Retrospective Evaluation of 35 Pediatric Tuberculosis Cases Proven by Histopathological and/or Microbiological Analysis

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Abstract

Objective: The progress and clinical findings of childhood tuberculosis are distinctly different from those of adult tuberculosis. Children have fewer positive mycobacterial cultures and less specific findings and symptoms than adults. Thus, diagnosis of tuberculosis is difficult and it is rarely evidenced.

Materials and Methods: The study involved retrospective evaluation of 35 confirmed tuberculosis cases between May 2009 and February 2013 by the Infectious Diseases Clinic of Şişli Hamidiye Etfal Training and Research Hospital.

Results: Of the 35 patients included in this study, 13 had pulmonary tuberculosis, 15 had extrapulmonary tuberculosis, and 7 had both pulmonary and extrapulmonary tuberculosis. Primary tuberculosis (34.3%) was the most commonly diagnosed form of pulmonary tuberculosis; tuberculosis lymphadenitis (25.7%) was the most frequently diagnosed form of extrapulmonary tuberculosis. Acid-resistant bacteria were observed in 40% of cases, mostly in the gastric lavage aspirate (31.4%). The culture was positive in 62.9% of cases, mostly in the gastric lavage aspirate (31.4%).

Conclusion: Diagnosis of tuberculosis in childhood is quite difficult and it is rarely confirmed because children have less specific signs and symptoms of the disease and fewer positive mycobacterial cultures than adults. The gold standards for diagnosing tuberculosis in childhood still include a history of close contact with a tuberculosis patient, tuberculin skin test reactivity, and clinical and radiological findings associated with tuberculosis. *(J Pediatr Inf 2015; 9: 97-101)*

Keywords: Tuberculosis, childhood, proven

Received: 17.05.2015
Accepted: 05.06.2015

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This study was presented at the 8th National Pediatric Infectious Congress, 28-30 April, Antalya, Turkey.

DOI:10.5152/ced.2015.2096

Introduction

Today tuberculosis (TB) still continues to be the number one cause of mortality amongst the preventable infectious diseases. According to the data of the World Health Organization (WHO), 8.6 million new TB cases were identified in 2012 and 1.3 million TB cases died. According to the WHO data, 16.000 new TB cases were identified in Turkey (1). According to the 2012 Tuberculosis Control Dispensary (TCD), it was reported that 15.183 new cases were identified in 2010 and the total annual case number was 16.551 (2). It was stated in the same report that regarding the classification of TB cases based on childhood age groups, 1.3% of the cases were aged 0-4, 4.1% aged 5-14 and 19.3% aged 15 and over.

The source of TB in childhood is usually infecting adult pulmonary cases. Under normal circumstances, while 5-10% of the adults infected with *Mycobacterium tuberculosis*, this rate can rise as high as 34% in children (3). TB can develop in 79% of the children aged under 5 who live in contact with TB in high risk regions (4).

Today tuberculosis classification in diagnosing TB recommended by the WHO is the three groups of “suspicious, possible and definite disease” (5). Diagnosis of definite disease can only be made through detecting or growing the TB bacillus from the clinical samples (6, 7). TB in children occur with the presence of few bacillus

and cavitation in the lungs is not expected; therefore, microbiologic methods, unlike the adult type TB, produce positive results only 30-40% of the pediatric cases (8-10). Due to the difficulties in the confirmed diagnosis of TB children, many diagnostic approaches such as score systems, diagnostic classifications, algorithms and their combinations have been developed (5, 11, 12). However, none of them have been found to be within the limits of specificity and sensitivity.

In this study, we aimed to retrospectively carry out epidemiologic, clinic, laboratory, microbiologic evaluation of treatment methods of 35 definite tuberculosis-diagnosed pediatric cases whose treatments started and thus identify the value of clinical and laboratory findings in the diagnosis of TC in childhood.

Materials and Methods

Thirty five 35 microbiologically and/or histopathologically confirmed tuberculosis cases were included in the study at the Infectious Diseases Clinic of Şişli Hamidiye Etfal Training and Research Hospital between May 2009-February 2013.

The medical records of the patients were searched and the information obtained was recorded on a standard form. On the form, data regarding age, gender, socioeconomic level, complaints, examination findings, contact history, tuberculin skin test (TST), BCG vaccine scar status, QuantiFERON-TB Gold test (Cellestis International, Carnegie, Australia) results, TB organ localization, laboratory and radiologic findings, existence of microbiologic and histopathological diagnosis, treatment regime and its period, and follow-up results were recorded.

TCT 0.1 mL 5 tuberculin unit was intradermally applied by using PPD solution on the inner face of the front arm and the vertical and horizontal diameter of the resultant induration after 48-72 hours was measured as millimeter via the pen point technique. The evaluation of the test was carried out based on the TCD criteria in our country. Accordingly, the patients without BCG scar with TCT ≥10 mm and with BCG scar TCT ≥15 mm were accepted to be TCT positive. QuantiFERON-TB Gold test is based measuring the interferon gamma (IFN- ã) levels by ELISA secreted by the memory T-cells invitro using the ESAT-6, CFP-10 ve TB 7.7 antigens only in M. tuberculosis but not in the other non-tuberculosis mycobacterium. It is a test used for the diagnosis of the infection caused by *M. tuberculosis*. It is diagnostic both in the active disease and latent disease periods. Test is based on stimulation of T cells through specific antigens, the response of T lymphocytes to these stimulations through IFN-γ response and the measurement of IFN-γ quantity. Chest radiographies, thorax computerized tomography (CT) and other radiological tests of the patients were evaluated in detail in terms of TB. TB compatible findings were sought in the thorax CT (budded three appearance, pleural effusion, pleural thickening, empyema, consolidation, cavitation, lymphadenopathy (LAP), calcified lymph node, nodule, sequels, atelectasis and lymph node stations). All the patients suspected of meningitis were performed lumbar puncture and their cerebrospinal fluid (CSF) was investigated. The treatment used and the patients' responses were recorded. The patients were given anti-TB treatment. All the patients were given the following treatments; isoniazid (10 mg/kg/day, maximum 300 mg/day), rifampicin (15 mg/kg/day, maximum 600 mg/day) for 6-12 months and additionally at the beginning phase of the treatment pyrazinamide (35 mg/kg/day, maximum 2 g/day), ethambutol (20 mg/kg/day, maximum 1 g/day) or streptomycin 25 mg/kg/day, maximum 2 g/day) for two months. Furthermore, the patients with military TB, meningoencephalitis, pericarditis and peritonitis were given steroid treatment. After their discharge, patients were followed up once every fortnight and then once a month until the completion of their treatment.

Statistical analysis

Statistical analysis and the data obtained from the record files were done on the SPSS 16.0 (SPSS Inc; Chicago, IL, USA) program.

Results

Twenty participants in the study were female and 15 were male and average of age was 111.93±63.8 month. 25.7% of the cases were under five years old. 60% of the patients did not have a story of contact with TB patient. 12 (34.3%) of those with story of contact with a TB patient had indoor contact and 2 (5.7%) outdoor contact. 13 patients had pulmonary TB, 15 extrapulmonary and 7 pulmonary and extrapulmonary TB. While primary TB was the most common form of pulmonary TB with 12 cases (34.3%), 11.4% cases had secondary cavitary TB, 5.7% cases pleuritic TB and 5.7% cases miliary TB. While lymphadenitis TB with 9 (%25.7) cases was the most common form of extrapulmonary TB, 20% cases had abdomen TB, 11.4% meningitis TB and 5.7% skeletal. BCG scar was seen in 22.9% of the cases and TCT positivity was found 48.6%. The test was positive in 90% of the cases scanned for QuantiFERON-TB Gold. 51.4% of the cases had anemia, 48.6% high erythrocyte sedimentation rate (ESR) and 28.6% leukocytosis. Chest radiographies of 8 cases out of 20 with pulmonary TB were normal and thoracic computerized tomography of 18 cases was compatible with TB. The results of acid resistant bacilli (ARB) positivity and growth of *M. tuberculosis*

in the culture is shown in Table 1. Histopathologic biopsy sites are illustrated in Table 2. The patients were started with the therapies of isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin. Steroid treatment was given 13 (37.1%) cases (7 cases were given peritonitis, 2 pleuritis, 2 meningoencephalitis, and 2 miliary TB). All the patients responded positively to the treatments and no patient died during the follow-up.

Discussion

Today, TB continues to be an important public health problem. Especially the prevalence of pediatric TB confronts us as the index of the public health services underway in the society. It is difficult for children to produce sputum and bacillus number in the sputum is low. Therefore, children are not expected to be index cases (13). Children are usually infected with the TB by the infecting adult TB patients; therefore, index cases are crucial in the diagnosis of TB (14). Diagnosis of pediatric TB is more difficult than adult TB. While detecting microbiological proof is compulsory in adults, it is not always possible to screen bacillus in pediatric TB (15).

While pulmonary TB is more frequently seen in adult patients, extrapulmonary TB is more frequent in children. Immune status of children, untreated HIV infection and if they are under two years old (especially in the neonatal period, due to weak cellular immunity) increase the risk of the condition converting into the disease, turning into a progressive/ fatal disease and the risk of extrapulmonary TB (16-19). In their study in which they study 60 pediatric TB patients, Shrestha et al. found pulmonary TB was more frequently seen (53.7%) than extrapulmonary TB; BCG scar was seen in 48.8% of the cases, story of contact with TB cases in 36.6% cases (20). Similarly, extrapulmonary TB cases in our study were more frequent and BCG scar was 22.9%. In their study in which Pekcan et al. (13) studied 539 pediatric cases with TB in different centers and followed them up for 12 years, they found 40% TB contact story. Unlike the case in the relevant literature, TB contact story in our study was 40% as well (13).

In children, out of the frequent TBs, the most frequent type is the lymphadenitis TB. In a study carried out by Coşar et al. (21) in Turkey, it was reported that in 38.6% of the 44 pediatric TB cases, extrapulmonary tuberculosis was found and 11.7% of those cases were lymphadenitis TB. In our study, similar to Coşar et al.'s (21) results, 42.8% of the confirmed TB cases constituted extrapulmonary TB cases. However, 40% of the cases with extrapulmonary TB were diagnosed with lymphadenitis TB. This rate in our study is higher than the one in Coşar et al.'s (21) study.

SSS involvement has the highest mortality rate among the extrapulmonary TBs. SSS TB is the most serious form of extrapulmonary TB causing 13-23% mortality and 30-40% sequellaes in untreated patients (11, 16, 17, 22, 23). In a 10-year-long follow-up study they carried out with children, Ting et al. reported that they found 5 confirmed TB meningitis cases, two cases died in the follow-up period and the average age was 7 years (24). In four-year long follow-up in our study, 4 cases were diagnosed with TB meningitis through the clinical, BOS findings, BOS TB polymerase chain reaction, BOS culture and cranial screening findings. No patient who had average age of 54 months died in the follow-up period. Short follow-up period may explain why there is no mortality in our patients.

TCT positivity alone is not sufficient to make the diagnosis of TB disease. Furthermore, it makes it more difficult to interpret the test in favor of TB in a society like ours that has high TB prevalence and BCG vaccine is routinely applied. After all, when assessed together with the other parameters, it still has a significant place for TB. According to the meta-analysis carried out by Colditz et al. (25), they calculated that BCG vaccine reduced the risk of getting tuberculosis 50%, the risk of mortality from tuberculosis 71%, and getting tuberculosis meningitis 64%. In a different multi-centered study, it was found that general protection rate was 0-80% (26). In their study in which they carried out in children in the elementary schools in Elazığ city center, they found that 21.7% did not have BCG scar, 65.7% had single scar and 12.6% double scars. Similarly

Table 1. Screening acid resistant bacillus (ARB) and growing *M. Tuberculosis*

	ARB		Culture	
	Number of patients (n=44)	%	Number of patients (n=44)	%
Fasting gastric aspiration fluid	6	17.1	11	31.4
Abscess	2	5.7	2	5.7
Peritoneal fluid	2	5.7	3	8.6
Bronchoalveolar lavage	1	2.9	-	-
Cerebrospinal fluid	1	2.9	2	5.7
Sputum	1	2.9	2	5.7
Pleural effusion	1	2.9	2	5.7
ARB: acid resistant bacillus				

Table 2. Histopathologic biopsy diagnosis site

	Number of patients (n=14)	%
Lymph node	7	50
Periton	3	21.3
Terminal ileum	2	14.2
Joint fluid	2	14.2

in our study, BCG scar was found in 22.9% of the patients. The fact that patients did not have the BCG vaccine that had high level of protection explains why they had higher risk of getting the disease in comparison to vaccinated patients.

Sensitivity of the QuantiFERON-TB Gold test of clinically diagnosed TB cases was 64% and specificity was 100% (28). In a study Debord et al. carried out with 19 pediatric patients diagnosed with active TB patients between 2008-2010, they found that 6 (60%) of the 10 confirmed TB cases microbiologically had QuantiFERON-TB Gold test positivity (29). In our study, 20 (90.9%) of the 22 cases who were QuantiFERON-TB Gold tested were positive. In a study in which Dogra et al. (30) carried out with 97 pediatric patients diagnosed with active TB disease between 2004-2005, confirmed TB was microbiologically found in 8 patients and the relationship of clinical form with QuantiFERON-TB Gold test was investigated. It was found that 4 of the microbiologically confirmed 8 patients were pulmonary, 4 were extrapulmonary and 3 were QuantiFERON-TB Gold test negative. It was stated that low number of patients used for evaluation did not generate statistically significant difference, but the results might be enlightening for the future studies (30). In our study, while QuantiFERON-TB Gold test positivity in pulmonary TB cases was 91.6%, it was 92.8% positive in extrapulmonary TB cases. In 4 pulmonary and extrapulmonary TB cases that were QuantiFERON-TB Gold tested, the results were positive. The leading hematologic changes encountered in TB were anemia, leukocytosis, leukopenia and leukemoid reactions. However, due to the prevalence of these parameters in many infections, clinical measures are limited (31). In our study, similar to the findings in the literature, despite anemia, increase in ESH and prevalence of leukocytosis, these findings were not instructive for us in the diagnosis.

It is both difficult and challenging to obtain samples from children for microbiological diagnosis due to the low level of bacillus content in the samples. Therefore, diagnosis in children is mostly made based on contact with index case and clinical findings. In the 65-patient series, while Demir et al. (32) found that bacillus positivity was 9.2%, Göçmen et al. (33) found 28% bacillus positivity in pediatric TB patients. The demonstrability of bacillus in the samples taken consecutively in three days from the patients in our study was as high as 40%. Low culture positivity in other studies may be related to the sample taking technique and laboratory conditions. The positivity rate in our study is in parallel to the positivity in the literature.

Conclusion

Due to the difficulties in making confirmed diagnosis in childhood TB, story of contact with TB infected adult, tuberculin skin test positivity and the presence of accompanying significant clinical and radiological findings continue to be gold standards. Cases that the index case is in contact with should be vigilantly followed up. If the chest radiography in TB suspicion is normal, thorax CT should certainly be required. In addition to TCT, QuantiFERON-TB Gold test should be planned. For TB that continues to be an important public health problem in childhood period, confirmed diagnosis should always be kept in mind and for confirmed TB diagnosis, ARB should be detected and *M. Tuberculosis* should be grown in the culture and finally efforts should be made for the histopathologic diagnosis. With the inclusion of more confirmed TB cases in multicentered studies in the future, we will have greater chance of success in the fight against this disease with regard to understanding the disease better and developing new diagnosis methods for it.

Ethics Committee Approval: Ethics committee approval was not obtained due to the retrospective nature of this study.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.D., H.G.; Design - N.D., H.G.; Supervision - N.D.; Funding - H.G., Ü.Ö.; Materials - D.K., Ü.Ö.; Data Collection and/or Processing - N.D., H.G.; Analysis and/or Interpretation - N.D., H.G.; Literature Review - N.D., H.G.; Writer - H.G.; Critical Review - İ.K.; Other - İ.K., D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Global tuberculosis report 2013. World Health Organization. Available from: URL: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf
2. Türkiye Ulusal Verem Savaş Dernekleri Federasyonu, Türkiye'de Verem Savaşı 2012 Raporu. Available from: URL: http://tuberkuloz.thsk.saglik.gov.tr/Dosya/Dokumanlar/raporlar/turkiyede_verem_savasi_2012_raporu.pdf
3. Beyers N, Gie RP, Schaaf HS, et al. A prospective evaluation of children under the age of 5 years living in the same household as adults with recently diagnosed pulmonary tuberculosis. Int J Tuberc Lung Dis 1997; 1: 38-43.
4. Rie AV, Beyers N, Gie RP, et al. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. Arch Dis Child 1999; 80: 433-7. [CrossRef]
5. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. Int J Tuberc Lung Dis 2002; 6: 1038-45.

6. Starke JR. Tuberculosis in children. Current Opinition in Pediatrics 1995; 7: 268-77. [CrossRef]
7. Özkara Ş, Aktaş Z, Özkan S, Ecevit H. Türkiye'de Tüberkülozun Kontrolü için Başvuru Kitabı. Ankara: Sağlık Bakanlığı, Verem Savaş Daire Başkanlığı, 2003.
8. Dufour G. Mycobacteriology. Semin. Pediatr Infect Dis 1993; 4: 205-13.
9. Pomputius W, Rost J, Dennehy PH, Carter EJ. Standartization of gastric aspirate technique improves yield in the diagnosis of tuberculosis in children. Pediatr Infect Dis J 1997; 16: 222-6. [CrossRef]
10. Somu N, Swaminathan S, Paramasivan C, et al. Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. Tuberc Lung Dis 1995; 76: 295-9. [CrossRef]
11. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. Lancet Infect Dis 2003; 3: 624-32. [CrossRef]
12. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Resp Crit Care Med 2006; 173: 1078-90. [CrossRef]
13. Pekcan S, Aslan AT, Kiper N, et al. Multicentric Analysis of Childhood Tuberculosis in Turkey. Turk J Pediatr 2013; 55: 121-9.
14. Wilfret C, Hotez P. Tuberculosis In: Gershon AA, Hotez PJ, Katz SL (eds.). Krugman's Infectious Disease of Children (Çeviri: Kanra G.) 11th. Ed St. Louis Missouri: Mosby; 2006; pp.731-62.
15. Arpaz S, Keskin S, Kıter G, Sezgin N, Uçan ES. Tüberkülozlu çocuk hastalarımızın geriye dönük olarak değerlendirilmesi. Toraks Dergisi 2001; 2: 27-33.
16. Carrol ED, Clark JE, Cant AJ. Non-pulmonary tuberculosis. Paediatr Respir Rev 2001; 2: 113-9. [CrossRef]
17. Lighter J, Rigaud M. Diagnosing childhood tuberculosis: traditional and innovative modalities. Curr Probl Pediatr Adolesc Health Care 2009; 39: 61-88. [CrossRef]
18. Rowinska-Zakrzewska E. Extrapulmonary tuberculosis, risk factors and incidence. Pneumonol Alergol Pol 2011; 79: 377-8.
19. Forssbohm M, Zwahlen M, Loddenkemper R, Rieder HL. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. Eur Respir J 2008; 31: 99-105. [CrossRef]
20. Shrestha S, Bichha RP, Sharma A, Upadhyay S, Rijal P. Clinical profile of tuberculosis in children. Nepal Med Coll J 2011; 13: 119-22.
21. Coşar H, Onay H, Bayram N, Özkınay F. Tüberkülozlu 44 Çocuk Hastanın Epidemiyolojik, Klinik ve Prognoz Yönünden Değerlendirilmesi. J Pediatr Inf 2008; 2: 1-6.
22. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev 2007; 8: 107-17. [CrossRef]
23. Kocabaş E. Çocukluk çağı tüberkülozunda klinik özellikler ve tanı. T Klin J Pediatr 2004; 2: 215-24.
24. Ting PL, Norton R. Central nervous system tuberculosis: a disease from Papua New Guinea in North Queensland. J Paediatr Child Health 2013; 49: 193-8. [CrossRef]
25. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG Vaccine In the Prevention of Tuberculosis: Metaanalysis of the published literature. JAMA 1994; 271: 698-702. [CrossRef]
26. Starke JR, Smith KC. Treatment of the Stages of Tuberculosis In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL. Textbook of Pediatric Infectious Diseases 5th ed. Saunders 2004; pp.1364-70.
27. Şen Ç, Aygün AD, Altunışık E, Kocabay K. Elazığ il merkezindeki ilköğretim okulu çocuklarında PPD ile BCG aşısının değerlendirilmesi ve tüberküloz enfeksiyon prevelansı. Çocuk Sağlığı ve Hastalıkları Dergisi 1998; 41: 497-508.
28. Sun L, Xiao J, Miao Q, et al. Interferon gamma release assay in diagnosis of pediatric tuberculosis: a meta-analysis. FEMS Immunol Med Microbiol 2011; 63: 165-73. [CrossRef]
29. Debord C, Lauzeanne A, Gourgouillon N. Interferon-gamma Release Assay Performance for Diagnosing Tuberculosis Disease in 0 to 5 Years Old Children. Pediatr Infect Dis J 2011; 30: 995-7. [CrossRef]
30. Dogra S, Narang P, Deepak K. Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India. J Infect 2007; 54: 267-76. [CrossRef]
31. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 1990; 12: 583-90. [CrossRef]
32. Demir T, Çelik E, Antmen E ve ark. Çocuk tüberkülozu olgularının retrospektif olarak incelenmesi. Solunum hastalıkları 1999; 10: 384-91.
33. Göçmen A, Cengizler R, Özçelik U, et al. Childhood tuberculosis: A report of 2205 cases. Turk J Pediatr 1997; 39: 149-58.