

Extra Pulmonary Tuberculosis in Children: Two Years Study

Nooshin Baghaie, Soheila Khalilzade, Mohammad Reza Boloursaz*, Amir Ali Khodayari, and Ali Akbar Velayati

Pediatric Respiratory Diseases Research Center, National Research Center of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran

Received: 14 May 2009; Received in revised form: 11 Aug. 2009; Accepted: 11 Sep. 2009

Abstract- Tuberculosis (TB) is an important health problem in developing countries, with varying clinical presentations depending on the organs/systems involved. To study the spectrum of clinical and paraclinical aspects of extra pulmonary TB in children suffering from pulmonary TB. This study has been carried out on 65 children with tuberculosis, admitted in TB wards of National Research Institute of Tuberculosis and Lung Disease (N.R.I.T.L.D) during 2004-2006. All patients were investigated according to specific diagnostic criteria including; history of contact with TB patient, clinical manifestations, radiological findings, tuberculin test and bacteriologic or pathologic results and after confirmation, treatment was administered. Out of 65 cases, 14 had different types of extra pulmonary tuberculosis, and data concerning following factors were studied: age, gender, race, site of involvement, bacteriology, pathology, ADA (ascitic fluid), PCR (tissue specimens), history of close contact, HIV tests (ELISA), tuberculin test, radiological findings, and immunological studies (in disseminated TB). Of 14 cases, 8 were girls and 6 were boys with mean age of 8.75 ± 4.2 . Nine patients were Iranian and 5 were Afghan. History of close contact was detected in 4 cases. Type of involvement was: 5 cervical adenitis, 3 osteoarticular disease, 2 peritonitis and 2 disseminated form of tuberculosis, one pericarditis, one renal tuberculosis. Radiological findings showed 4 pulmonary disease and 3 osteoarticular involvement. Tuberculin skin tests greater than 15 mm observed in 5 cases, 9 patients had 0-5 mm induration. 4 cases had concomitant pulmonary and extra pulmonary involvement. Positive AFB in gastric lavage was recognized in 4 cases, in which 3 showed positive cultures for MTB. Pathological examinations in 10 cases revealed granuloma with caseation compatible with tuberculosis, five in lymphadenopathy, three in osteoarticular, two in abdominal tuberculosis. According to this study, 20% of patients had extra pulmonary involvement, which is comparable to other reports (20-25%) and TB lymphadenitis is the most common form of presentation.

© 2010 Tehran University of Medical Sciences. All rights reserved.

Acta Medica Iranica 2010; 48(4): 239-243.

Key words: *Mycobacterium tuberculosis*; tuberculosis; pediatrics

Introduction

Tuberculosis (TB) constitutes the main infectious cause of death and morbidity worldwide (1).

It has been suggested that several factors have been implicated in the current resurgence of tuberculosis, including the acquired immunodeficiency syndrome (AIDS) epidemic, the emergence of multiple drug resistant *Mycobacterium tuberculosis* (MTB) strains, poverty, immigration, homelessness, and inadequate tuberculosis control programmes (2).

An estimated 1.3 million cases of tuberculosis and 450000 associated deaths occur annually in children (2).

Extra pulmonary tuberculosis accounts for up to one third of all cases (3,4).

The most striking feature of tuberculosis in patients with HIV infection is the extremely high frequency of extra pulmonary involvement usually with concomitant pulmonary involvement.

Children show a higher predisposition to the development of extra-pulmonary tuberculosis (4). The impact of extra pulmonary tuberculosis is greatest among infants and young children who tend to develop more severe extra-pulmonary disease, especially meningitis and military tuberculosis (4-6).

A significant increase in number of children with tuberculosis has been noticed in other studies (7).

*Corresponding Author: Mohammad Reza Boloursaz

Pediatric Respiratory Diseases Research Center, National Research Center of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 21 27122004, Fax: +98 21 21609549, E-mail: Boloursazm@yahoo.com

In particular, the annual incidence of childhood tuberculosis in our area is 1.33 cases per 100000 children during one year (8).

According to high incidence of tuberculosis in our country and the high predisposition of children to develop of extra pulmonary tuberculosis and its complications, we studied the spectrum of clinical and paraclinical aspects of extra pulmonary TB in children suffering from extra-pulmonary tuberculosis.

Patients and Methods

This study has been carried out on 65 children with tuberculosis, admitted in TB wards of N.R.I.T.L.D during 2004-2006.

All patients were investigated according to specific diagnostic criteria including; history of contact with TB patient, clinical manifestations, radiological findings, tuberculin test and bacteriologic or pathologic results and after confirmation, treatment was administered. Out of 65 cases, 14 patients had different types of extra pulmonary tuberculosis, and data concerning following factors were studied: age, gender, race, site of involvement, bacteriology, ADA (ascitic fluid), PCR (tissue specimens), pathology, HIV test (ELISA), history of close contact, tuberculin test, radiological findings, and immunological studies (in disseminated TB).

Results

During the study, 14 children were admitted with extra pulmonary tuberculosis in our hospital. 8 were girls and 6 were boys with mean age of 8.75 ± 4.2 . Nine patients were Iranian and 5 were Afghan.

Five of fourteen patients had a lymphadenopathy that 4 of them were cervical and one was axillary node, 3

patients had osteoarticular diseases, 2 peritonitis and 2 disseminated form of tuberculosis, 1 pericarditis, 1 renal tuberculosis. History of close Contact was detected in 4 cases that consist of 2 osteoarticular, renal and pericardial tuberculosis.

Radiological findings showed concomitant pulmonary and extra-pulmonary diseases in 4 patients with one renal involvement, 2 osteoarticular involvements and one cardiac pericarditis.

Tuberculin skin tests greater than 15 mm observed in 5 cases (two with adenopathy, one with osteoarticular tuberculosis and two with miliary tuberculosis).

9 patients had 0-5 mm indurations.

Positive AFB in gastric washing were recognized in 4 cases that two were in abdominal tuberculosis and one in miliary tuberculosis and one in specimen of lymph node. In which 3 of them showed positive culture for MTB. In one patient the smear of urine specimen was positive for M.tuberculosis. Pathological studies in 10 cases were performed on lymph nodes (5 cases), peritoneal biopsy with laparoscopy (2 cases) and bone biopsy specimens (3 cases) that revealed granuloma with caseation compatible with tuberculosis.

PCR evaluation on tissue sampling was performed on 8 patients (5 lymphadenitis, 2 peritonitis and one miliary tuberculosis) that PCR results for M.tuberculosis were positive in three patients with peripheral lymphadenitis, one with peritonitis, and one miliary tuberculosis.

Measurements of Adenosine de Aminase (ADA) on peritoneal fluid were positive in two cases with abdominal tuberculosis. All patients had negative HIV tests (ELISA). Overall, extra pulmonary tuberculosis accounted for 20% of the total 65 cases of tuberculosis admitted in TB ward.

Table 1. Characteristic of children with extra-pulmonary infection

Site of extra-pulmonary Involvement	No of patients (percent)	Close Contact	Positive TST	CXR Involvement	Bacteriologic AFB(+) in GW	Pathologic Caseation Granoloma
Peripheral						
Lymphadenitis	5(35/7%)	Negative	2	NO	1	5
Osteoarticular						
Abdominal	3(21/4%)	Positive	2	2	NO	3
Tuberculosis	2(14/2%)	Negative	None	NO	2	2
Miliary						
Tuberculosis	2(14/2%)	Negative	1	NO	1	NO
Pericarditis						
Renal	1(7/1%)	Positive	None	1	NO	NO
Tuberculosis	1(7/1%)	Positive	None	1	NO	NO

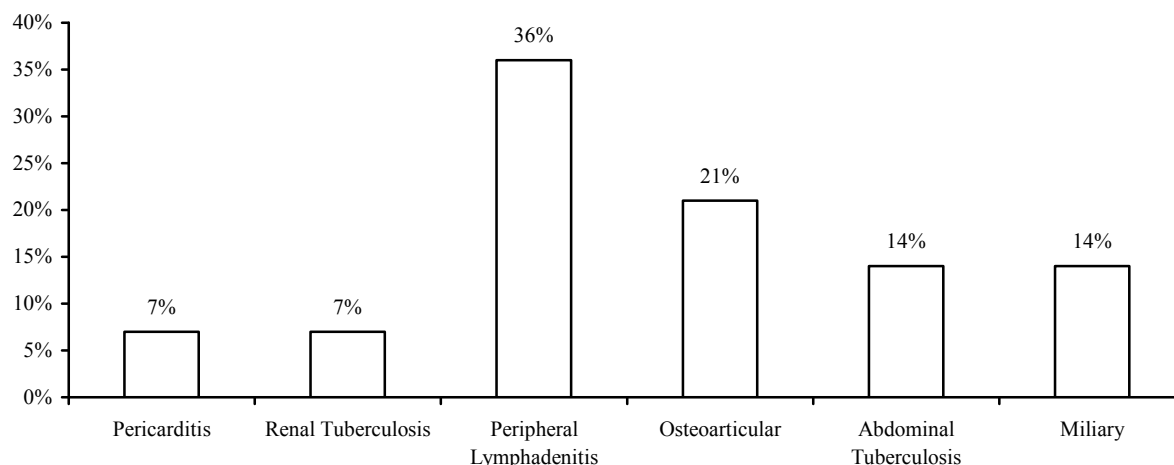


Figure 1. Distribution of patients with extra-pulmonary tuberculosis with reference to site of infection

Discussion

Tuberculosis has been declared global emergency. It is one of the most devastating and widespread infections in the world.

Before the availability of agents with activity against *Mycobacterium tuberculosis*, the development of tuberculosis was associated with a progressive course and fatal outcome in up to 50% of patients (2).

Children are more likely to develop disease after infection and are significantly develop extra-pulmonary and severe disseminated disease than adults. According to other studies infants are more susceptible to severe forms of tuberculosis and miliary tuberculosis (1).

Superficial lymphadenitis and meningitis more seen in preschool children, and pleural effusion and skeletal tuberculosis are dominant in older children, our findings confirmed age dependent changes in extra pulmonary tuberculosis.

According to this study 20% of patients had extra-pulmonary involvement, with is comparable to other reports (20%-25%) and TB lymphadenitis is the most common form of presentation (8).

As expected, superficial lymphadenitis constituted the predominant manifestation of extra pulmonary tuberculosis among the patients studied (35%).

The cervical (4 patients) and axillary (1 patient) lymphadenopathies were the most frequently involved nodes. One Patient had concurrent site of hilar adenopathies, compare with other article that patients with lymphadenitis had hilar lymphadenopathy and adenoid tonsils and nasal tubercle (7).

For diagnosis we performed excisional biopsy in all patients for pathological and bacteriological studies and detection of MTB with PCR, that in three patients PCR results for MTB were positive.

Jain et al in a tertiary care teaching hospital in India evaluated dot-ELISA and PCR by using the IS 6110 primer and claims that ELISA was more sensitive and detected 93.2% percent of tuberculosis lymphadenitis; where as PCR and FNA cytology (FNAC) detected 82.5 and 61 percent cases (9).

Four patients (28%) had pulmonary and extra pulmonary involvement; other studies have reported the increase in the number of children that present with pulmonary and extra pulmonary tuberculosis (7).

In the present series, 21% of patients developed skeletal tuberculosis, the following sites were affected: thoracic vertebra and one knee joint. Tuberculosis of the spine is more severe in children less than 10 years of age. The rate of musculoskeletal tuberculosis in another study was reported 5% of 102 patients (7).

The average of vertebral involvement and destruction is more in children leading to more severe deformity and disability (10). Atypical spinal tuberculosis manifestation as an involvement of single vertebral extradural extra osseous involvement presenting as abscess, and isolated infection of the neural arch and spinal tuberculosis in newborn have been reported (11). In a systematic review of chemotherapeutic treatment for spinal TB, was concluded that 9 months of therapy is probably sufficient for the majority of cases (12). Our cases were treated medically for 9 months. In other trials they

treated skeletal tuberculosis surgically that isn't comparable with our report (7).

Two patients (14%) developed peritonitis with abdominal pain and fever and ascites. In such other study abdominal tuberculosis is reported about 2% of patients with extra pulmonary tuberculosis. In India, abdominal tuberculosis (AFB) accounts for 0/8 percent of all hospital admissions.¹³ Gastrointestinal tuberculosis is reported in 10 to 20 percent of patients suffering from pulmonary tuberculosis, whereas associated pulmonary tuberculosis is noted in 20-75 percent of patients with ATB (1).

In our series we hadn't any association with pulmonary tuberculosis and ATB.

These two cases of peritonitis had negative PPD compare to other reports that patients with abdominal tuberculosis had positive PPD (7). Our two patients had positive smear for AFB and positive culture for ascitic fluid. Most cases of ATB are due to the human strain of *M.tuberculosis* are reported (1), such our study. In a recent study of 26 children from San Diego, *M.bovis* was isolated in 80% of the 71% culture positive cases.¹⁴ PCR may be used to diagnosis tuberculosis rapidly by identifying DNA from *M.T.B* in clinical samples negative by microscopic examination. Result of PCR Sampling for *M.tuberculosis* was positive in one patient. A major recent advance in the diagnosis of TB peritonitis is the determination of ADA activity. Levels rise as a result of stimulation of T cells in response to mycobacterial antigens (15).

A peritoneal fluid ADA value of over 33 μ L has been reported to have a sensivity of 93 percent, as specificity of 96 percent and positive predictive value of 93 percent in the diagnosis of abdominal tuberculosis.¹⁶ False negative results may be noted in AIDS related tuberculosis and when the ascitis total protein is low.¹⁶ In our two cases of abdominal tuberculosis ADA detection of ascitis specimens were positive.

Two patients had disseminated form of tuberculosis, the following symptoms were present: fever, cough, FTT, tachypnea, night sweats.

One patient had positive PPD up to 15mm, compare with other data's that reported the median tuberculin skin test induration's in miliary tuberculosis about 10mm (7). One of patients had positive smear of AFB and no one had positive culture. Maltezou was detected that their patients with miliary tuberculosis had positive cultrers for *M.T.B* in gastric washing (7). One of our patients had positive PCR for *M.tuberculosis* on gastric washing specimens. Immunological studies (Immunoglobulin measures, NBT test and floctometry) in two patients

were normal. The most common form of cardiac tuberculosis is pericarditis. It is rare occurring in 0/5-4% of tuberculosis cases in children (8), one child was admitted with fever, chest pain, weight loss and respiratory distress, chest imaging findings included cardiomegaly, miliary tuberculosis, pericardial thickening, accumulating of pericardial fluid, and adhesions within the pericardial space. The patient treated with pericardial window and medical therapy, compare with the case of pericarditis that reported was treated with paracentesis and 12 months INH and RIF (7).

Renal involvement in tuberculosis is reactivation of primary tuberculosis and one of the late presentations of tuberculosis (1). Renal infection is by definition bilateral owing to the hematogenous spread but clinically significant involvement is usually unilateral (1). The kidney may be involved in miliary tuberculosis but renal dysfunction is not a common feature of such a presentation. Urinary PCR is recommended for instant diagnosis and screening before further examination (1). In our cases, a 4 years girl with pulmonary tuberculosis and microscopic pyuria, sterile urine on routine culture but acid-fast bacilli in the urinary sedimentation, negative TST and pulmonary involvement in CXR with unilateral pyelocalyceal dilation and erosion of the papillary tip in IVP, that indicates renal tuberculosis.

Maltezou *et al.* was reported that 13% of patients with extra pulmonary tuberculosis had meningitis.⁷ Tuberculous meningitis remains the most serious form of extra-pulmonary tuberculosis and long term complications only occurred in patients with younger age with involvement of CNS.⁷ In the present study we hadn't any cases with neurotuberculosis, may be due to mass prophylaxis with BCG vaccination in our population.

Extra pulmonary involvement occurs in more than 70 percent of patients with tuberculosis and preexisting AIDS or AIDS diagnosed soon after but only in 24 to 45 percent of patients with tuberculosis and less advanced HIV infection (17).

HIV tests in our patients were negative.

The treatment of extra-pulmonary tuberculosis is medically and surgical (6). But in the current study all children with extra pulmonary tuberculosis were successfully treated medically with anti tuberculosis drugs. In conclusion, child hood tuberculosis reflects the inadequacy of public health system in controlling transmission of infection in the community. Prompt and efficient identification of the source of transmission and application of effective environmental measures are

intimately linked to the control of childhood tuberculosis.

References

1. Vimlesh S, Kabra SK. Essentials of Tuberculosis in Children. 3th ed. New Delhi; Jaypee Brothers Medical Publishers; 2006.
2. Raviglione MC, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA 1995;273(3):220-6.
3. Rieder HL, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. Am Rev Respir Dis 1990;141(2):347-51.
4. Weir MR, Thornton GF. Extrapulmonary tuberculosis. Experience of a community hospital and review of the literature. Am J Med 1985;79(4):467-78.
5. Starke JR. Resurgence of tuberculosis in children. Pediatr Pulmonol Suppl 1995;11:16-7.
6. Smith S, Jacobs RF, Wilson CB. Immunobiology of childhood tuberculosis: a window on the ontogeny of cellular immunity. J Pediatr 1997;131(1 Pt 1):16-26.
7. Maltezou HC, Spyridis P, Kafetzis DA. Extra-pulmonary tuberculosis in children. Arch Dis Child 2000;83(4):342-6.
8. Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics. 17th ed. Philadelphia: WB Saunders; 2004.
9. Jain A, Verma RK, Tiwari V, Goel MM. Dot-ELISA vs. PCR of fine needle aspirates of tuberculous lymphadenitis: a prospective study in India. Acta Cytol 2005;49(1):17-21.
10. Chang JH, Kim SK, Lee WY. Diagnostic issues in tuberculosis of the ribs with a review of 12 surgically proven cases. Respirology 1999;4(3):249-53.
11. Beekarun DD, Govender S, Rasool MN. Atypical spinal tuberculosis in children. J Pediatr Orthop 1995;15(2):148-51.
12. van Loenhout-Rooyackers JH, Verbeek AL, Jutte PC. Chemotherapeutic treatment for spinal tuberculosis. Int J Tuberc Lung Dis 2002;6(3):259-65.
13. Chuttani HK. Intestinal tuberculosis. In: Card WI, Creamer B, editors. Modern Trends in Gastroenterology. London: Butterworths; 1970. p. 308-27.
14. Veeragandham RS, Lynch FP, Canty TG, Collins DL, Danker WM. Abdominal tuberculosis in children: review of 26 cases. J Pediatr Surg 1996;31(1):170-5.
15. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol 1993;88(7):989-99.
16. Sathar MA, Simjee AE, Coovadia YM, Soni PN, Moola SA, Insam B, et al. Ascitic fluid gamma interferon concentrations and adenosine deaminase activity in tuberculous peritonitis. Gut 1995;36(3):419-21.
17. Chan SP, Birnbaum J, Rao M, Steiner P. Clinical manifestation and outcome of tuberculosis in children with acquired immunodeficiency syndrome. Pediatr Infect Dis J 1996;15(5):443-7.