Clinical features of extrapulmonary tuberculosis in children

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ABSTRACT

Objective: To review the clinical features of the extrapulmonary tuberculosis (TB) in children.

Method: Sixty-four children with extrapulmonary TB followed in Ankara Social Security Children's Hospital between June 1995 and May 2003 were reviewed.

Results: The mean age was 7.5 ± 4.1 years. The most commonly involved sites were the central nervous system [(CNS) 16 cases] and pleura (14 cases). Aside from this, 10 children had a diagnosis of miliary TB. Abdominal TB (median age of 12 years) and pleural effusion (median age of 10.9 years) were mostly seen in older children while miliary TB was encountered more frequently in younger children (median age 2.5 years). A positive family history of active TB was detected in 39% of the cases. There was consanguinity between parents in 23 (35.9%) of the cases. Twenty-five (39%) cases had no Bacillus Calmette-Guerin vaccination scar. One case with CNS TB expired. Sequelae observed during the follow up were; motor-mental retardation in 3 cases, hemiparesis in 2 cases, strabismus in one case with CNS TB and vertebral deformation in 2 cases with Pott's disease.

Conclusion: Severe forms such as CNS and miliary TB constituted an important percentage of childhood extrapulmonary TB cases.

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Tuberculosis (TB) is an important cause of mortality and morbidity in childhood. The World Health Organization reports that there are 1.3 million new cases of TB and 450,000 deaths from the disease in developing countries every year.[1,2] Children have a much higher risk of developing TB compared to adults after being infected by the tuberculosis bacillus and they also have a higher chance of developing severe pulmonary disease and severe extrapulmonary forms such as meningitis and miliary TB.[3,4] We aimed to review the clinical features of the extrapulmonary TB in children followed up in our Hospital.

Methods. This retrospective study includes 64 children with extrapulmonary TB followed in Ankara Social Security Children's Hospital, Ankara, Turkey between June 1995 and May 2003. A diagnosis of TB was established by isolation of *Mycobacterium tuberculosis* (*M. tuberculosis*) in body fluids and pus cultures or by obtaining a biopsy with histopathological findings resembling tuberculosis in patients with usual signs and symptoms of the disease. In cases, where there was no growth on the cultures or a biopsy could not be carried out, the diagnosis was made with the presence of at least 2 of the following criteria: 1. detection of acid-fast bacilli in body fluid samples with the Ziehl-Neelsen stained preparations, 2. history of exposure to an adult with active TB, 3. positive tuberculin skin test (TST). The TST was evaluated 48-72 hours after intradermal injection of 5 tuberculin units of purified protein derivative. An induration larger than 15 mm in cases who had been

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vaccinated with Bacillus Calmette-Guerin (BCG) vaccine and 10 mm in those who had not been vaccinated were evaluated as positive.[5,6]

The central nervous system (CNS) and miliary TB cases received isoniazid, rifampin, pyrazinamide and streptomycin treatment for 2 months and only isoniazid and rifampin for the following 10 months. In addition, tuberculous meningitis and severe miliary TB cases received corticosteroid treatment for the first 6 weeks and a ventriculoperitoneal shunt was placed in severe hydrocephalus cases. Patients with other forms received isoniazid, rifampin and pyrazinamide for the first 2 months and then isoniazid and rifampin until the end of the therapy. A case with Pott's disease required surgical intervention.

Table 1 - Distribution of cases according to site and age of infection.

Site of infection	Cases		Median age	
	n	(%)	years	(minimum - maximum)
CNS	16	(25)	7.5	(1.5-13)
Pleura	14	(21.8)	10.9	(5-15)
Miliary tuberculosis	10	(15.6)	2.5	(5/12-14)
Skeletal system	9	(14.1)	5	(10/12-9)
Abdominal tuberculosis	6	(9.4)	12	(2.5-12)
Superficial lymph node	6	(9.4)	6.5	(3-13)
Parotid tuberculosis	2	(3.1)	7.5	(7-8)
Renal tuberculosis	1	(1.6)	12	

CNS - central nervous system

Results. There were 64 cases aged, 5 months to 15 years; 25 (39%) were female and 39 (61%) were male. The mean age was 7.5 ± 4.1 years. The most commonly involved site was CNS with 16 (25%) cases (**Table 1**). Nineteen (29.7%) children were under 5 years of age. Miliary TB developed most frequently in young children. The median age for CNS was 7.5 years and 5 years for skeletal TB, whereas abdominal, renal and pleural TB developed in older children. The diagnosis of skeletal TB cases were Pott's disease in 5, arthritis in 4 (a case with Pott's disease also had arthritis) and osteomyelitis of the fibula in one patient. Intracranial tuberculomas were detected in 3 children with CNS TB. The main symptoms of the cases are shown in **Table 2**.

Consanguinity between parents was detected in 23 (35.9%) children mostly those who had abdominal and skeletal TB. The history of consanguinity was unknown in 13 children.

There was a history of an adult previously treated for TB in the family of 6 cases (9.4%), and 22 cases (34.4%) had a history of exposure to an individual case with active TB within the family. In addition, screening for TB revealed that 5 more cases (7.8%) had someone with active TB (one was reactivation) and this increased the percentage of cases with positive family history of active TB to 42.2%.

Twenty-five (39%) cases had no BCG vaccination scar and 10 of them were CNS and miliary TB cases. When we compare the cases according to their vaccination history, no significant difference was found between the cases with CNS and miliary TB and cases with other sites of involvement ($p>0.05$). Upon evaluation of CNS and miliary TB cases, it was found that there were 11 children under 5 years old and 6 of them (54.5%) had no BCG scar. However, only 4 (26.6%) of the children were found to have no vaccination scar, when we examined 15 CNS and miliary TB cases who were 5 years old or older.

Mycobacterium tuberculosis was isolated from the cultures of body fluids or tissue samples in 11 (17.2%) cases (gastric aspirate in 7 cases, cerebrospinal fluid in 2 cases and sputum and tissue sample in one case each). Acid-fast bacilli were detected in the body fluids of 16 (25%) cases (gastric aspirate in 14 cases, cerebrospinal fluid (CSF) in 2 cases). Biopsy specimen (superficial lymph node biopsy in 7, synovial biopsy in 3, mesenteric lymph node biopsy in 3, peritoneal biopsy in 2 cases, pleural biopsy in 1, bone biopsy in 1 and parotid gland biopsy in 1 case) showed histopathology supporting the diagnosis of TB in 18 cases (28.1%). The chest x-ray was abnormal in 44 (68.7%) cases (**Table 3**). None of the cases had immunodeficiency virus infection.

A case with multiple tuberculoma expired on the second month of treatment. Sequelae of CNS TB cases included motor - mental retardation in 3, hemiplegia in 2 cases and strabismus in one case. Two cases with Pott's disease did not attend follow-up visits after the third month of treatment and 2 cases of Pott's disease had kyphosis as a sequela. The other forms of TB cases recovered completely with antituberculous treatment.

Discussion. Extrapulmonary involvement in childhood TB was most commonly observed in the CNS in this study. Studies on Greek and Swedish children and French adults have reported the lymph nodes as the most commonly involved area.[1,7,8] An extensive study from our country and a study from the United States (US) have found the second most frequently involved system after the lungs to be the CNS, as in our study.[4,5] The fact that our hospital serves to a population from a lower socioeconomic and cultural status may be a reason for our cases being diagnosed with more severe forms of the disease. Besides, some tuberculous lymphadenitis

Table 2 - Most commonly encountered symptoms and their duration.

Site of infection	n of cases	Symptoms	n of cases	Duration of symptoms (min – max.)
Central nervous system	16	Fever headache vomiting seizure altered consciousness	10 9 9 9 8	1 day - 1 month
Pleura	14	Fever cough dyspnea chest pain	11 9 3 7	1 week - 2 months
Miliary tuberculosis	10	Fever cough fatigue dyspnea	8 8 2 2	2 weeks – 7 months
Skeletal system	9	Knee swelling inability to walk back pain neck pain	4 3 3 1	2.5 months – 4 years
Abdominal tuberculosis	6	Abdominal pain abdominal swelling vomiting	5 3 3	15 days - 2 months
Superficial lymph node	6	Neck swelling retroauricular swelling	5 1	1 week - 4 months
Parotid tuberculosis	2	Cheek swelling	2	3-5 months
Renal tuberculosis	1	Fever, abdominal pain	1	4 months

Table 3 - Diagnostic characteristics of the cases.

Site of infections		BCG (+) cases		TST (+) cases		Active TB case in the family		Chest x-ray pathology (+)		AFB (+) case		Culture (+) case		Histopathologic diagnosis
	n	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
CNS	16	9	(56.2)	10	(62.5)	7	(43.7)	9	(56.2)	3	(18.7)	4	(25)	-
Pleura	14	9	(64.3)	13	(92.8)	4	(28.6)	14	(100)	2	(14.3)	2	(14.3)	1 pleural biopsy
Miliary	10	7	(70)	4	(40)	5	(50)	10	(100)	7	(70)	4	(40)	-
Skeletal system	9	3	(33.3)	7	(77.7)	6	(66.6)	4	(44.4)	2	(22.2)	1	(11.1)	3 synovial biopsy 1 bone biopsy
Abdominal tuberculosis	6	4	(66.6)	3	(50)	-	-	3	(50)	2	(33.3)	-	-	2 peritoneal, 3 mesenter lymph
Lymph node	6	4	(66.6)	5	(83.3)	2	(33.3)	3	(50)	-	-	-	-	nodes biopsies) 6 lymph nodes
Parotid	2	2/2		2/2		2/2		-	-	-	-	-	-	1 parotid, 1 lymph node biopsy
Renal	1	1/1		1/1		1/1		1/1	1/1	-	-	-	-	-

CNS - central nervous system, TST (+) - positive tuberculin skin test, BCG (+) - Bacillus Calmette-Guerin vaccination, AFB (+) - acid-fast bacilli positive, TB - tuberculosis.

cases may have not reached us, as our hospital is a referral hospital and they can be cured in primary health clinics. In addition, an interesting finding in this study was the frequency of consanguinity between the parents. Genetic defects including complete or partial deficiency of either of the 2 IFN-γ receptor components or the signal transducer and activator of transcription molecule and complete deficiency of IL-12 p40 or IL-12 receptor β1 are associated with disseminated BCG or atypical mycobacterial infections.[9,10] Recently clinical tuberculosis in 2 of 3 siblings with IL-12 receptor beta 1 deficiency was reported. One of the siblings had disseminated TB.[11] We could not investigate IFN-γ or IL-12 receptor deficiency in this study, but such molecular defects in the immune system may be a reason for severe extrapulmonary TB forms seen in some of our patients.

It is known that severe forms of tuberculosis such as miliary and CNS TB usually develop within 2 - 6 months after primary infection while bone and joint infections are seen after a year and renal lesions are seen much later, 5 - 25 years after the primary infection.[4] Maltezou et al[1] found that miliary TB was more frequent in infants, whereas lymphadenitis and meningitis were more frequent in preschool children and pleural effusion and skeletal TB in older children. In a study from US, the median age was one year for miliary TB, 2 years for meningeal TB, 8 years for skeletal tuberculosis, 13 years for peritoneal tuberculosis and 16 years for pleural and genitourinary tuberculosis.[4] We similarly detected pleural, renal and abdominal TB in children older than 10 years old and skeletal tuberculosis in children approximately 7 years old. The median ages of our CNS and miliary TB cases were higher than that reported from the US and Greece. The fact that TB vaccination is carried out at the end of the second month in our country may be an important factor in this difference.

Mortality and morbidity is mostly encountered in the more severe forms of TB such as CNS and miliary TB.[6,12,13] A case with widespread CNS tuberculomas expired in our study and various sequelae developed in 37.5% of the CNS TB cases.

In conclusion, we determined that CNS and miliary TB constituted an important percentage of extrapulmonary TB. Besides, there was a high percentage of consanguinity between the parents of the patients. Investigations of the defects in the immune system may have important clues in the pathogenesis of extrapulmonary TB.

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