while the lifetime incidence of symptoms in infected adults is 5-10% [4]. The lack of familiarity with the spectrum and changing trends in risk factors for TB in children may lead to delayed diagnosis. The purpose of this study was to analyze the clinical and radiologic manifestations of childhood TB at a referral center in the north of Taiwan.

Materials and Methods

The medical records of children aged less than 18 years with TB managed in Chang Gung Children's Hospital in the north of Taiwan from January 1998 to December 2002 were retrospectively reviewed. The diagnosis of TB was made based on a positive result of culture, acid-fast stain, histopathology, or polymerase chain reaction (PCR) and clinical presentation. Data including demographic characteristics, presenting symptoms, history of BCG vaccination, lesion site, laboratory data, image findings, diagnosis, tuberculin skin test, risk factors, treatment, and outcome were collected. A total of 112 children were included in this study. TB was categorized according to the site of involvement as isolated pulmonary, extrapulmonary TB, or combined intra- and extrapulmonary. Pulmonary TB was defined as disease confined to lungs, pleura, and intra-thoracic lymph nodes. Extrapulmonary TB was defined as disease beyond the thorax with negative findings on chest radiograph and sputum (or gastric aspiration) culture. Combined intra- and extrapulmonary TB was defined as the presence of intra- and extrapulmonary disease

involvement. The chest radiographs were interpreted by radiologists and pediatric pulmonologists. Tuberculin skin test was done using the purified protein derivative RT23 intradermal injection method (2 tuberculin units, 0.1mL) and interpreted within 48-72 h.

Statistical analysis

Statistical analysis was performed using chi-squared test and ANOVA using SAS software (Version 8.2; SAS Institute, Cary, NC, USA). Data are shown as mean \pm standard deviation or number (percentage). A *p* value less than 0.05 was considered statistically significant.

Results

Demographic data

A total of 112 children with TB were included in this study. TB was confirmed by positive culture (76.8%, 86/112), acid-fast stain (60.7%, 68/112), histopathology (30.4%, 34/112), or PCR (12.5%, 14/112). The male-to-female ratio was 0.93 (54/58), and the mean age was 10.7 ± 6.4 years (range, birth to 18 years). The age distribution of the children is shown in Fig. 1. The majority (57.1%) of the children with TB were older than 12 years and less than 18 years, the next largest group (31.2%) was younger than 6 years of age, while 11.6% of children were between 6 and 12 years of age.

There was a predominance of males among children below 6 years of age (Table 1) [*p*=0.105]. Fifty percent of 100 children that could be traced were from a household with a TB history. Twenty nine percent of 106 children were aboriginal, among whom a household

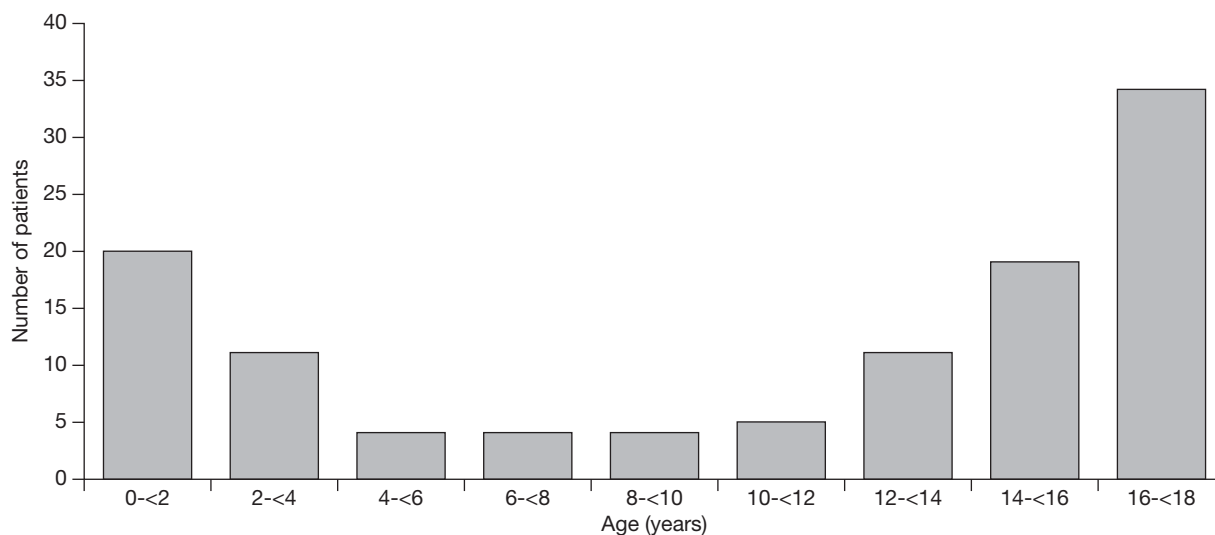


Fig. 1. Age distribution of 112 children with tuberculosis at Chang Gung Children's Hospital between 1998 and 2002.

TB history could be traced in 20 children (64.5%; $p=0.03$).

Underlying diseases included prematurity (gestation age ≤ 36 weeks) in 4 children, autoimmune disease in 3 (systemic lupus erythematosus, juvenile rheumatoid arthritis, and Behçet's disease, respectively), thalassemia in 2, malignancy in 2 (leukemia, primitive neuroectoderm tumor), and 1 patient had end-stage renal disease treated with chronic hemodialysis.

BCG vaccination

Among the 107 children in whom BCG vaccination history could be traced, 100 (93%) had received BCG vaccination. Among the 7 children who had not received BCG vaccination, 5 had combined intra- and extrapulmonary TB ($p=0.002$); the age of onset was from 1 month to 2.8 years and the mean age was 1 year. Prematurity and low birth weight were the most common associated conditions in children without BCG vaccination.

Tuberculin skin test

Tuberculin skin test was performed in 63 cases and indurations no less than 10 mm were noted in 46 cases (73%), and more than 15 mm in 27 cases (42.9%). Children more than 12 years of age were significantly reactive to tuberculin skin test ($p=0.018$; Table 1).

Clinical manifestations

TB was classified as isolated pulmonary in 65 (58%) cases, extrapulmonary in 25 (22.3%) cases, and combined intra- and extrapulmonary in 22 (19.6%) cases. The incidence of extrapulmonary TB was significantly higher in children less than 6 years of age, while 73% of the children older than 12 years of age had isolated pulmonary TB ($p=0.001$; Table 1).

Multiple lobe involvement was found in 35% of patients with isolated pulmonary TB, and the 2 most common sites in these patients were the right upper lobe (34%) and the left upper lobe (24%). Consolidation (27%) and infiltration (24%) were the 2 most common patterns on chest X-ray in children with pulmonary TB.

Bone and/or joint (35%), lymph node (24%), and central nervous system (21%) were the 3 most common sites of extrapulmonary involvement. Among the 21 cases with bone and/or joint involvement, tibia (33%) and spine (33%) were the 2 most common sites.

Fever was noted in 80 patients, with a mean duration after onset of 13.9 ± 19.3 days. Fever was not an initial manifestation in 32 patients (29%), including 16 with isolated pulmonary TB and 14 with extrapulmonary TB ($p=0.001$). Fever was not found in 12 (70%) of the 17 patients with bone involvement alone.

Patients with combined intra- and extrapulmonary TB had a significantly longer hospital stay, a higher peak body temperature, and a longer duration of fever. Patients with extrapulmonary TB had a significantly lower incidence of fever, a lower segment count and a lower serum C-reactive protein level (Table 2).

Outcome and mortality

Four patients (3.6%) died during the study period. Two of them had combined intra- and extrapulmonary TB with meningitis and pericarditis, respectively. The other 2 had isolated pulmonary TB, including 1 with underlying malignancy (primitive neuroectoderm tumor). Miliary TB was found in 3 of 4 patients with pulmonary involvement. The mean age of the fatal cases was 15.2 years (range, 13.4 to 17.5 years). Pneumothorax, pericarditis, sepsis, and underlying malignancy were the causes of death.

Table 1. Comparison of gender, tuberculin skin test results, tuberculous disease category and household tuberculosis (TB) history among children with TB in different age groups

Characteristics	Total [no. (%)]	<6 years [no. (%)]	6~12 years [no. (%)]	>12 years [no. (%)]	p
Case number	112 (100)	35 (31)	13 (12)	64 (57)	
Male:Female	54: 58	22:13	6:7	26:38	0.105
Tuberculin skin test	63	20	8	35	0.018
<10 mm	17 (27)	6 (35.3)	6 (35.3)	5 (29.4)	
10~15 mm	19 (30.2)	8 (42)	0 (0)	11 (58)	
>15 mm	27 (42.8)	6 (22.2)	2 (7.4)	19 (70.4)	
TB disease					
Isolated pulmonary	65 (58.0)	11 (31.4)	7 (53.8)	47 (73.4)	0.001
Extrapulmonary	25 (22.3)	15 (42.9)	3 (23.1)	7 (11.0)	
Combined	22 (19.6)	9 (25.7)	3 (23.1)	10 (15.6)	
Household TB history	50/100 (50)	17/28 (61)	5/13 (38)	28/59 (47)	0.345

Table 2. Comparison of clinical presentations and laboratory findings of 112 children with tuberculosis (TB) by tuberculous disease category

Characteristics	Isolated pulmonary No. (%)	Extrapulmonary No. (%)	Combined No. (%)	<i>p</i>
Number (%)	65 (58.0)	25 (22.3)	22 (19.6)	
Age (years)	12.8 ± 5.6	6.47 ± 6.0	9.21 ± 6.8	0.001
Household TB history (50/100)	29/63 (46)	8/18 (44)	13/19 (68)	0.22
No previous BCG (7/107)	1/63 (1.6)	1/24 (4.2)	5/20 (25)	0.002
PPD test ≥10 mm (46/63)	31/37 (84)	9/13 (69)	6/13 (46)	0.4
Hospital stay (days)	12.7 ± 15.7	14.6 ± 12.3	32.2 ± 29.4	<0.001
Body temperature (BT)				
Peak BT (°C)	38.5 ± 1.2	37.8 ± 1.0	39.2 ± 0.8	<0.001
Fever duration (days)	11.6 ± 16.7	9.5 ± 18.0	23.2 ± 22.9	0.024
No fever (<38°C)	19 (29)	14 (56)	1 (4.6)	0.001
Low-grade fever	18 (28)	5 (20)	3 (13.6)	
High-grade fever (≥38.5°C)	28 (43)	6 (24)	18 (81.8)	
Cough	61 (94)	2 (8)	11 (50)	0.001
Hemoptysis	19 (29)	0	1 (4.55)	0.001
Laboratory data				
WBC (/mm ³)	10986 ± 4743	11088 ± 3621	12009 ± 4789	0.65
Segment (%)	70.0 ± 16.9	55.5 ± 20.9	68.5 ± 18.2	0.007
Lymphocyte (%)	20.7 ± 15.9	35.0 ± 20.6	22.4 ± 16.2	0.006
Band (%)	0.4 ± 1.0	0.1 ± 0.3	0.55 ± 1.33	0.3
Hb (g/dL)	11.4 ± 1.7	11.5 ± 1.7	10.5 ± 1.6	0.057
Platelet (10 ³ /mm ³)	366 ± 133	378 ± 100	415 ± 139	0.32
CRP (mg/L)	62.5 ± 63.6	17.7 ± 31.9	59.7 ± 52.0	0.019
AST (U/L)	34.1 ± 32.9	32.9 ± 22.2	32.8 ± 22.3	0.98
ALT (U/L)	73.8 ± 86.1	58.3 ± 86.3	31.4 ± 43.43	0.39

Abbreviations: BCG = Bacille Calmette-Guérin; PPD = purified protein derivative; WBC = white blood cells; Hb = hemoglobin; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase

Among the 12 patients with central nervous system involvement, ventriculoperitoneal shunt was inserted in 8 (67%), mild to moderate psychomotor retardation was found in 5, severe psychomotor retardation with long-term confinement to bed was found in 2, visual impairment was noted in 3, and only 2 of these patients had an uneventful recovery. One case died from the complications of deep coma with sepsis.

Primary drug resistance

The rate of primary resistance of isolates to at least 1 anti-TB drug was 17.5% (15/86). Resistance to 1 class of anti-TB drug was found in 12 isolates, including resistance to pyrazinamide (PZA) in 7, resistance to streptomycin (SM) in 3, and resistance to ethambutol (EMB) in 2. Three isolates (3.5%) were resistant to 2 anti-TB drugs [isoniazid (INH) and SM, PZA and EMB, and EMB and kanamycin (KM), respectively]. Multidrug-resistant (MDR) TB against both INH and rifampin (RIF) was not isolated in this study. The resistance rate to PZA, SM, EMB, INH, and KM was 9.3%, 4.7%, 4.7%, 1.2% and 1.2%,

respectively. There was no relationship between resistant strains and fatal cases in this study.

Discussion

Despite the gradual worldwide decrease in morbidity and mortality due to TB since 1960, there has been an apparent resurgence of the incidence of TB during the 1990s [5]. Over the 5-year period of this study, more cases of childhood TB were noted compared with a study by Wong et al during 1994-1999 in the same hospital [6]. The most common cause of the rising incidence of TB in other parts of the world is concomitant human immunodeficiency virus (HIV) infection; however, this has only been a comparatively recent influencing factor on incidence for residents of Taiwan. The most likely explanations for the higher incidence of childhood TB include the widespread use of immunosuppressive agents [7], the high incidence of immunodeficient disease, and increased awareness by pediatricians of the high prevalence of TB.

In this study, a “U” (bimodal)-shape age distribution of TB was found in children. The first peak in prevalence was among children less than 4 years old and the second was in children greater than 12 years old. Previous studies have found that pulmonary involvement accounted for 70-80% of cases of TB [8-10]. In this study, pulmonary involvement was noted in 77.6% of patients, 19.6% having combined extra- and intrapulmonary involvement, and 58% having intrapulmonary involvement alone. Children less than 6 years of age had a higher incidence of extrapulmonary TB (42.9%) and combined intra- and extrapulmonary TB (25.7%) [Table 1]. The prevalence of pulmonary TB was higher in children older than 12 years of age (73.4%).

Previous studies from the United States found that extrapulmonary TB accounted for 25% of total TB cases less than 15 years of age, and about 15% of adult TB (>18 years) [8,11]. Recently, the proportion of extrapulmonary TB has increased to 20% of total TB cases in the United States [12,13]. The most likely explanation for the higher incidence of childhood extrapulmonary TB in recent years is the increased awareness by pediatricians of the presence of the disease, commensurate with an increasing worldwide awareness of the potential for such infection.

TB of the superficial lymph nodes is the most common form of extrapulmonary TB among children, accounting for approximately 46-67% of cases in previous studies from the US [14,15]. In our study, lymph node involvement was found in only 24% of extrapulmonary TB; this discrepancy may be due to differences in inclusion criteria, since only hospitalized cases were included in this study.

Skeletal TB was previously considered a rare extrapulmonary manifestation and was reported in only 1-3% of all TB cases, accounting for approximately only 5-10% of extrapulmonary TB cases in studies from the United States [11,15]. Recently, the proportion of bone and/or joint TB has progressively increased to 27% and was the most common site of the extrapulmonary TB in a study from the United States [13]. Our study had similar findings, with bone and/or joint involvement accounting for 35% of extrapulmonary TB.

Spinal TB is common and is seen in 50-65% of cases with skeletal TB [11,16,17]. Some studies have reported peripheral long bones to be more commonly involved than the spine in young TB patients in developing countries [16,18-22]. In this study, the tibia (33%) and spine (33%) were the 2 most common sites of bone and/

or joint involvement. Among the 21 cases with bone and/or joint TB in this study, all were initially overlooked by pediatricians and orthopedists, and diagnosis was delayed until open biopsies or curettage were performed by orthopedic surgeons in the hospital. Possible factors responsible for the delay in diagnosis in these cases include the absence of pulmonary disease, the presence of few systemic symptoms and only isolated peripheral joint involvement. Hence, pediatricians and orthopedists should be alert to the potential for tuberculous infection in children who present with an unexplained medical course involving the bones and joints, particularly in patients living in TB-endemic areas.

In Taiwan, the aboriginal people account for about 1.7% of the total population [23]. In the regions of our hospital service (Taoyuan, Hsinchu, Miaoli), aboriginals account for 2.1% (60,361/2,811,188) of the population. In this study, 29% of 106 children with TB were aboriginal, leading to a risk of TB that was 14 times higher than that in non-aboriginal children. Low socioeconomic status, poor access to medical treatment and poor compliance with medication are some of the reasons generally considered to account for the high TB incidence in aboriginal people in Taiwan. Recently, numerous studies [24,25] have suggested that some patients have a genetic predisposition to TB infection. Whether genetic factors contribute to the high incidence of TB in the aboriginal population of Taiwan remains to be investigated.

In this series, household TB history was found in 50% of children with TB, particularly in those patients younger than 6 years and in cases of combined intra- and extrapulmonary TB. These results suggest that most children, especially those with young age or severe clinical presentations, acquired *M. tuberculosis* infection in the household.

Evaluation for the presence of acid-fast bacilli (AFB) in sputum, body fluids or surgical specimens is the first step in screening for TB. However, almost 40% of the specimens in this study were initially negative on AFB staining. The diagnosis of TB was not confirmed until a positive result of either culture, PCR or histopathological finding was evident several days to months later. Empirical antituberculous therapy should be given to patients with a high suspicion of TB despite initial negative AFB findings in clinical specimens.

No MDR organisms were isolated, and the drug resistance rate was relatively low compared with that of adult TB patients in Taiwan. The reported rate of primary resistance of *M. tuberculosis* to at least 1 anti-TB drug

in adult TB patients in Taiwan has ranged from 28-35% in recent reports [26,27]. Comparison of our results with recent findings for adult TB patients in Taiwan revealed that children with TB have a high rate of fever (71% vs 47%), and a low rate of mortality (3.5% vs 6.4%) [27].

In conclusion, risk factors significantly associated with extrapulmonary TB and combined extra- and intrapulmonary TB were age younger than 6 years and lack of BCG vaccination. Combined intra- and extrapulmonary TB had a significantly higher incidence of high fever, a longer duration of fever, a longer hospital stay, and a higher C-reactive protein level (≥ 60 mg/L). Most children with TB had a household TB history. In this series from Taiwan, the risk of TB infection in aboriginal children was 14 times higher than that in non-aboriginal children. No MDR *M. tuberculosis* isolate was identified in this series.

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