



Clinical Features in Childhood Tuberculosis Followed in Our Clinic

Kliniğimizde Takipli Çocukluk Çağı Tüberkülozlarında Klinik Özellikler

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Abstract

Objective: Childhood tuberculosis constitutes an important part of the global burden of tuberculosis. Childhood tuberculosis is also important in that it shows that the burden of tuberculosis continues in society. In our study, demographic, clinical, radiological features and treatment modalities of childhood tuberculosis cases were evaluated during 3 years.

Material and Methods: This study covers 33 children diagnosed with tuberculosis in the Adana Numune Training and Research Hospital Department of Pediatrics between January 2012 and December 2014.

Results: Eleven of the 33 children with tuberculosis were male (33%) and 22 were female (66%) and the median age was 11 (1-17) years. Of the patients, 14 (42%) were pulmonary tuberculosis and 19 (57%) were extrapulmonary tuberculosis. 14 cases (42%) were primary pulmonary tuberculosis, 14 (42%) were tuberculosis of superficial lymph node, 2 (6%) were miliary tuberculosis, 1 (3%) were tuberculous meningitis, 1 (3%) were intestinal tuberculosis, 1 (3%) were vertebra tuberculosis. Household contact was present in 50% of patients who received a diagnosis of pulmonary tuberculosis and in 32% of patients who received a diagnosis of extrapulmonary tuberculosis. Weight loss and fever were the most common complaints. 36% in pulmonary tuberculosis, 32% in extrapulmonary tuberculosis had tuberculin skin test positivity. Acid-resistant bacilli (ARB) was positive in 6 (18%) of the patients. 15% of the patients had culture positivity. Treatment regimens were well tolerated in pulmonary and extrapulmonary tuberculosis. The treatment was interrupted because only the findings of acute hepatitis developed during the first month of treatment in one patient. A patient was died.

Öz

Giriş: Çocukluk çağı tüberkülozu dünya çapında tüberküloz yükünün önemli bir kısmını oluşturmaktadır. Çocukluk çağı tüberkülozu toplumda tüberküloz yükünün devam ettiğini göstermesi bakımından da önemlidir. Çalışmamızda 3 yıllık sürede ilimizdeki çocukluk çağı tüberküloz olgularının demografik, klinik, radyolojik özellikleri ve tedavi yöntemleri değerlendirildi.

Gereç ve Yöntemler: Bu çalışma Ocak 2012-Aralık 2014 tarihleri arasında Adana Numune Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniğinde tüberküloz tanısı alan 33 çocuğu kapsamaktadır.

Bulgular: Otuz üç tüberkülozlu çocuk hastanın 11 (%33.3)'i erkek, 22 (%66.7)'si kız olup, ortanca yaş 13 (1-17) yıl idi. Hastaların 14 (%42)'ü akciğer tüberkülozu, 19 (%57)'u akciğer dışı tüberküloz idi. Tutulum yerine göre incelendiğinde hastaların 14 (%42)'ü primer akciğer tüberkülozu, 14 (%42)'ü yüzeysel lenf bezi tüberkülozu, 2 (%6)'si miliary tüberküloz, 1 (%3)'i tüberküloz menenjit, 1 (%3)'i intestinal tüberküloz, 1 (%3)'i vertebra tüberküloz idi. Ev içi temas öyküsü akciğer tüberkülozu tanısı alan hastaların %50'sinde, akciğer dışı tüberküloz tanısı alan hastaların %32'sinde mevcuttu. Kilo kaybı ve ateş en sık rastlanan şikayetlerdi. Akciğer tüberkülozunda %36, akciğer dışı tüberkülozda %32 tüberkülin cilt testi pozitifliği vardı. Hastaların 6 (%18)'sında aside dirençli basil (ARB) pozitif saptandı. Hastaların %15'inde kültürde üreme mevcuttu. Tedavi rejimleri akciğer ve akciğer dışı tüberkülozda iyi tolere edildi. Yalnızca bir hastada tedavinin ilk ayında tedaviye ara verecek düzeyde transaminaz yüksekliği saptandığından tedaviye ara verildi. Bir hasta kaybedildi.

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Conclusion: In this study, extrapulmonary tuberculosis was more common than pulmonary tuberculosis. It was determined that the treatment was generally well tolerated and the culture positivity rates were low.

Keywords: Tuberculosis, childhood, pulmonary, extrapulmonary

Introduction

Tuberculosis (TB) infection and disease are seen in developing countries, especially in children with increasing frequency (1). Pediatric tuberculosis is an indicator of the fact that tuberculosis in adults is not controlled and is the basis of adult TB cases. Therefore, the identification and effective treatment of children with tuberculosis in the community is an important point in the fight against TB (2).

Today, there are problems in microbiological confirmation of childhood tuberculosis diagnosis. Initial criteria for the diagnosis of tuberculosis are history of contact with tuberculosis patients, tuberculin skin test (TST) positivity and positive radiological findings. For final diagnosis, the agent should be detected with microbiological methods. Detection of TB bacilli with microscopic examination is the fastest and most useful method in diagnosis. However, the indicator with the highest diagnostic value is to suspect from the disease undoubtedly (3,4).

In our study, the in-and out of-house contact features of TB patients who were diagnosed and treated in our clinic, their immunization status, their complaints, their laboratory and radiological data, TST results, culture results, treatment regimens, and the distribution of the disease according to the lungs and out of the lungs were evaluated and we aimed to determine the characteristics of the disease in our region.

Materials and Methods

This study includes retrospectively evaluating 33 cases diagnosed with TB in the Pediatric Clinic of Adana Numune Training and Research Hospital between 1 January 2012 and 31 December 2014. History, clinical, radiological, microbiological and other laboratory findings were evaluated for the diagnosis of tuberculosis, analyzing the files obtained from the archive of the hospital. Patients with only pulmonary parenchymal involvement, and possible clinical, radiological and microbiological tuberculosis are defined as pulmonary tuberculosis, and patients who have clinical findings belonging to organs other than lung parenchyma and are diagnosed with tuberculosis radiologically, microbiologically and histo-pathologically are defined as non-pulmonary tuberculosis. The contact history of patients included in the study with adult patients with tuberculosis was obtained from the history part of the patient files. Whether

Sonuç: Bu çalışmada akciğer dışı tüberküloz akciğer tüberkülozundan daha yaygın olarak saptandı. Tedavinin genellikle iyi tolere edildiği ve kültür pozitifliği oranlarının düşük olduğu saptandı.

Anahtar Terimler: Tüberküloz, çocukluk çağı, akciğer, akciğer dışı

the patients were vaccinated was evaluated by looking at their vaccination cards, and in patients without vaccination card by looking at BCG scars.

Acid resistant bacillus (ARB) was analyzed from sputum of the patients who could discharge sputum and from fasting gastric juice, for three days at early hours before stomach began to peristalsis the swallowed lung secretions during night and before the child moved after eight-ten-hour fasting period, of the patients who could not discharge sputum and who were in small age. Lumbar puncture was performed in patients who were thought to have tuberculosis meningitis and miliary tuberculosis, and ARB and culture were sent.

The tuberculin skin test was performed by the trained nurse using a tuberculin injector on the volar side of the left forearm by applying 0.1 mL of PPD solution intradermally according to the Mantoux method. The transverse diameter of the induration that occurred 48 hours after the application was measured by a pediatric infectious disease specialist or a pediatrician with the ballpoint pen method. Ethical approval was obtained by the decision numbered 131 and dated 11.03.2015 of Adana Numune Training and Research Hospital non-interventional Clinical Research Ethics Board.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA) program. Whether the numerical measurements in the study group provided the assumption of normal distribution were tested by Shapiro Wilk test, the descriptive statistics of the normal distribution groups were calculated as mean \pm standard deviation, and the descriptive statistics of those who did not show normal distribution were calculated as median (min-max). Categorical data are provided in the form of percentage (%). Chi-square test was used to compare categorical measurements between groups. T test was used in the case assumptions were met in comparison of numerical measurements between groups, and Mann-Whitney U test was used if assumptions were not met in independent groups. The significance limit was defined as $p < 0.05$.

Results

Of the 33 children with tuberculosis, 11 (33.3%) were male and 22 (66.7%) were female. The median age was 13 (1-17). When tuberculosis patients were examined according to their

place of residence, 14 (42%) patients had pulmonary tuberculosis and 19 (57.6%) patients had non-pulmonary tuberculosis. When they were examined in terms of involvement area, 14 patients (42.5%) had primary pulmonary tuberculosis, 14 (42.5%) had superficial lymph node tuberculosis, 2 (6%) had miliary TB, 1 (3%) had tuberculosis meningitis, 1 (3%) had intestinal tuberculosis, and 1 (3%) had vertebral tuberculosis (Pott disease).

Of the patients with pulmonary tuberculosis, 11 (78.6%) were female and the mean age was 13.5 ± 5.53 years. Of the patients diagnosed with non-pulmonary tuberculosis, 11 (57.8%) were female and the mean age was 12 ± 4.99 years (Table 1). There was no significant difference between the mean age of the patients with pulmonary tuberculosis and patients with non-pulmonary tuberculosis ($p= 0.67$). In 7 (50%) of the patients diagnosed with pulmonary tuberculosis, there was a history of in-home contact, 2 (14.3%) had history of out off-house contact, and 5 (35.7%) had no history of contact. In 6 (31.6%) of the patients diagnosed with non-pulmonary tuberculosis, a history of in-home contact was found, and 13 (68.4%) did not have a history of any contact (Table 1).

In 9 (64%) of the patients diagnosed with pulmonary tuberculosis, BCG scar was present, and 5 (36%) had no BCG scar. In 15 (79%) of the patients diagnosed with non-pulmonary tuberculosis, BCG scar was present, and 4 (21%) had no BCG scar.

The most common complaints were weight loss (45.4%), fever (42.4%), lymphatic swelling (42.4%), coughing (42.4%) and night sweats (36.3%) (Table 2). One (3%) patient with Pott disease had complaints of inability to walk, urinary and fecal incontinence.

When the physical examination findings of the cases were examined, physical examination findings were normal in 7 (50%) of the patients with pulmonary tuberculosis. As lung listening findings, 4 patients (28.6%) had diffuse crepitant rale, 2 (14.3%) had wheezing and 1 (7.1%) had coarse rale and wheezing. Of the patients diagnosed with non-pulmonary tuberculosis, 14 had superficial lymph node tuberculosis and all

had lymphadenopathy (LAP) as a physical examination finding. 9 (65%) of the patients had cervical, 2 (14%) had submandibular, 1 (7%) had inguinal, 1 (7%) had supraclavicular and 1 (7%) had axillary lymph node.

Acid-resistant bacillus (ARB) was analyzed in fasting gastric juice of all of 14 patients with pulmonary TB diagnosis for three consecutive days and it was positive in 4 (28.6%). Out of 19 patients diagnosed with non-pulmonary tuberculosis, 15 had at least 1 ARB analysis in body fluids and total 2 patients including 1 patient with TB meningitis and 1 patient with diagnosis of miliary TB (13.3%, 2/15) had positive ARB.

Mycobacterium tuberculosis culture was sent from all 14 patients diagnosed with pulmonary TB. *M. tuberculosis* growth was detected in a total of 3 (21.4%) patients (in sputum of 1 patient and in AMS of 2 patients). Out of 19 patients diagnosed with non-pulmonary TB, *M. tuberculosis* culture of 15 patients was sent and Tuberculosis growth was detected in AMS of totally 2 (13.3%, 2/15) patients (1 patient with TB meningitis and 1 patient with miliary tuberculosis). No multi-medicine resistance was found in any of the patients with culture growth.

It was detected that one patient with pulmonary tuberculosis had lobectomy in histopathological examination and it also revealed granulomatous inflammation and necrosis. Out of the patients diagnosed with non-pulmonary tuberculosis, 14 (73.7%) had total lymph node excision, 1 (5.3%) had bone biopsy and 1 (5.3%) had appendectomy. When the histopathological results of lymph node excisional biopsies of patients diagnosed with tuberculosis lymphadenitis were examined, caseificated granulomatous inflammation was found in 11 patients (78.6%) and granulomatous inflammation was detected in 3 (21.4%) patients.

When the TST results of the cases were examined, of the patients with pulmonary tuberculosis, 5 (35.7%) had a positive TST and 9 (64.3%) had a negative TST. In patients with BCG vaccine scar, TST positivity was found to be 44.4%, whereas TST positivity was found to be 20% in patients without BCG vaccine scar. Of the patients diagnosed with non-pulmonary

Table 1. Demographic characteristics and laboratory findings of patients in terms of tuberculosis location

	Number of patients n	Gender	Age* (year)	TST **	Contact history	ARB positivity	Culture positivity
Pulmonary Tuberculosis	14	11 (78.6%) females 3 (21.4%) males	13.5 ± 5.53	5 (35.7%)	7 (50%) *** 2 (14.3%) ****	4 (28.6%)	3 (21.4%)
Non-pulmonary Tuberculosis	19	11 (57.8%) females 8 (42.2%) males	12 ± 4.99	6 (31.6%)	6 (31.6%) ***	2 (10.5%)	2 (10.5%) * Mean \pm standard deviation
* Mean \pm standard deviation, ** Tuberculin skin test positivity, *** In-home contact history, **** Out-of-home contact history. TST: Tuberculin skin test, ARB: Acid resistant bacillus.							

Table 2. Distribution of complaints of patients diagnosed with tuberculosis

Symptoms	Number of patients (n)	Percentage (%)
Weight loss	15	45.4
Fever	14	42.4
Swelling in Lymph gland	14	42.4
Cough	14	42.4
Night sweating	12	36.3
Sputum extraction	9	27.2
Loss of appetite	8	24.2
Nausea/vomiting	8	24.2
Dyspnea	4	12.1
Headache	4	12.1
Chest pain	2	6
Stomachache	2	6
Non-Symptoms	2	6
Hemoptysis	1	3
Other (unable to walking, urinary and stool incontinence)	1	3

tuberculosis, 6 (31.6%) had positive TST and 13 (68.4%) had negative TST. In patients with BCG vaccine scar, TST positivity was found to be 33.3% and TST positivity was 25% in patients without BCG vaccination scar.

Pneumonic infiltration and hilar LAP were the most common findings in the anteroposterior chest radiographs (PAAG) of patients with pulmonary tuberculosis, and these findings were found in 6 (42.9%) of the patients. 3 (21.4%) of the patients had hilar LAP, 2 (14.3%) had pneumonic infiltration, 1 (7.1%) had cavity and 1 (7.1%) had endobronchial spread. While 17 (89.5%) of the patients with non-pulmonary tuberculosis had normal POAG, there were miliary spread findings on chest radiographs of patients with miliary TB. 5 (41.7%) of 12 patients with pulmonary tuberculosis who underwent computed tomography had pneumonic infiltration and hilar LAP, 3 (25%) had hilar LAP, 2 (16.7%) had pneumonic infiltration and cavity, and 2 (16.7%) had pneumonic infiltration, hilar LAP and endobronchial spread. Of 8 patients with non-pulmonary tuberculosis who underwent computed tomography, 1 (12.5%) had paratracheal LAP and 1 (12.5%) had axillary LAP. Thorax tomography was normal in 6 (75%) patients.

The initial treatment of 6 patients (42.8%) diagnosed with pulmonary tuberculosis was isoniazid-rifampicin-pyrazinamide and the initial treatment of 8 (57.2%) was isoniazid-rifampicin-pyrazinamide-ethambutol. At the end of the second month, the treatment was continued with isoniazid-rifampicin. 3 patients (21.4%) received treatment for 6 months, 8 patients (57.1%) received treatment for 9 months, and 1 patient

(7.1%) received treatment for 12 months, and 1 patient (7.1%) had no follow-up, and 1 (7.1%) left the treatment. One patient who was diagnosed with miliary TB died due to recurrent ventriculo-peritoneal shunt infection and recurrent pneumonia. It was detected that the treatment period of one patient with a diagnosis of miliary TB, 1 with TB meningitis, 1 with intestinal TB and 1 with pott disease lasted 12 months. Fourteen patients who were diagnosed with superficial lymph node TB were treated for 6 months. The initial treatment of 14 patients diagnosed with superficial lymph node TB was isoniazid-rifampicin-pyrazinamide for 2 months and the continuation treatment was isoniazid-rifampicin for 4 months.

In 8 (24.3%) of the patients diagnosed with tuberculosis, side effects were observed. 6 (18.2%) patients had high levels of uric acid and 2 (6.1%) had increase in liver enzymes. High level of uric acid was detected in 5 of 6 patients in the first month of treatment while high level of uric acid was detected in 1 in the third month of treatment. The high level of uric acid was not sufficient to interrupt treatment. Liver enzyme increase was detected in 2 of 2 patients in the first month of treatment and 1 patient had moderate transaminase elevation, while the other patient had high transaminase at acute hepatitis level. In this patient, all medications were discontinued and treatment was resumed when liver enzymes were normal.

Discussion

Tuberculosis is the ninth cause of deaths resulting from a single infectious agent worldwide (5). Although childhood tuberculosis is ignored by many clinicians and tuberculosis is seen as an adult disease, it may cause pulmonary and non-pulmonary disease in children, especially in societies with low socioeconomic status (6). Childhood TB is a completely curable disease if diagnosed. A delay in diagnosis and treatment is also important in terms of causing disruption of the TB control program in the society (6).

According to the 2015 Tuberculosis Control Report published by TR Ministry of Health, Turkey Health Agency, 41.2% of the patients in all age groups are female and 58.8% are male. And also, the male/female ratio is 1.7 according to the World Health Organization (5,7). In our study, 66.7% of the patients were female and 33.3% were male. The mean age of the cases was 13 ± 5.14 in our study and it is a high value compared to the children series in the literature (8,9). One of the possible reasons is the age of contact with bacillus. It is observed that lung involvement is lower than the literature in terms of distribution according to the location in the body (7,8,10). The reason for this difference may be the old age of the cases, late consultation or late diagnosis. The most common form of non-pulmonary tuberculosis in children is superficial lymph node tuberculo-

sis and the frequency order of other forms of non-pulmonary tuberculosis is tuberculosis meningitis, tuberculous pleurisy, miliary tuberculosis, bone-joint tuberculosis, respectively (11). Similarly, the most common form of non-pulmonary tuberculosis in our study was superficial lymph node tuberculosis. The frequency order of other forms of non-pulmonary tuberculosis is tuberculosis, tuberculosis meningitis, intestinal tuberculosis and vertebral tuberculosis, respectively.

The presence of a history of contact with the patient with tuberculosis has an important role in the diagnosis of childhood tuberculosis. Tuberculosis infection in children is mostly caused by adults with TB and the most common form of contact is in-home contact (10). In our study, the history of in-home contact was found in 50% of the patients diagnosed with pulmonary tuberculosis and the history of out off-house contact was found in 14.3% of the patients while there was no any history of contact in 35.7% of the patients. 31.6% of the patients diagnosed with non-pulmonary tuberculosis had a history of in-home contact.

Cough, night sweats, weight loss, and fever which are the most common complaints are not special to tuberculosis. They are given in the most frequent and close proportions in various series (12). In our study, the patients' initial symptoms were similar; weight loss, cough, fever, swelling of the lymph gland and night sweat. The reason for the high rate of admission due to swelling in the lymph nodes was thought to be the fact that the patients who were admitted to the neighboring hospitals due to the swelling in the lymph nodes were directed to our hospital.

Tuberculosis in adults is not usually seen in children, and the disease is usually occult in children and different findings may be observed according to the involvement organ. As a symptom of listening in the lung, ral may be seen in adolescents, wheezing may be observed in children under one year of age and sometimes findings resembling foreign body aspiration can be detected (13). As in literature, the physical examination findings of the patients diagnosed with pulmonary tuberculosis were asymptomatic in 50% of the cases, while crepitant ral was detected in 28.6%, wheezing was detected in 14.3% and rough ral and wheezing were detected in 7.1% (14). In our study, physical examination findings of patients with non-pulmonary tuberculosis were found to vary according to the involvement organ. All patients diagnosed with superficial lymph node tuberculosis had LAP and most of the patients had cervical lymph nodes as in literature (65%).

Unlike adult tuberculosis, it is often not possible to indicate bacilli in childhood tuberculosis. The main reason for this is the difficulty of sampling and weak samples in terms of bacilli. Tuberculosis bacillus positivity in sputum or gastric juice of adults was reported to be 75%, whereas in childhood tubercu-

losis, this rate was reported to be less than 20% (14). Similarly, in our study, 28.6% of patients with pulmonary tuberculosis were found to have positive ARB. 10.5% of the patients diagnosed with non-pulmonary tuberculosis had positive ARB. It was thought that ARB positivity was lower in the non-pulmonary tuberculosis group because of the high number of cases with tuberculosis lymphadenitis and the fact that there were fewer bacilli in the samples than the pulmonary tuberculosis. *M. tuberculosis* can be growth at 30-40% rate in culture. (15). In our study, *M. tuberculosis* growth was detected at low rate as in literature and this growth was observed in 21.4% of patients diagnosed with pulmonary tuberculosis and 10.5% of patients diagnosed with non-pulmonary tuberculosis.

TST plays an important role in the diagnosis of childhood tuberculosis. In various studies conducted in our country, it has been found that TST positivity ranges between 47% and 75%, and TST has been found to be more positive in the patients with BCG than patients who did not receive BCG (9,16). However, many children with BCG vaccination do not develop TST positivity (14). In our study, as other studies conducted in Turkey, TST was positive in 35.7% of patients with pulmonary tuberculosis while TST was positive in 44.4% of the patients with pulmonary tuberculosis with BCG scar. While TST was positive in 31.6% of the patients diagnosed with non-pulmonary tuberculosis, 33.3% of the patients diagnosed with non-pulmonary tuberculosis with BCG scar had positive TST.

Before the tuberculin skin test is positive in children smaller than five year-old who have contacted with someone with tuberculosis, the miliary tuberculosis and tuberculosis meningitis, which are the early complications of pulmonary tuberculosis, may develop with intense lymphohematogen proliferation (1). In our study, TSTs of patients diagnosed with miliary TB and tuberculosis meningitis were negative.

In radiological examination, the main finding in pulmonary tuberculosis in infants and children is hilar or paratracheal LAP in a relatively large size and primer infection focus at a less rate. In adolescents with pulmonary tuberculosis, LAP may be accompanied by segmental lesions or infiltration in apex with or without cavitation like adult active tuberculosis finding (1). In our study, chest X-Ray was performed in all patients, and the most common X-Ray finding was the presence of pneumonic infiltration and hilar LAP in patients with pulmonary tuberculosis.

In the last 30 years, in many studies about the effectiveness of anti-tuberculosis treatment approaches, it is recommended that the most appropriate treatment period for medicine-sensitive pulmonary tuberculosis is 6 months and the pre-treatment should start with isoniazid-rifampicin-pyrazinamide as triple therapy. In many non-life-threatening forms of non-pulmo-

nary tuberculosis as well as pulmonary tuberculosis, six-month treatment containing three or four medicines is enough for pre-treatment. 9-12 months of treatment is recommended for bone-joint tuberculosis and tuberculosis meningitis (17). In our study, it is possible to say that the treatment protocols and treatment period are compatible with the literature and the treatment is well tolerated.

Conclusion

Childhood tuberculosis is very important because it leads to reactivation tuberculosis in adulthood period, it may also lead to waste time due to being diagnosed as bacterial pneumonia, and it can transform into miliary tuberculosis and tuberculosis meningitis forms with high mortality and morbidity rates due to delay in diagnosis and treatment and it should be considered in the differential diagnosis of infectious diseases in our country.

Ethics Committee Approval: Ethics committee approval was received for this study from the "Adana Numune Training and Research Hospital non-interventional Clinical Research Ethics Board.

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

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