PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPINES

Vol.18 No.2
July - December 2017

PIDSP JOURNAL

Vol 18, No. 2
July - December 2017

ORIGINAL ARTICLE

Clinical Profile and Treatment Outcomes of Childhood Extra-pulmonary Tuberculosis in a Children's Medical Center

Melody O. Kiat, MD*

*Section of Pediatric Infectious Diseases,
Philippine Children's Medical Center, Philippines

Correspondence:
Dr. Melody O. Kiat
Email: melodykiat@yahoo.com

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Background: Extrapulmonary tuberculosis comprises 1.1% of all tuberculosis (TB) cases notified in the Philippines.[34] Its diagnosis poses a challenge for clinicians due to the protean ways in which the disease presents. Monitoring its treatment outcome is essential to evaluate the effectiveness of the intervention.

Objective: This study aims to determine the clinical profile and treatment outcomes of children with extrapulmonary tuberculosis in a children's medical center.

Methods: This is a retrospective cross-sectional study conducted in a children's medical center. The medical records of children less than 15 years with extrapulmonary tuberculosis from 2010 to 2014 were reviewed. Demographic, clinical data and treatment outcome were noted.

Results: A total of 140 charts were reviewed. Male to female ratio is 2.3:1. The most common age group was 0-4 years and central nervous system (CNS) was the most predominant site. New cases were 96.4% and 97.1% were clinically diagnosed. History of TB contact was elicited in 36.4% and tuberculin skin test was positive only in 39.3%. The most common presenting symptoms were in association with the site of infection. Results of the different diagnostic modalities used have contributed significantly in establishing the diagnosis. Treatment outcome was favorable at 79.3% while deaths were seen in 11.4% of cases.

Conclusion: The study has shown that proportion of patients with extra-pulmonary tuberculosis was 3%. Treatment outcome was satisfactory at 79.3% but was not significantly associated with the site of infection.

KEYWORDS:

extra-pulmonary TB, children, TB treatment outcome

INTRODUCTION

Tuberculosis (TB) remains to be a major global health problem. It is an infectious disease caused by *Mycobacterium tuberculosis* that typically affects the lungs but can affect other sites as well. Globally in 2014, there was an estimated 9.6 million new cases of TB. The World Health Organization (WHO) current estimates in 2015 are that 1 million children (< 15 years)—suffer from TB worldwide and that more than 136,000 die each year.[1] 75% of them occur in high-burden countries such as the Philippines. Based on the 2010 statistics, TB is the 6th leading cause of morbidity and mortality in the Philippines. According to the surveillance report of TB profile in the Philippines from 2003-2011, pulmonary TB comprises 98.9% of all TB cases notified and extra-pulmonary TB made up the remaining 1.1%.[34]

Extra-pulmonary TB (EPTB) refers to TB involving organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, bones and joints, meninges or the brain). Mycobacteria may spread to any organ of the body through lymphatic or hematogenous dissemination and lie dormant for years at a particular site before causing disease. Manifestations may relate to the system involved or may be non-specific, hence the diagnosis may be elusive and is usually delayed. A definitive diagnosis can be obtained by culture of specimen obtained from a patient. However, diagnosing EPTB remains challenging because most samples are obtained in an invasive procedure and these specimens from relatively inaccessible sites may be paucibacillary, hence diagnosis is often based on presumptive and circumstantial evidence. Also, it is believed that the low case detection may be due to the limited capability of primary care facilities to diagnose these cases and some are diagnosed in hospitals that are not part of the National TB Program, hence they are not reported. There was a local study published in 2013[23] regarding EPTB but the study focused on the prevalence and pattern of EPTB cases. Monitoring the outcome of treatment using standardized approach is essential in order to evaluate the effectiveness of the intervention. Hence this study is being undertaken to assess and document the outcome and clinical profile of these patients in a tertiary care setting.

OBJECTIVES:

This study aims to determine the clinical profile and treatment outcomes of children with extra-pulmonary tuberculosis admitted or seen on an out-patient basis in a children's medical center. Specifically, to describe the clinical profile of the children with extra-pulmonary tuberculosis according to age group, gender, site of infection, history of TB contact and category of treatment, to describe the distribution and diagnosis of extra-pulmonary tuberculosis cases by the site of infection and to document the outcome and compare them as to the different sites of extra-pulmonary tuberculosis.

OPERATIONAL DEFINITION OF TERMS AND VARIABLES

(as defined in the Manual of Procedures of the National Tuberculosis Control Program 5th ed, 2014 DOH)

1. Children–any person who is less than 15 years old
2. Extra-pulmonary TB (EPTB) – refers to a case of tuberculosis involving organs other than the lungs such as pleura,

lymph nodes, abdomen, CNS, GUT, skin, joints and bones.

3. Classification based on bacteriological status are as follows:
   a. Bacteriologically-confirmed (BC)–biological specimen in an extra-pulmonary site is AFB positive by smear microscopy, culture or Xpert MTB/Rif
   b. Clinically-diagnosed (CD)– does not fulfill the criteria of BC but has been diagnosed by a clinician on the basis of histological and/or clinical or radiologic evidence consistent with active EPTB with decision to treat with anti-TB drugs.
4. Category of Treatment:
   a. New case–never had treatment for TB or has taken anti-TB drugs for less than one month
   b. Retreatment–previously treated with anti-TB drugs for at least one month in the past regardless of the outcome.
5. Treatment Outcome:
   a. Cured (C)–patient with BC-TB at the beginning of treatment and who was smear or culture negative in the last month of treatment and on at least one previous occasion in the continuation phase.
   b. Treatment Completed (T)–a patient who completes treatment without evidence of failure but with no record to show that sputum smear or cultures result in the last month of treatment and on at least one previous occasion were negative for BC patient and for CD patient who has completed treatment.
   c. Failure (F)–a patient whose sputum smear or culture is positive at 5 months or later during treatment for BC or does not show clinical improvement anytime during treatment for CD patient.
   d. Died (D)–patient who dies for any reason during the course of treatment.
   e. Lost to follow-up–whose treatment was interrupted for 2 consecutive months or more.
   f. Not Evaluated–a patient for whom no treatment outcome is assigned. This includes cases transferred to another DOTS facility and whose treatment outcome is unknown.
6. Disseminated TB–refers to TB that involves 2 or more non-contiguous sites via lympho-hematogenous and spread to visceral sites that have rich vascular supply such as liver, spleen, brain and bone marrow or miliary TB[16].

METHODOLOGY

This is a retrospective cross-sectional study conducted in a children's medical center. Children less than 15 years of age treated as a case of clinically diagnosed or bacteriologically confirmed extra-pulmonary TB (EPTB) who were previously admitted or treated on an out-patient basis within 2010 to 2014 were included in the study, while those with missing information as pertains to the patient's data checklist were excluded.

The sample size of at least 140 achieves 95% confidence level with 5% margin of error in the estimation of prevalence. The data were described using the frequency counts and percentages. To determine the association among variables with frequency data, extended Fischer's Exact test was used, using SPSS software (with Exact module).

The medical records of EPTB patients meeting the criteria were thoroughly reviewed and the following data were obtained: demographic data

(age, sex), clinical data (history of TB contact, site of infection, category of treatment, classification of TB according to bacteriological status), diagnostic criteria (most common presenting symptom or sign, tuberculin skin test results, radiologic, microbiologic, biochemical and histologic results suggestive of TB) and treatment outcome according to the site of infection.

Approval from the Hospital IRB-Ethics Committee was secured prior to data collection. Only the pertinent data obtained from the patients' charts were utilized with utmost confidentiality for the purpose of this study.

RESULTS

Of the 226 patients diagnosed and treated for extra-pulmonary tuberculosis registered, 140 charts with complete data in their medical records were thoroughly reviewed. The number and proportion of the patients according to the different sites were described in Table 1. More than fifty percent (56.4%) of the cases had TB of the central nervous system, followed by TB of the abdomen (12.9%), TB of the pleura (11.4%) and TB of the lymph nodes (10.8%). Prevalence of skeletal and disseminated TB were 5.7% and 2.8% respectively.

Table 1. Distribution of Subjects by Extra-pulmonary Sites of Infection

Sites of Infection	Number N=140	Percent %
Central Nervous System (CNS)	79	56.4
Abdomen	18	12.9
Pleura	16	11.4
Lymph Nodes	15	10.8
Skeletal	8	5.7
Disseminated	4	2.8

Table 2. Demographic Profile of Subjects by Site of Infection

	CNS n=79	Abdomen n=18	Pleura n=16	Skeletal n=8	Lymph Nodes n=15	Dissemi-nated n=4	Total n=140
Age *p = <0.0001*							
0-4	59	6	5	2	4	1	77
5-9	9	2	6	3	4	2	26
10-14	11	10	5	3	7	1	37
Gender *p = 0.251*							
male	62	10	10	5	9	2	98
female	17	8	6	3	6	2	42

Patient's characteristics such as age and sex in relation to the different sites of infection were shown in Table 2. The age distribution of the subjects according to the site of infection was significantly different. There was a significantly higher proportion of subjects with TB of the CNS among the very young or 0-4 years old, whereas, a higher proportion of older children or 10-14 years old were seen with TB of the lymph nodes and TB of the abdomen. Gender was not significantly associated with the site of infection with overall male to female ratio of 2.3:1.

Table 3 shows the variation in number and proportion of patients according to their clinical profile. Majority were all new cases with regards to the treatment category. Two retreatment cases were seen in abdominal TB and one each for CNS, skeletal and disseminated TB. No retreatment cases were noted in Pleural TB and TB of the Lymph Nodes. These differences were found to be statistically significant.

Of all the EPTB cases, 36.4% had a known history of TB exposure. With regards to the bacteriological status, 97.1% of the cases were clinically diagnosed and 2.9% were bacteriologically confirmed. There were no significant differences with the history of TB exposure and the bacteriological status in association to the site of infection.

Table 3: Clinical Profile of Patients by Site of Infection

	CNS n=79	Abdomen n=18	Pleura n=16	Skeletal n=8	Lymph Node n=15	Disseminated n=4	Total n=140
Treatment Category *p = 0.030*							
New	78	16	16	7	15	3	135 (96.4 %)
Retreatment	1	2	0	1	0	1	5 (3.6%)
With history of TB contact *p = 0.396*	32	3	7	3	4	2	51 (36.4 %)
Bacteriological Status Classification *p = 0.250*							
Bacteriologically Confirmed (BC)	2	1	0	0	0	1	4 (2.9%)
Clinically Diagnosed (CD)	77	17	16	8	15	3	136 (97.1 %)

The distribution of clinical presentation and diagnostic criteria of EPTB according to site of infection are described in Table 4a and 4b. With regards to tuberculin skin testing, only 39.3% were noted to be positive. The most common presenting symptom were in association with the site of infection. Fever was only noted among 42.9% of all cases. Of the 79 patients with TB of the CNS, majority presented with fever (44.3%) and seizure (29.1%) while the rest presented with headache, vomiting and cough. Cranial Ultrasound or Computed Tomography examinations were done in all patients and were all abnormal. Findings included basal meningeal enhancement and hydrocephalus in most of the patients, basal ganglia infarcts and tuberculoma. CSF MTB/RIF Assay was positive in 2.5% and CSF analysis with lymphocytic pleocytosis (leukocyte count of 20-100 cells with lymphocytes predominating at 60-75%) and increased protein levels (1.0-3.0g/L) were present in all patients.

For abdominal TB, 66.7% presented with fever and 33.3% had abdominal pain and/or distention. All patients underwent abdominal imaging, variable results noted were enlarged mesenteric lymph nodes, calcifications and ascites. One patient showed positive ascitic fluid AFB smear. Ten patients had abnormal ascitic fluid results (lymphocytic pleocytosis, high protein content) and 2 patients showed histologic results of caseating granulomas suggestive of tuberculosis.

For Pleural TB, 16 patients had tuberculous pleural effusion. Symptoms included fever (31.2%), cough (50%) and dyspnea (18.8%). In addition to effusion, chest radiographs showed enlarged hilar lymph nodes in 4 patients and atelectasis in 2 other patients. All patients had lymphocytic exudative effusions but none showed presence of AFB in the pleural fluid

smears. For Skeletal TB, the sites affected were thoracic spine in 4, lumbosacral spine in 2 and knee joints in 2 patients. Symptoms included fever (25%), weakness (25%), low back pain (25%) and localized inflammation/swelling (25%). One patient presented with gibbus deformity. A needle aspiration was done in 1 patient and synovial fluid analysis showed an elevated protein level but was negative for AFB smear. Radiologic changes characteristic of tuberculosis noted were lytic lesions, sclerosis, or calcification.

In TB of the lymph nodes, a total of 15 patients were included. Lymph node enlargement and/or painful adenopathy was the only significant sign of infection among 66.7% while the remaining 33.3% presented with high grade fever but noted with lymph node enlargement upon physical examination. The most frequently involved sites were the submandibular and anterior cervical nodes with lymph node sizes around 2-3 cm. Chest radiographs showed hilar lymph nodes in 3 patients, calcified lymph nodes in 2 others, while the remaining 10 had normal chest radiographs. Lymph node biopsy was done in 5 patients which showed caseating granuloma suggestive of tuberculosis. Mycobacterial TB culture was requested among these patients but were not done due to financial reasons. Disseminated TB was diagnosed in 4 patients. Two patients had TB of the CNS and abdomen, 1 patient with miliary TB and TB of the CNS and 1 had TB of the CNS, skeletal TB and pulmonary TB. Two of the patients presented with prolonged fever, increased sleeping time and weight loss while the other 2 had chronic cough, headache and intermittent fever. All had radiologic findings suggestive of tuberculosis. All patients had hydrocephalus with basal enhancement on cranial computed tomography. Two showed concomitant abdominal calcification with enlarged mesenteric lymph nodes on abdominal radiograph. The other 1 had concomitant lytic lesions in the thoracic spine and hilar adenopathy and 1 had miliary nodules seen in the chest radiography. Only 1 patient had positive sputum AFB smear and Xpert MTB/RIF assay. Two patients who underwent lumbar tap showed lymphocytic pleocytosis in CSF with increased protein and low sugar while the other 2 died prior to contemplated lumbar tap.

Overall, the radiologic, biochemical and histologic findings suggestive of TB were all significantly associated with the site of infection.

Table 4a: Diagnostic Criteria Fulfilled by the Site of Infection

Diagnostic Criteria	CNS n-79	GIT n=18	Pleura n=16	Bones/ Joints n=8	Lymph Nodes n=15	Disse-minated n=4	Total n=140
*** positive tuberculin skin test** *p = 0.160*	25	10	5	5	8	2	55 (39.3%)
suggestive radiologic findings *p = <0.001*	79	18	16	8	5	4	127 (90.7%)
(+) microbiology results (AFB, TB culture, Xpert) *p = 0.250*	2	1	0	0	0	1	4 (2.9%)
**** compatible biochemistry results** *p = <0.001*	79	10	16	0	0	2	107 (76.4%)
*****compatible histologic results** *p = <0.001*	0	2	0	0	5	0	7 (5%)

*TST positive: ≥ 5 mm in the presence of: history of close contact w/ a TB source, clinical findings suggestive of TB, CXR suggestive of TB, immunocompromised condition, otherwise ≥ 10mm induration is considered positive

**radiologic/US findings: hilar adenopathy, miliary nodules, pleural effusion, mesenteric adenopathy with calcifications, ascites, lytic lesions, hydrocephalus, basal enhancement etc

***body fluids analysis: increased protein, low glucose, lymphocytic pleocytosis in CSF, pleural, peritoneal or synovial fluid

****histopathologic findings: chronic granulomatous inflammation with caseation necrosis.

Table 4b: Clinical Presentation According to Site of Infection

Symptoms/Signs	CNS N=79	Abdomen n=18	Pleura n=16	Bones /Joints n=8	Lymph Nodes n=15	Dissemi-nated n=4	Total n=140
fever *p = 0.246*	35	12	5	2	5	2	60 (42.9%)
cough ***p = <0.001***	8	0	8	0	0	2	18 (12.9%)
seizure ***p = <0.001***	23	0	0	0	0	0	23 (16.4%)
headache *p = 0.639*	7	0	0	0	0	0	7 (5%)
vomiting *p = 0.718*	6	0	0	0	0	0	6 (4.3%)
abdominal pain / distention ***p = <0.001***	0	6	0	0	0	0	6 (4.3%)
dyspnea ***p = 0.012***	0	0	3	0	0	0	3 (2%)
weakness ***p = 0.003***	0	0	0	2	0	0	2 (1.4%)
low back pain ***p = 0.003***	0	0	0	2	0	0	2 (1.4%)
swelling of extremity ***p = 0.003***	0	0	0	2	0	0	2 (1.4%)
adenopathy ***p = <0.001***	0	0	0	0	10	0	10 (7.1%)

Treatment outcome in relation to the different sites of EPTB is presented in Table 5. A combined outcome of cured and treatment completed were seen in 79.3% or 111 patients. Two failed treatments were noted in CNS and abdomen. There was a total mortality of 16 out of 140 cases where 69% had CNS TB, 19% with abdominal TB and 12% with disseminated TB. Lost to follow up rate was 2.1% and 5.7% were not evaluated. The treatment outcome based on this study was not significantly associated with the site of infection.

Table 5: Treatment Outcomes According to Site of Infection

Treatment Outcome	CNS N=79	Abdomen n=18	Pleura n=16	Bones /Joints n=8	Lymph Nodes n=15	Dissemi-nated n=4	Total n=140
Cured	1	1	0	0	0	0	2 (1.4%)
Completed	61	10	15	7	15	1	109 (77.9%)
Failed	1	1	0	0	0	0	2 (1.4%)
Died	11	3	0	0	0	2	16 (11.4%)
Lost to Follow up	1	1	0	1	0	0	3 (2.1%)
Not Evaluated	4	2	1	0	0	1	8 (5.7%)
p = 0.184							

DISCUSSION

Children can present with tuberculosis at any age and every organ could be the target organ. Estimating the exact proportion of extra-pulmonary tuberculosis in the community is difficult. Difficulties are attributed to the diagnosis and reporting. The diagnosis is a difficult challenge and frequently delayed especially in children since the signs and symptoms are non-specific depending on the affected sites and the relative unavailability of diagnostic tools. In this study, the frequency of EPTB cases based on the hospital registry including the TB-DOTS is 3% of all TB cases. This is consistent with a local study done on the same population by Santos[23] where EPTB constituted 3.54% of all TB cases from 2006-2010. This is in contrast to a study done in Greece where EPTB in children accounted for 9% of their total TB cases. The increased incidence was mainly attributed to the immigration shift from Eastern Europe during the past decade[6].

Children show a higher predisposition to the development of extra-pulmonary tuberculosis. In a study done by Marais et al, host immunity was considered to be the major determinant of risk for disease development following infection. Infants with immature immune systems were at highest risk for extra-pulmonary such as TB meningitis or disseminated miliary disease developing in 10-20% then further decreased to 2-5% in the second year of life. The risk further decreased to less significant levels at 2-5 years of age before reaching its lowest level (<0.5%) at 5-10 years of age[30]. The age distribution in our study is significantly associated with the site of infection. Majority of the subjects fall in the very young age group of 0-4 years (77%) where TB of the CNS predominates. This is in congruence with the study done in 2002[21] where their results revealed that there were significantly more subjects in the younger age group (< 5 years) who had TB of the CNS. This was also similar to the study of Van Well GT et al[26] where 82% of TB of the CNS were less than 5 years of age. Disease occurred less frequently in children aged 5-10 years while pleural effusion became more common throughout this period[30]. This appeared to be the same with our results where pleural TB was seen predominantly among the 5-9 years old. Older age groups (10-14 years) showed higher predilection to abdominal TB and TB of the lymph nodes. This was

also noted in a study done by Alavi et al where the highest percentage of TB of the lymph nodes was seen in the older age group (10-15 years).[5] Over all in this study, the most predominant site is CNS accounting for 56% of all EPTB cases and this finding is similar to the local study done by Santos et al where 72.7% of EPTB cases involved the meninges[23]. This was also observed in the study by Gosai et al[25] which involved CNS in 46% of all EPTB cases. This is in contrast with other studies[3,5,6,22,27,28,33] where the lymph node is the predominant site. This higher percentage may be due to the higher number of admissions of TB of the CNS due to its complications, since this children's medical center is a referral center, while TB of the lymph node is usually treated on an outpatient basis. For the gender differentiation, no significant difference was observed in the distribution according to the sites of infection. Our study showed a higher number of cases in male than female with 2.3:1 ratio in all sites. This finding was in accordance with the earlier observations made by Pama and Gatchalian[21] with 1.2:1 male to female ratio. Similarly, in India, the male to female ratio was 1.9:1[25].

Among the 140 cases reviewed, exposure to a known TB source was elicited only in 51 cases or 36% of the subjects which is not significantly associated with the site of infection. This is consistent with the study done in Nepal by Shrestha et al[14] where exposure was established in only 32% of their respondents, while 49% was found in a study done in South Africa[17]. This may be due to the social stigma attached to the disease or due to undiagnosed cases[14]. Hence, intensive contact tracing should be pursued upon diagnosis of an EPTB in a child to prevent delays in diagnosis and treatment leading to high mortality and prevent further spread of the disease.

Bacteriologic confirmation, the accepted gold standard in its diagnosis, is hard to obtain in children because of the paucibacillary nature of the disease and poor bacteriologic yield[14]. So, the diagnosis in children mainly depends on the clinical features accompanied by high index of suspicion. In this study, 97% were clinically diagnosed, while 3% were bacteriologically confirmed mainly because not all specimens were submitted for cultures or Xpert MTB/RIF Assay due to financial reasons and or unavailability of this diagnostic tool. The sensitivity of diagnostic techniques including acid fast smear and culture is low. Only 5-13% are acid fast bacterium smear positive and only 40-50% of cases are culture proven.[21] Aside from the paucibacillary nature of the illness, poor yield of AFB may be due to poor sample collection. Most of the cases (96.4%) are newly diagnosed and only 3.6% were retreatment cases. This high percentage of new cases may suggest a continuing transmission of the disease to the young from adults infected with the disease.

Tuberculin skin testing (TST) is the basic screening tool for TB infection among children. There is no diagnostic criteria being followed for EPTB. TST may be a supportive method for diagnosing EPTB but has limited diagnostic value. Hence the need to review its utility in diagnosis is warranted or the call for newer modalities like IGRA may warrant further investigations. This study showed positive results of TST only in 39% of the cases. This low proportion of patients is the same as what was noted in other studies[18,19] where it was reported to be around 30-40%. But negative test results should not exclude the disease since its reactivity can be

complicated by a variety of factors that can reduce the response. The result must be interpreted in the context of the clinical features. False negative results can be as high as 50% which could explain the rate of negative results in this study.[20]

The clinical presentation of TB in children takes many forms. The diagnosis in most cases is still based on clinical evidences accompanied by a high index of suspicion. The occurrence of fever which is the most common presenting symptom in this study was universal among all cases but is not significantly associated with the site of infection since it is non-specific and can be seen in almost all kinds of infection. For TB of the CNS, seizure was found to be significant in 29.1% of the cases. This was also noted in two other studies[25,26] which showed that seizure and altered sensorium were present in 80% and 96% of the cases, respectively. The presence then of fever and seizures should make a clinician include CNS TB as a differential diagnosis especially in the younger age group where the incidence of CNS TB is higher. For abdominal TB, abdominal pain and or distention was significant in 33% of the cases. In a recent local study, it was also the most common presenting symptom in 77.3% of the patients[31]. This was also similar in another study done in India where it was observed to be 40% of the cases[25]. Cough and dyspnea were significantly associated with pleural TB accounting for 50% and 18.8% of the cases respectively. For TB of the lymph nodes, adenopathy was noted in 66.7% of cases. This was also similar to a study done in Greece, where 98% presented with adenopathy[6]. The greatest challenge in diagnosis of skeletal TB is to consider the diagnosis, since it is often overlooked or misdiagnosed especially some do not have signs or symptoms of TB. In addition, delays in diagnosis are common given the indolent nature of tuberculous bone and joint disease. In this study, weakness, low back pain and swelling were significantly associated in 75% of the diagnosed skeletal TB cases.

Diagnosing extra-pulmonary TB is invariably more difficult since signs and symptoms are non-specific and in most cases the specimens obtained or submitted are paucibacillary, thereby decreasing the sensitivity of the diagnostic tests[24]. As a result, the diagnosis mostly depends on the use of imaging modalities such as radiography, ultrasonography, computed tomography or MRI as well as histologic evidences obtained from biopsies. These then becomes a useful adjunct in the diagnosis of EPTB in children. Consequently, more easily accessible body fluids can often provide valuable diagnostic clues in EPTB patients. In this study, almost all patients had different imaging modalities and body fluid analysis which were used in establishing the disease.

Treatment outcomes especially cure rate which strictly denotes bacteriologic cure is difficult to assess in children since majority were diagnosed clinically. Hence for children, the favorable outcome was treatment completion. A favorable outcome was achieved in 111/140 (79.3%) of the cases, consisting of those cured (1.4%) and treatment completed (77.9%). Failed treatment was noted in 1.4% while 11.4% died. Among the 11.4% deaths, 69% were TB of the CNS. Treatment failure and higher deaths were due to late diagnosis of TB which already had complications upon diagnosis and non-compliance to treatment. No drug resistance was documented among the patients included in this study. This result was comparable to a previous study done

with 86% success rate and 1.6% mortality[29]. Another study done in Africa also showed 95% treatment completion and 3% mortality[15]. The treatment outcome was not significantly associated with the site of infection.

CONCLUSION

The study has shown that the proportion of patients diagnosed with extra-pulmonary tuberculosis was 3% of all TB cases seen in our children's medical center. CNS is the predominant site of infection and majority of the subjects belong to the very young age group of 0-4 years old. No association was noted between the gender and the site of infection. Most of the cases were new cases (96.4%) and clinically diagnosed (97.1%). The most common presenting symptoms such as seizure, cough, dyspnea, abdominal pain/distention, adenopathy, weakness, low back pain and swelling of extremity were all in association with the site of infection. The diagnostic tests results (radiologic, histologic, biochemical analysis) were significantly helpful in establishing the diagnosis. Treatment outcome was favorable at 79.3%.

The diagnosis of extra-pulmonary TB poses a particular challenge for clinicians because of the protean ways in which the disease presents. Diagnosis requires high clinical suspicion and special diagnostic procedures. Delay in identification and treatment results in significant morbidity and mortality.

RECOMMENDATION

EPTB is less frequent than pulmonary TB, thus there is paucity of data on its incidence in children. It constitutes about 1% of all TB cases in our country but it poses a serious threat in children particularly since in many studies central nervous system is the most common site. Hence a more effective diagnostic strategy, control measures and intensive monitoring and surveillance must be implemented. Since this is a retrospective single-center study, a more comprehensive study involving multi centers and larger population is recommended to document its occurrence throughout the country. Monitoring the outcome and emphasizing the importance of follow-up as well are important to ensure treatment compliance and effective care for patients, and reduce drug resistance. Including EPTB as reportable in private and government institutions with complete recording can contribute towards improving the detection, care and outcomes of EPTB in children and further help the National TB Program of the government to effectively reduce if not eradicate the burden of this disease.

REFERENCES

1. Global Tuberculosis Report 20th edition, WHO, 2015
2. Chandir S, Hussain H, Salahuddin N, Amir M, Ali F, Lotia I, et al. Extrapulmonary Tuberculosis: A Retrospective Review of 194 Cases at a Tertiary Care Hospital in Karachi, Pakistan. 2010 February Vol 60 No 2
3. Jamtsho T, Harries A, Malhotra S, Wangchuk D, Dophu U, Dorji T, et al. The Burden and Treatment Outcomes of Extra-pulmonary Tuberculosis in Bhutan. 2013 March Vol 3 No 1, 21
4. De Gracia ME, Sosa M, Reyes B. Comparison of Treatment Outcomes Among Children Diagnosed with Pulmonary Tuberculosis Treated at the TB DOTS and Pediatric Out Patient Department. *PIDSP Journal* 2014 Jan-Jun Vol 15 No 1 pp 2-8
5. Alavi S, Salmanzadeh S, Pejman B, Albagi A, Hemmatuia F, Alavi L. Prevalence and Treatment Outcome of Pulmonary and Extrapulmonary Pediatric Tuberculosis in Southwestern Iran. 2015 Sept 1

6. Maltezou H, Spyridis P, Kafetzis D. Extra-pulmonary Tuberculosis in Children. *Arch Dis Child* 2000
7. Lee J. Diagnosis and Treatment of Extrapulmonary Tuberculosis. *The Korea Academy of Tuberculosis and Respiratory Diseases*. 2015 March 3
8. Vasankari T, Holmstrom P, Ollgren J, Liippo K, Ruutu P. Treatment Outcome of Extrapulmonary Tuberculosis in Finland: A Cohort Study. *BMC Public Health* 2010
9. Bukhary Z, Alrajhi A. Extrapulmonary Tuberculosis, Clinical Presentation and Outcome. *Saudi Med J* 2004 Vol 25
10. Pusch T, Pasipanodya J, Hall R, Gumbo T. Therapy Duration and Long Term Outcomes in Extrapulmonary Tuberculosis. *BMC Infectious Diseases* 2014
11. Olarewaju S, Olanrewaju O, Ebenezer F, Akintunde B, Temitayo-Oboh A, Saliu A. Treatment Outcome of Tuberculosis Patients Registered at DOTS Center in Ogbomoso, Southwestern Nigeria: A 4-Year Retrospective Study. *Hindawi Publishing Corporation* 2014 September 28
12. Endris M et al. Treatment Outcome of Tuberculosis Patients at Enfraz Health Center, Northwest Ethiopia: A Five-Year Retrospective Study. *Hindawi Publishing Corporation* 2014
13. Ali F, Salahuddin N, Subash C. Extrapulmonary Tuberculosis: A Retrospective Review of 194 Cases at a Tertiary Care Hospital in Karachi, Pakistan. *Journal of Pakistan Medical Association*. 2010 February
14. Shrestha S, Marahatta SB, Poudyal P, Shrestha SM. Clinical Profile and Outcome of Childhood Tuberculosis at Dhulikhel Hospital. *J. Nepal Pediatric Society* 2011 January- April Vol 31 Issue 1
15. Ade S, Harries A, Trebucq A, Ade G, Agodokpessi G, Adjonou C et al. National Profile and Treatment Outcomes of Patients with Extrapulmonary Tuberculosis in Benin. PLoS One 2014 April Vol 9 Issue 4
16. Schaaf HS, Zumla A. Tuberculosis: A comprehensive Clinical Reference 2009
17. Culture-confirmed chilhood Tuberculosis in Cape Town, South Africa: A Review of 596 cases. *BMC Infectious Disease* 2007,7:140
18. Vijaysekaran D, Kumar RA, Gowrishankar NC et al. Mantoux and Contact Positivity in Tuberculosis. *Indian J Pediatrics* 2006; 73:989-93
19. Kabra SK, Lodha R, Seth V. Category based Treatment of Tuberculosis in Children. *Indian J Pediatric* 2004, 41:927-37
20. Kimerling ME, Vaughn ES, Dunlap NE. Childhood Tuberculosis in Alabama: Epidemiology of Disease and Indicators of Program Effectiveness, 1983-1993. *Pediatric Infectious Disease Journal* 1995: 14:678-84
21. Pama, C., Gatchalian S. Clinical Profile of culture-proven Tuberculosis cases among Filipino children aged 3 months to 18 years. *Phil J Microbiol Infect Disease* 2001; 30(4):133-143
22. Sandgren A, Hollo V, Van Der Werf, MJ. Extrapulmonary Tuberculosis in the European Union and European Economic Area 2002-2011. *Euro Survieill* 18(12). 2013 Dec 9
23. Santos, R. Clinical Profile of Extrapulmonary Tuberculosis Cases Admitted and Diagnosed in a Tertiary Government Hospital From January 2006 to June 2010. *PIDSP Journal* 2013 vol 13 No 2
24. Schaaf H, Zumla A. Tuberculosis: A Comprehensive Clinical Reference. 2009, Elsevier Inc.
25. Gosai, D, Gosai J, Shukla O. Study of Clinical Profile of Childhood Extra-pulmonary Tuberculosis. *International journal of Research in Medical Sciences*. 2014 May; 2(2)
26. Van Well GT. Twenty Years of Pediatric Tuberculous Meningitis: A Retrospective Cohort Study in the Western Cape of South Africa. Netherlands, *Neoreviews Official J American Academy of Pediatrics* 2009
27. Fawzia A., Otaibi, Malak. King Khalid University Hospital:Study on Extra-pulmonary TB in Saudi Arabia. 2010
28. Nelson L, Wells Co. Global Epidemiology of Childhood Tuberculosis. *Inst J Tub Lung Disease* 2004; 8(5):636-47
29. Tilahun G, Gebre-Selassie S. Treatment Outcomes of Childhood Tuberculosis in Addis Ababa: A Five Year Retrospective Analysis. *BMC Public Health* July 2016 16:612
30. Marais BJ, Gie RP, Schaaf HS. The Natural History of Childhood Ibtrathoracic Tuberculosis- A Critical Review of the Literature from Pre-chemotherapy Era. *Inter J Tuberc Lung Disease* 2004
31. De Castro SV. Clinical Profile and Factors Associated with Gastrointestinal Tuberculosis among Filipino Children. *Int J Gastroenterol Hepatol Transl Nutr* 2016

32. Khalilzadeh S, Zahirifard S, Velayati A. Tuberculosis of the Spine in Children. *National Research Institute of Tuberculosis and Lung Disease*, Iran 2002
33. Mazta S, Kumar A, Kumar P. Demographic Profile of Childhood TB cases under Revised National Tuberculosis Program in Himacahal. 2010
34. Vianzon R, Garfin A, Lagos A, Belen R. The Tuberculosis Profile of the Philippines, 2003-2011: Advancing DOTS and Beyond. *Western Pacific Surveillance and Response Journal*. 2013 4(2)