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EDITORIAL

Arlene Dy-Co, MD
Editor-in-Chief, PIDSP Journal

Correspondence:
Dr. Arlene Dy-Co
Email: pidsp2009@yahoo.com

SECOND STOP

If the first was fast… the second will be faster…

This second issue from your new editors and editorial board is by no means fast but faster than the first one. Without any formal training on medical journal editing, this task is definitely overwhelming if not daunting. A noted medical journal editor once wrote and I quote "I hope that one day every editor gets some training before beginning work." And we began our work… we have to adapt to you, our reader's point of view while upholding the author's voice. More than checking a paper's spelling and grammar, we prioritize readability instead of merely coming out with a repository of data.

We decided to come out with an issue focused on a particular infectious disease for various reasons. First, this disease remains to be a scourge. Second, there are many aspects of the disease that remains a challenge. Third, we get quite a number of submissions about the disease enough to make up one issue.

TB or not TB? A question asked many times over in your minds, your clinical practice, in round-table discussions, local and international conferences and even in clinico-pathologic presentations. We wish we had the definite answer to this question whenever we are faced with it. Yes, this issue will be all about Mycobacterium.

The scourge remains centuries after it was discovered but the efforts are not wanting. From the Millennium Development Goals to the Sustainable Development Goals up to the WHO Global TB Programme and the Department of Health's National Tuberculosis Control Program, tuberculosis has clearly been a priority. Children remains at high risk and comprise a significant proportion. As there are many ways to skin a cat, we hope that this issue will be a contribution to the call for ways to end TB. We share the vision of a WORLD FREE OF TB.

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.

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ORIGINAL ARTICLE

A META-ANALYSIS ON GENEXPERT USING STOOL SAMPLES IN DIAGNOSING PEDIATRIC PULMONARY TUBERCULOSIS

Othella Mary Ann S. Cacayorin, MD*

*Philippine Children's Medical Center, Philippines

Correspondence:
Dr. Othella Mary Ann S. Cacayorin
Email: othella07@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

OBJECTIVES: To find an alternative specimen for GeneXpert assay in the diagnosis of pediatric pulmonary tuberculosis (PTB). To determine the sensitivity and specificity of using stool samples as an alternative to sputum for GeneXpert assay.

METHODS: A systematic search was done using an electronic database (e.g. Pubmed). Using the keywords "GeneXpert", "tuberculosis", "Stool samples". QUADAS-2 checklist was used in assessing the studies gathered. Revman 5.3 was used to determine the sensitivity and specificity of the study included in this meta-analysis.

RESULTS: A total of 185 stool samples were included in this review, which showed a median sensitivity of 77% (IQR 0.63-0.87) and median specificity of 98% (IQR 0.95-1.0).

CONCLUSION: Despite the heterogeneous sensitivity, GeneXpert has a high specificity, which enabled rapid diagnosis of pulmonary tuberculosis promoting timely initiation of appropriate therapy.

KEYWORDS:

gene xpert, stool, pulmonary tuberculosis

INTRODUCTION

Tuberculosis is one of the most prevalent causes of mortality and morbidity in developing countries affecting both the adult and pediatric population. The diagnosis of pulmonary tuberculosis (PTB) remains challenging in young children because they cannot expectorate spontaneously, making it difficult to obtain a representative specimen from the lower respiratory tract, and because PTB in children is typically paucibacillary. Thus, PTB in children is probably underdiagnosed, hence maybe left untreated due to the challenging diagnostic confirmation or late diagnosis is maybe the typical clinical scenario. (1). Most often, children are treated empirically based on clinical features, chest X-ray findings, tuberculin skin testing, and contact with an index patient.

Microbiological identification of *Mycobacterium tuberculosis* from cultures is the gold standard for diagnosing tuberculosis infection. However, culture of mycobacteria is not able to provide a rapid diagnosis for the clinical management of severe cases, and requires expensive and sophisticated laboratory facilities, which is not available in most resource-limited settings (2). GeneXpert was introduced in 2008 capable of identifying tuberculosis within a few hours and at the same time detect multidrug resistant Tuberculosis (MDRTB) with a high sensitivity and specificity. Extrapulmonary samples can also be tested using the GeneXpert to detect *Mycobacterium tuberculosis.*

A sample that is easy to obtain or obtained in a non-invasive means that will yield a high sensitivity and specificity using GeneXpert for the diagnosis of PTB in children would increase the likelihood of early and accurate diagnosis thus enable a clinician to institute early treatment for this vulnerable population.

Since sputum samples are difficult to obtain in pediatric patients, alternative specimen has been gastric aspirates. However, this specimen's diagnostic yield only ranges from 20-40% (3).

"Young children tend to swallow sputum when they cough or even when asleep. It is also known that *Mycobacterium tuberculosis* DNA can survive intestinal transit" (4). Thus, the rationale for getting gastric aspirate as an alternative to sputum for diagnosing pediatric PTB. Testing stool for *Mycobacterium tuberculosis* DNA from swallowed sputum with the bacteria surviving intestinal transit can possibly be a good alternative for diagnosing pulmonary tuberculosis. Besides, stool collection is easier and non-invasive.

GeneXpert is a portable, highly sensitive, user-friendly and rapid molecular assay with a turnaround time of less than 2 hours (5). It is a nucleic acid amplification test which simulatenously detects DNA of *Mycobacterium tuberculosis* complex and resistance to Rifampicin in less than 2 hours. In comparison to standard cultures that can take 2-6 weeks for MTBC to grow and conventional drug resistance tests can add 3 more weeks. The primer in the XpertMTB/RIF assay amplify a portion of the *rpoB* gene containing the 81 base pair "core" region. The probes are able to diffentiate between the conserved wild-type sequence and mutation in the core region that are associated with rifampicin resistance (6).

The Centers for Disease Control and Prevention (CDC) recommends that testing be performed on at least one respiratory specimen from patients who have a moderate to high risk of having pulmonary TB (6).

"The GeneXpert MTB/RIF test offers a potential solution for improving

tuberculosis diagnosis. By 2013, the first year of full Xpert coverage, 30% more patients were diagnosed in the Xpert scenario than in the baseline scenario. The test appeared to be as sensitive as culture with smear-positive specimens, but less sensitive with smear-negative pulmonary and extrapulmonary specimens that include low numbers of bacilli."(7)

Stool sample can be a good alternative to sputum on detecting *Mycobacterium tuberculosis* using Gene Xpert MTB/RIF assay. This could be a solution to the current challenge of getting respiratory samples in children and become a routine means of diagnosing pulmonary tuberculosis in children.

OBJECTIVES OF THE STUDY

The general objective of the study is to determine the usefulness of geneXpert using stool samples in diagnosing pulmonary tuberculosis in children and to determine its sensitivity and specificity.

Ethical Considerations

The study will use secondary data from previously published studies. No actual patient- researcher interaction will be done. No ethical concerns were encountered in both the data gathering and methodology of this study.

MATERIALS AND METHODS

Systematic Search Strategy

We did a thorough literature search on available publicly accessible scientific journal databases such as MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, HERDIN, other non-English databases and unpublished trials. Using the keywords "GeneXpert", "tuberculosis", "Stool samples", wherein an exhaustive literature search was performed. A manual search in the references and citation lists of eligible studies was also done to further look into relevant studies. Authors of significant journals that were freely accessible were contacted via e-mail.

Inclusion Criteria

Inclusion criteria were used to select appropriate journals to be included in this meta-analysis, as outlined by the PRISMA guidelines. All studies included are randomized controlled trials with a target pediatric population between 1 to 15 years old that have been diagnosed to have pulmonary tuberculosis and PTB suspect. The eligibility, quality assessment and data extraction were done by the author.

Assessment of Study Quality

The study used the QUADAS- 2 checklist to assess the quality of the studies.

Statistical Analysis

A meta-analysis tool Review Manager version 5.3 downloaded from the Cochrane website was used to conduct the meta-analysis. It provided a forest plot of the variables in the studies being compared, as well as their homogeneity and sensitivity.

Studies included

Of a total of 13 citations, 4 potentially relevant citations were identified and 2 of these were further excluded after evaluation. Of these 4 studies, 2 used cross-sectional studies, 1 of which had limited information. Two remaining cohort studies were eligible for inclusion in the qualitative and quantitative synthesis, and reported 185 stool samples using cohort studies. The 2 studies were both done in South Africa. "South Africa is one of the countries with the highest burden of TB, with the World Health Organization (WHO) statistics giving an estimated incidence of 450,000 cases of active TB in 2013. About 1% of the population of about 50 million develop active TB disease each year." (8)

Figure 1. Selection of studies reporting on the use of GeneXpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis using stool samples.

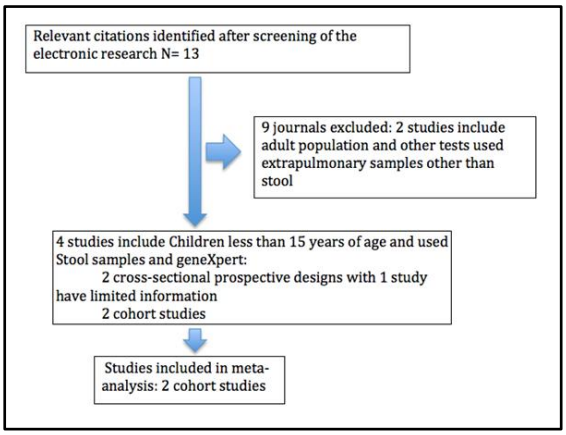


Figure 2. Inclusion criteria used in the study

	Nicol 2013 (published article) N= 115	Banada 2016 (published article) N= 71
Study design: RCT	Cohort	Cohort
Population	< 15 years	< 15 years
Diagnosed with PTB or PTB suspects	Suspected PTB	TB positive
Sample	Stool	Stool
Diagnostic test	GeneXpert	GeneXpert
Gold standard	Induced sputum	Induced sputum
Analysis	Liquid culture	Liquid culture (MGIT)

Diagnostic accuracy of GeneXpert in stool samples for PTB

In the 2 studies included, the study of Nicol et al. showed a sensitivity of 54% (CI 95% 0.25-0.81) and specificity 98% (CI 95% 0.93 -1.0) while the study of Banada et al. showed sensitivity of 85% (CI 95% 0.69-0.81) and specificity of 100% (CI 95% 0.93 – 1.0).

In the study of Nicol, the 0.15 g of thawed stool (confirmed by weighing) was retrieved using pediatric FLOQSwabs (Copan Italia, Brescia, Italy). Swabs were then placed in 2.4 mL PBS and vortexed briefly before being removed. The sample was left undisturbed for 20 minutes at room temperature to allow large particles to settle before 2 aliquots of 1-mL supernatant were removed. One aliquot was tested immediately with Xpert and the other was stored at 4°C for later duplicate testing (within 1 week). Prior to Xpert testing, the sample was centrifuged at 3200 x g for 15 minutes. The supernatant was discarded and pellet was resuspended in 1 mL PBS. Xpert testing was then performed per the manufacturer's instructions using a 2:1 ratio of Xpert reagent to sample (1).

Figure 3. Summary of Sensitivity and Specificity with its PPV and NPV studies

Study	True Positive	False Positive	False Negative	True Negative	Sensitivity	Specificity	PPV	NPV
Banada 2016	33	0	6	32	85%	100%	100%	84.2%
Nicol 2013	7	2	6	99	54%	98%	77.8%	94.3%

In the study of Banada, between 0.2g to 1.2g of stool were processed. Two mls of a stool processing buffer (SPB), containing AL buffer (Qiagen, Valencia, CA) and 10% Polyvinylpyrrolidone (Sigma Aldrich, St. Louis, MO), two ml of Xpert MTB/RIF sample reagent (SR) (Cepheid), and 3 mm glass beads (Fisher Scientific, Pittsburgh, PA) were added to the mixture. The final stool and buffer combination were mixed by snap vortexing (for <10 seconds), incubated for 30 min at room temperature and then passed through a syringe filter (fitted with glass wool to capture the stool debris) into a clean collection vial. Two ml of this filtrate was then loaded into the sample loading chamber of an Xpert assay cartridge. Subsequent sample processing and PCR were performed in accordance with the manufacturer's recommendations using G3 cartridges in GeneXpert instrument (11)

RESULTS

In this meta-analysis, 2 studies were evaluated on the diagnostic accuracy of the GeneXpert MTB/RIF when used to test non-respiratory samples, specifically

stool samples. The specificity of the 2 studies are very high, highlighting its utility as a rule-in test for tuberculosis diagnosis that can be used to reliably prescribe the start of TB treatment when positive. In contrast, sensitivity of the 2 studies was heterogeneous. This heterogeneity could be attributed to how the stool samples have been prepared.

Figure 4. Sensitivity and specificity of Xpert MTB/RIF on stool samples in the 2 studies

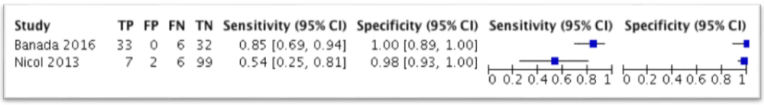
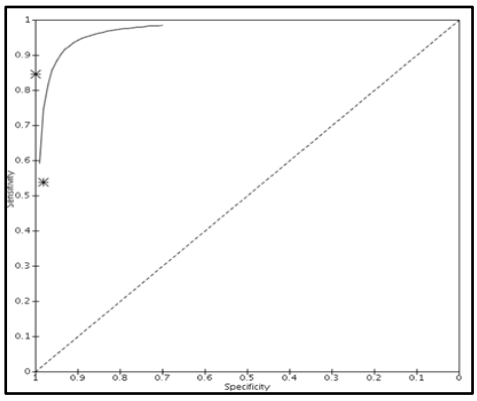


Figure 5. Summary of results of sensitivity and specificity of GeneXpert using stool samples with median sensitivity of 77% (IQR 0.63-0.87) and median specificity of 98% (IQR 0.95-1.0)

BANADA 2016			
	Disease	No Disease	Total
Positive	33	0	33
Negative	6	32	38
Total	39	32	71
NICOL 2013			
	Disease	No Disease	Total
Positive	7	2	9
Negative	6	99	105
Total	13	101	114

Figure 6. Comparison of the Positive Predictive Value and the Negative Predictive Value of both studies



DISCUSSION

In a study done by Hillemann et al., "3 strains were recovered from urine specimens from 1 patient (all of them were culture positive and Xpert assay positive), 2 stool specimens from 1 patient were positive for MTBC (both of them were culture positive and Xpert assay positive)" and in a study done by Taylor et al., 2 studies that evaluated the sensitivity of the GeneXpert system with actual patient stool samples showed a sensitivity of 100% compared to culture, although only 3 samples were tested."(8) These demonstrate that stool samples can be a good alternative to gastric aspiration, using GeneXpert to help in the diagnosis of tuberculosis in children.

In a study done by Walters et al, they found that stool sampling is "child-friendly" and has minimal infectious risk, and can overcome some barriers to bacteriologic investigation of tuberculosis in children. Rapid confirmation using noninvasive sampling may be particularly useful in young children with extensive tuberculosis or suspected drug resistance, and its potential clinical impact should be systematically investigated." (9)

In a cross-sectional prospective study done by Welday et al., "stool Xpert showed 100% sensitivity and 89.36% specificity without missing any positive from sputum ZN smear microscopy. Thus, using stool as a sample is a good alternative to the invasive procedure for collecting respiratory samples or sputum from children. (12)

In a study done by Kokuto et al in which the subjects were adults with difficulty in obtaining sputum samples, "The sensitivity of testing stool samples using the GeneXpert MTB/RIF was 100% (81.7%–100%) for detection of MTB in specimens from sputum smear-positive (1+ to 3+) patients, 81.0% (58.1%–94.6%)

in specimens from sputum smear scanty positive patients, and 50.0% (15.7%–84.3%) in specimens from sputum smear-negative patients. Meanwhile, each of the fecal specimens from the non-TB group was negative for MTB (specificity 100%; 95% confidence interval, 86.2–100)" (5)

In a study by Marcy et al, which uses extrapulmonary samples for the geneXpert in HIV infected children, GeneXpert performed on 1 stool sample had intention-to-diagnose and per-protocol sensitivities of 62.1% and 68.8%, respectively (13).

In some studies using extrapulmonary samples and a small number for stool samples, both the sensitivity and specificity are high as mentioned in the study of Hillemann et al, (8) Welday et al., (12), and Kokuto et al., (5). Meanwhile, in this analysis, the fecal GeneXpert MTB/RIF method is associated with lower levels of sensitivity, and this could be due to the paucibacillary nature of the pediatric TB. Another factor that could have also affected the result of this study is the age of the population. Older children in this study probably already know how to expectorate sputum, hence, spitting the phlegm out instead of swallowing it compared to the younger population of the study.

In this meta-analysis, only 2 studies were included due to the limited numbers of studies done on stool samples using geneXpert, probably due to the fact that this machine is relatively new and has only been introduced a few years ago. Other than that, an optimized protocol on testing stool sample needs to be developed to permit proper testing of stool likely to enhance the test's sensitivity. On the other hand, with the high specificity, GeneXpert enabled the rapid diagnosis of pulmonary tuberculosis enabling timely initiation of the appropriate therapy. The findings in this analysis confirm that the geneXpert MTB/RIF assay is an important advancement in the diagnosis of tuberculosis. More so, in the pediatric population, using a specimen that can be obtained in a non-invasive means using a new technology like geneXpert with a high specificity will lessen overtreatment of children who doesn't have TB. It will also lessen delays in the treatment of children that does not fulfill the current 3 out of 5 criteria of diagnosing pulmonary tuberculosis and cannot produce an adequate sputum specimen for further diagnosis.

RECOMMENDATIONS

Due to the limited number of journals that were accessed, it can be recommended that a larger scale clinical randomized controlled trial be done in testing stool samples using GeneXpert. The promise shown by this test using an accessible specimen cannot be overemphasized. Once an acceptable specificity and sensitivity is shown, it can lead to a change in the current diagnostic protocol of pulmonary tuberculosis in children.

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Ancheta JB and Garcia RD. A Retrospective Study on Sensitivity, Specificity, Negative Predictive Value, Positive Predictive Value of TB PCR Versus TB Culture in Diagnosing Tuberculosis in Filipino Children Aged 3 Months to 18 Years at a Tertiary Care Center

ORIGINAL

A RETROSPECTIVE STUDY ON SENSITIVITY, SPECIFICITY, NEGATIVE PREDICTIVE VALUE, POSITIVE PREDICTIVE VALUE OF TB PCR VERSUS TB CULTURE IN DIAGNOSING TUBERCULOSIS IN FILIPINO CHILDREN AGED 3 MONTHS TO 18 YEARS AT A TERTIARY CARE CENTER

Jesanel B. Ancheta, MD*
Robert Dennis J. Garcia, MD*

* Makati Medical Center

Correspondence:
Dr. Jesanel B. Ancheta
Email: jesan.ancheta@outlook.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.

4TH PRIZE PIDSP RESEARCH

ABSTRACT

Objectives: This study aimed to establish the accuracy of TB PCR versus TB culture and rifampicin resistance detection by PCR versus conventional susceptibility testing of body fluids in diagnosing tuberculosis in pediatric patients 3 months to 18 years with suspected tuberculous disease at a tertiary care center.

Methods: This is a retrospective analytical study of patients seen between January 1, 2012 to May 31, 2017, with clinical and radiographic features suggestive of tuberculosis, who had diagnostic testing of body fluids for TB PCR and TB culture.

Results: Among 159 patients suspected of TB, 46 (28%) tested positive by PCR, of which one was rifampicin-resistant. The sensitivity, specificity, positive predictive value and negative predictive values of TB PCR, using TB culture as the gold standard were 90%, 91.6%, 78.3%, and 96.5% respectively. The sensitivity, specificity, positive predictive value, and negative predictive values of TB PCR for detecting rifampicin resistance, using TB culture and sensitivity as the gold standard, were 33%, 100%, 100%, and 95%, respectively. Overall, the accuracy of TB PCR in detecting TB disease is 91.2% and the accuracy of TB PCR in detecting rifampicin resistance is 95%.

Conclusion: Findings in our study suggest that TB PCR play an important role in TB disease diagnosis, but clinical and radiological assessment continue to be essential in the diagnosis of childhood tuberculosis. The accuracy of TB PCR in detecting TB disease in children is 91.2% and the accuracy of TB PCR in detecting Rifampicin resistance is 95%.

KEYWORDS: *TB PCR, tuberculosis, Filipino, pediatrics, accuracy*

INTRODUCTION

Tuberculosis (TB) is both a preventable and treatable illness. In children it is infrequently confirmed bacteriologically due to the lack of effective diagnostic tools.[1] Early identification of TB is very important, as it can help in the initiation of adequate treatment for patients and in the prevention of further spread of drug-resistant strains.[2] Tools for the diagnosis of active disease include clinical suspicion, chest radiographs, staining for acid-fast bacilli (AFB), culture for mycobacteria, nucleic acid amplification assays, and response to treatment.[3] The current gold standard for the diagnosis of tuberculosis is the combination of culture and clinical diagnosis.[4] However, there are shortcomings to the standard diagnostic methods. The direct smear for acid-fast bacilli has low sensitivity, while mycobacterial culture usually requires two to six weeks to yield a result. [2] TB Polymerase Chain Reaction (TB PCR) can detect a 3-fold greater number of confirmed tuberculosis cases compared to AFB smear microscopy but with equal rapidity. [5] The TB PCR has the advantage of high sensitivity and specificity for the diagnosis of TB, and has the capacity to detect resistance to rifampicin.[6] An ideal test for active TB is one that would produce rapid results, has high sensitivity and specificity, with low-cost, easily performed without the need for excessive sample preparation or technical expertise, and able to provide drug-susceptibility data.[3]

Despite the development of quick and more sensitive diagnostic techniques, the high cost has limited their use in many resource-poor countries. Due to the rapidly growing TB problem in developing countries like the Philippines, there is an urgent need to assess alternative methodologies in settings with high disease prevalence.[4] It is necessary to investigate the diagnostic accuracy of TB PCR in the local setting since positive predictive value (PPV) and negative predictive value (NPV) are directly related to the prevalence of the disease in the population.

This study aims to determine the diagnostic accuracy of TB PCR versus TB culture in terms of its specificity, sensitivity, positive predictive value and negative predictive value in the diagnosis of TB in all in-patient and out-patient Filipino children 3 months to 18 years with suspected active TB seen in a tertiary care center. [7.] Moreover, this study sought to determine the accuracy of TB PCR in establishing rifampicin resistance in comparison to conventional mycobacterial susceptibility testing. It also intended to determine the yield of TB PCR and TB Culture among specimens submitted and tested, according to body fluid sampled.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective analytical study of all patients (out-patients and in-patients) seen at a tertiary care center between January 1, 2012 to May 31, 2017. During the study period, all patients suspected to have TB disease based on clinical features and radiograph findings, who had diagnostic TB sampling (TB PCR, culture) of body fluids (sputum, endotracheal, gastric lavage, cerebrospinal fluid) were included in the study.

Subject selection

Inclusion criteria

All in-patient and out-patient Filipino children aged 3 months to 18 years who underwent TB PCR and mycobacterial culture and susceptibility testing (Lowenstein Jensen and MGIT culture media) were included. The following data were obtained: sex, age, weight, height, body mass index (BMI), chest radiograph results, and CSF and MRI/CT scan results, if with suspected TB meningitis, and clinical findings relevant to MTB disease. A person with TB disease is someone with presumptive TB who, after clinical and diagnostic evaluation is done, is confirmed to have TB disease.[8] A definitive diagnosis of TB was made by positive TB culture result. For those patients with a negative culture for *M.*

tuberculosis, a clinical diagnosis was made with respect to the clinical and radiological presentation and tuberculin skin tests, hematological findings, histological findings (when available), and clinical response to anti-TB treatment.[6]

Exclusion criteria

All patients (out-patients and in-patients) aged 3 months to 18 years who underwent mycobacterial culture (Lowenstein Jensen and MGIT culture media) without TB PCR or underwent TB PCR without mycobacterial culture, were not included in the study.

Data Collection

TB PCR results from the hospital's molecular laboratory and TB culture and susceptibility results from the hospital's bacteriology laboratory of suspected pediatric TB cases were reviewed and analyzed in relation to signs and symptoms. Clinical, radiologic and culture information for each pediatric in-patient were collected from the medical records ArchiveOne database, Radiologic information system and Picture Archiving and Communication System (RIS PACS) and the laboratory. Clinical, radiologic and culture information for each pediatric out-patient were retrieved from the medical records of pediatric infectious disease and pediatric pulmonology specialists who requested for TB PCR and TB Culture, as well as the Radiologic information system and Picture Archiving and Communication System (RIS PACS) and the laboratory.

The presence or absence of the following clinical findings were noted: 1) fever, 2) cough, 3) pleuritic or retrosternal pain of gradual onset, 4) anorexia, 5) night sweats, 6) weight loss, 7) lymphadenopathy, and 8) signs and symptoms suggestive of non-pulmonary TB.[5] Moreover, exposure to an adult/adolescent with active TB disease, positive tuberculin skin test, abnormal chest radiograph suggestive of TB and laboratory findings suggestive of TB (TST, smear microscopy, culture and TB quantiferon result) were also analyzed.

The TB PCR is an automated, cartridge-based system, which makes use of a closed amplification system that reduces the potential for cross-contamination between specimens.[9] A region of the mycobacterial 16S DNA, conserved in all members of the MTB complex, is amplified and detected by a flurogenic probe. The assay system contains, in one master mix, all reagents and enzymes for the specific amplification and detection of a 155-base pair region of the MTB genome.[6] A sample is considered positive when a fragment of the 155-base pair is observed in the ultraviolet transilluminator.[10]

This assay is used for the rapid identification of MTB-complex (i.e., M. tuberculosis, M. bovis, M. africanum, M. canettii, M. microti, M. caprae, M. pinnipedi, M. mungi, and M. orygis) in clinical samples and the detection of mutations affecting resistance to rifampicin.[7] It also provides information about potential rifampicin resistance, by detecting mutations in an 81-base pair region of the rpoB gene that is responsible for conferring approximately 96% of rifampin resistance in the MTB complex. Rifampicin resistance is a predictor of multi-drug resistant TB since majority of rifampicin-resistant isolates are also isoniazid-resistant.[11]

Statistical Methods

Sample size determination

A minimum of 156 subjects were required based on a level of significance of 5%, a prevalence of 12%, sensitivity of 62% with a width of the confidence interval of 0.22. The values for the prevalence of a positive TB culture, and sensitivity of the TB PCR (Xpert) test for tuberculosis detection were based on the study by Detjen et al., 2015[12].

Legend:

n = minimum sample
P = Prevalence of a positive TB culture test = 12%
S= Sensitivity of TB PCR test for tuberculosis detection = 62%
L = width of the confidence interval = 51% to 73% = 22%
$z_\alpha = 1.96$

Sample size formula[21]:

$$n \geq \frac{Z^2{}_\alpha \times S_N \times (1 - S_N)}{L^2 \times \text{Prevalence}}$$

$$n \geq \frac{1.96^2 \times 0.62 \times (1 - 0.62)}{0.22^2 \times 0.12}$$

$$n \geq 155.83 \approx 156$$

Statistical Analysis

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Sensitivity, specificity, PPV, NPV and likelihood ratio of TB PCR were compared to TB culture as the gold standard. Crude and adjusted odds ratios with corresponding 95% CI were determined via binary logistic regression. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

Ethical consideration

The protocol of this study adhered to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethics Guidelines for Health Research.

IRB approval and informed consent

The study commenced upon the approval of the Institutional Review Board of the hospital.

Data safety and confidentiality

Subject information was kept in a secure office, with access available only to members of the research team. Computerized study information was stored in a secured network with password access. All identifiable information and data were given a code number. A master list linking the code number and subject identity was kept separately from the research data. Only members of the research team had access to the list. The research records are to be stored for at least five years following completion of the study. Individually identifiable research data was not shared with others outside of the research team. The investigator and all key personnel were able to complete the Good Clinical Practice (GCP) training on the responsible conduct of research with human data.

Compensation

This study was initiated and funded wholly by the principal investigator.

Adverse events

No adverse events were seen in this retrospective study.

Vulnerability

We recognize the vulnerability of our subjects and extra care was done to assure the confidentiality of their identities.

Conflict of Interest

There are no potential conflicts of interest.

RESULTS

We reviewed the charts of 159 pediatric patients suspected with TB disease. Forty-six (28%) were found positive on PCR, of whom one was rifampicin-resistant. Forty (25%) were TB culture-positive, four (2%) of whom were PCR-negative. The overall pediatric Rifampicin resistance was 1.8% (Figure 1).

Figure 1. Diagnostic pathway results among children suspected to have TB Disease.

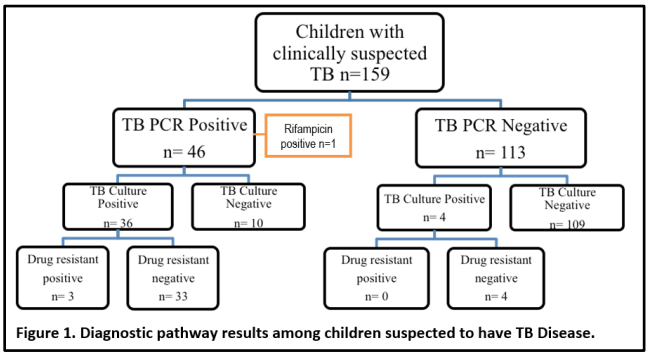

Figure 1. Diagnostic pathway results among children suspected to have TB Disease.

Our patients had a median age of 15 years (range 3 months to 18 years) and were more commonly male (54%). The most common presenting signs and symptoms were fever (87%), cough (67%) and anorexia (47%). Active TB exposure was disclosed in 31%. Other diagnostic results are tabulated in Table 1.

Table 1. Demographic and clinical profile of pediatric patients suspected of TB Disease (n=159)

	Frequency (%); Mean ± SD; Median (Range)
Age (years)	15 years (3 months – 18 years)
Sex	
Male	86 (54.09)
Female	73 (45.91)
Height (cm)	155 (58 – 185)
Weight (kg)	47 (3.1 – 85.5)
BMI	18.56 (9.22 – 28.98)
Active TB exposure	50 (31.45)
Chest x-ray	
Positive	29 (18.2)
Negative	130 (81.8)
Signs and symptoms	
Fever	139 (87.4)
Cough	108 (67.9)
Anorexia	76 (47.8)
Weight loss	54 (33.9)
Vomiting	32 (20.1)
Lymphadenopathy	26 (16.4)
Pleuritic or retrosternal pain	23 (14.5)
	22 (13.8)
Crackles	16 (10.1)
Headache	8 (5.0)
Abdominal pain	4 (2.5)
Night sweats	77 (48.4)
Others	
TST (n=131)	
Positive	27 (20.6)
Negative	104 (79.4)
AFB smear (n=157)	
Positive	4 (2.6)
Negative	153 (97.5)
TB quantiferon (n=33)	
Positive	15 (45.5)
Negative	18 (54.6)
TB PCR	
Positive	46 (28.9)
Negative	113 (71.1)
RIFAMPICIN RESIS by PCR	
Positive	1 (0.6)
Negative	158 (99.4)
TB Culture	
Positive	40 (25.2)
Negative	119 (74.8)
Drug susceptibility (n=40)	
Positive for Rifampicin resistance	3 (7.5)
Negative for Rifampicin resistance	37 (92.5)

Specimens were mostly pulmonary (59.1%), coming from sputum and pleural fluid.

Table 2. Specimen type, pediatric patients (n=159)

	Frequency (%)
Pulmonary	94 (59.12)
Sputum	79 (84.04)
Pleural fluid	15 (15.96)
Non-pulmonary	65 (40.88)
Gastric/NGT aspirate	11 (16.92)
Others	54 (83.08)

We assessed for the diagnostic accuracy of TB PCR in comparison to TB culture (Table 3). With TB culture as a gold standard, TB PCR had good sensitivity and specificity to detect TB disease in children. Among patients who were

TB culture-positive, there was a 90% probability that PCR would be positive (sensitivity). Among patients without TB, there was a 91.6% probability that PCR would be negative (specificity). Patients who were TB culture-positive were 10.71 times more likely to yield a positive PCR compared to patients who were TB-negative (LR+), and were 89% less likely to yield a negative PCR result (LR-). When PCR was positive, there was a 78.26% probability that TB culture was positive (PPV). When PCR was negative, there was a 96.46% probability that the patient was TB culture-negative (NPV). Overall, the accuracy of TB PCR in detecting TB disease was 91.19%

Table 3. Diagnostic accuracy of TB PCR versus conventional TB culture in detecting presence of TB in pediatric patients (n=159).

	TB culture positive	TB culture negative	Total
	Frequency (%)		
TB PCR positive	36 (22.6)	10 (6.3)	46 (28.9)
TB PCR negative	4 (2.5)	109 (68.6)	113 (71.1)
Total	40 (25.2)	119 (74.8)	159 (100)
Sensitivity	90% (76.3% - 97.2%)	Positive LR	10.71 (5.9 – 19.6)
Specificity	91.6% (85.1% - 95.9%)	Negative LR	0.11 (0.04 – 0.28)
PPV	78.26% (66.4% - 86.8%)	Accuracy	91.19% (85.7% – 95.1%)
NPV	96.46% (91.5% - 98.6%)		

PPV, positive predictive value; NPV, negative predicted value; LR, likelihood ratio.

With conventional mycobacterial susceptibility as the gold standard, TB PCR was highly specific in detecting rifampicin resistance. Among patients who were TB culture-positive, there was a 33% probability that PCR would be positive (sensitivity). Among patients without TB, there was nearly 100% probability that PCR would be negative (specificity). That is, patients who were rifampicin-resistant by conventional mycobacterial susceptibility testing were 33% less likely to have a negative RIF-PCR result (LR). When PCR rifampicin resistance was present, there was a nearly 100% probability that TB conventional rifampicin resistance was present (PPV). When PCR rifampicin resistance was not present, there was a 94.87% probability that the patient is did not have rifampicin resistance (NPV). Overall, the accuracy of TB PCR in detecting TB disease was 95% (Table 4).

Table 4. Diagnostic accuracy of RIF versus drug susceptibility as a gold standard in pediatric patients (n=40)

	Drug susceptibility testing		Total
	Resistant/positive	Sensitive/negative	
	Frequency (%)		
RIF resistance	1 (2.5)	0	1 (2.5)
RIF negative	2 (5)	37 (92.5)	39 (97.5)
Total	3 (7.5)	37 (92.5)	40 (100)
Sensitivity	33.33% (0.84% - 90.57%)	Positive LR	-
Specificity	100% (90.51% - 100%)	Negative LR	0.67 (0.30 to 1.48)
PPV	100%	Accuracy	95% (83.1% - 99.4%)
NPV	94.87% (89.25% - 97.63%)		

PPV, positive predictive value; NPV, negative predicted value; LR, likelihood ratio.

The following clinical characteristics were associated with a positive TB culture in children (Table 5): older age (cOR 1.093, 95% CI 1.01 – 1.18, p value = 0.019), an active TB exposure (cOR 3.43, 95% CI 1.62 – 7.25, p value = 0.001), a positive chest x-ray (cOR 19.56, 95% CI 7.3 – 52.39, p value <0.0001), presence of fever (cOR 0.275, 95% CI 0.10-0.72, p value = 0.009), weight loss (cOR 2.88, 95% CI 1.38 – 6.03, p value = 0.005), presence of pleuritic/retrosternal pain (cOR 3.382, 95% CI 1.35 – 8.45, p value = 0.009), a positive TST (cOR 20.07, 95% CI 7.1 – 56.6, p value <0.001), and a positive TB quantiferon test (cOR 25.5, 95% CI 2.65 – 245.83, p value = 0.005).

We performed a stepwise backward elimination logistic regression to determine the

predictors of positive TB culture in children (Table 5.1). These were age, active TB exposure, positive chest radiograph findings, and positive TST. For every unit increase in age, the odds of a positive TB culture increases by approximately 16.6%. Patients with active TB exposure were 3.94 times more likely to have a positive TB culture. Patients with positive chest radiograph were 6.51 times more likely to have a positive TB culture. Patients with positive TST were 25.96 times more likely to have a positive TB culture. This model predicts 47.67% in the variation of positivity of TB cultures, and is statistically significant at p = 0.0001.

Table 5. Predictors of positive TB culture in children

	TB Culture Positive (n=40)	**TB Culture Negative (n=119)**	**Crude Odds Ratio (95% CI)**	**P-value**
	Frequency (%); Mean ± SD			
Age (years)	17 (4 mos – 18 years)	14 (3 mos – 18 years)	1.093 (1.01 – 1.18)	**0.019**
Sex (Male)	22 (55)	64 (53.78)	1.05 (0.51 – 2.16)	0.894
BMI (kg/m^2)	18.5 (13.4 – 28.4)	18.6 (9.2 – 28.98)	0.953 (0.86 – 1.05)	0.344
Active TB exposure	21 (52.5)	29 (24.4)	3.430 (1.62 – 7.25)	**0.001**
Chest x-ray				
Positive	22 (55)	7 (5.88)	19.56 (7.3 – 52.39)	**<0.0001**
Negative	18 (45)	112 (94.12)	(reference)	-
Signs and symptoms				
Fever	30 (75)	109 (91.6)	0.275 (0.10 – 0.72)	**0.009**
Cough	29 (72.5)	79 (66.39)	1.335 (0.60 – 2.95)	0.474
Anorexia	21 (52.5)	55 (46.22)	1.286 (0.63 – 2.64)	0.492
Weight loss	21 (52.5)	33 (27.73)	2.88 (1.38 – 6.03)	**0.005**
Vomiting	6 (15)	26 (21.85)	0.631 (0.24 – 1.67)	0.353
Lymphadenopathy	9 (22.5)	17 (14.3)	1.742 (0.71 – 4.29)	0.228
Pleuritic/Retrosternal pain	11 (27.5)	12 (10.1)	3.382 (1.35 – 8.45)	**0.009**
Crackles	3 (7.5)	19 (16)	0.427 (0.12 – 1.53)	0.190
Headache	2 (5)	14 (11.8)	0.395 (0.09 – 1.82)	0.223
Abdominal pain	3 (7.5)	5 (4.2)	1.849 (0.42 – 8.11)	0.415
Night sweats	3 (7.5)	1 (0.84)	9.57 (0.97 – 94.77)	0.054
TST (n=131)				
Positive	19 (63.33)	8 (7.92)	20.08 (7.1 – 56.6)	**<0.0001**
Negative	11 (36.67)	93 (92.08)	(Reference)	-
AFB smear (n=157)				
Positive	3 (7.5)	1 (0.85)	9.41 (0.95 – 93.18)	0.055
Negative	37 (92.5)	116 (99.15)	(reference)	-
TB quantiferon (n=33)				
Positive	9 (90)	6 (26.1)	25.5 (2.65 – 245.83)	**0.005**
Negative	1 (10)	17 (73.9)	(reference)	-

Table 5.1. Predictors of positive TB culture in children

	Adjusted Odds Ratio	95% CI	P-value
Age	1.166	1.02 – 1.33	**0.024**
Active TB exposure	3.94	1.12 – 13.9	**0.032**
Positive Chest x-ray	6.51	1.59 – 26.69	**0.009**
Positive TST	25.96	6.37 – 105.8	**<0.0001**

R^2 = 47.67%, p = 0.0001

We had insufficient evidence to demonstrate an association between age, sex, BMI, and other clinical findings with drug resistant TB (Table 6). Two of the three drug resistant TB patients presented with crackles, which was a higher proportion compared to the one of 37 patients who were rifampicin-susceptible (p = 0.007).

Table 6. Association of select clinical features with rifampicin resistant TB in children (n=40)

	Rifampicin-resistant (n=3)	Rifampicin-susceptible (n=37)	Crude Odds Ratio (95% CI)	P-value
	Frequency (%); Mean ± SD			
Age (years)	14 (4 months – 18 years)	17 (1 year – 18 years)	0.927 (0.77 – 1.12)	0.425
Sex (Male)	3 (100)	19 (51.35)	(omitted)	-
BMI (kg/m^2)	14.2 (13.7 – 28.4)	18.56 (13.4 – 24.98)	1.028 (0.73 – 1.44)	0.872
Active TB exposure	1 (33.33)	20 (54.05)	0.425 (0.04 – 5.11)	0.500
Chest x-ray				
Positive	2 (66.7)	20 (54.05)	1.7 (0.14 – 20.42)	0.676
Negative	1 (33.3)	17 (45.95)	(reference)	-
Signs and symptoms				
Fever	3 (100)	27 (72.97)	(omitted)	-
Cough	3 (100)	26 (70.27)	(omitted)	-
Anorexia	2 (66.7)	19 (51.35)	1.895 (0.16 – 22.75)	0.614
Weight loss	2 (66.7)	19 (51.35)	1.895 (0.16 – 22.75)	0.614
Vomiting	0	6 (16.22)	(omitted)	-
Lymphadenopathy	2 (66.7)	7 (18.92)	8.571 (0.68 – 108.4)	0.097
Pleuritic/Retrosternal	1 (33.3)	10 (27.03)	1.35 (0.11 – 16.57)	0.815
pain	2 (66.7)	1 (2.70)	72.0 (3.19 – 1624.3)	**0.007**
Crackles	0	2 (5.41)	(omitted)	-
Headache	0	3 (8.1)	(omitted)	-
Abdominal pain	1 (33.3)	2 (5.41)	8.75 (0.54 – 142.68)	0.128
Night sweats				
TST (n=30)				

	Rifampicin-resistant (n=3)	Rifampicin-susceptible (n=37)	Crude Odds Ratio (95% CI)	P-value
	Frequency (%); Mean ± SD			
Positive	1 (33.3)	18 (66.7)	0.25 (0.02 – 3.14)	0.283
Negative	2 (66.7)	9 (33.3)	(reference)	-
AFB smear (n=40)				
Positive	0	3 (8.11)	(omitted)	-
Negative	3 (100)	34 (91.89)	-	-
TB quantiferon (n=10)				
Positive	1 (100)	8 (88.89)	(omitted)	-
Negative	0	1 (11.11)	-	-
Rifampicin (resistant)	1 (33.3)	0	(omitted)	-

DISCUSSION

This retrospective study of childhood TB seen at a private tertiary care center showed the following key findings: of 159 children clinically suspected to have TB disease, the TB culture yield was 25% and TB PCR yield was 28%. Specimen samples were mostly pulmonary (59.1%), consisting of 84% sputum and 16% pleural fluid, while 40.9% were non-pulmonary specimens. The sensitivity, specificity, PPV and NPV of TB PCR, using conventional TB culture as the gold standard were 90%, 91.6%, 78.3%, and 96.5% respectively. Rifampicin resistance for TB-PCR positive and TB culture-positive children were 2% and 8%, respectively. The sensitivity, specificity, PPV and NPV of TB PCR rifampicin resistance detection, using conventional TB susceptibility as the gold standard, were 33%, 100%, 100% and 95%, respectively. Overall, the accuracy of TB PCR in detecting TB disease is 91.2% and the accuracy of TB PCR in detecting rifampicin resistance is 95%. Among selected demographic and clinical variables, the following were found to be significant predictors for a positive TB culture: older age, known TB exposure, a chest radiograph compatible with TB disease; presence of fever, weight loss, pleuritic or retrosternal pain; a positive TST and a positive TB quantiferon test. Presence of rales was significantly associated with having a rifampicin-resistant isolate.

The TB culture yield was 25% and TB PCR yield was 28%. In a study done in Philippine General Hospital (PGH) and Research Institute for Tropical Medicine (RITM), the TB culture yield of all pediatric samples ranged from 40-50%[13]. In a study done in New York City, culture was positive for TB in 12% of all children assessed and TB PCR was positive in 11%[12]. In a meta-analysis, the yield of culture in childhood TB ranged from 20% to 70% depending on factors such as age, disease severity, and type and quality of the specimen, and culture method used[12]. TB culture has a generally low yield in children due to the difficulty in specimen collection especially in those under seven years. Also, childhood TB is a paucibacillary illness, so that even with the best effort to submit samples, there may be too small a population in the child's diseased organ to produce a culture yield [14]. There is no local study on TB PCR in children as this is a relatively new test and is only available at national reference centers in the Philippines. The diagnosis of TB in children is difficult in many cases. The factor of age, stage of development and the vulnerability of the young are considered important. A Shortened time to detection of TB is an important comparative

advantage of TB PCR over conventional culture. It also offers the opportunity for prompt clinical management of pediatric TB cases[15].

Specimen samples were obtained mostly from respiratory specimens (59.1%), consisting of 84% sputum and 16% pleural fluid, while 40.9% were non-pulmonary specimens. Studies in children showed an improved yield of TB PCR from various specimens. A systematic review and meta- analysis in the accuracy of TB PCR to diagnose TB in children showed sensitivities of 55-90% from sputum samples, and 40-100% for gastric lavage or aspirate specimens. Specificities for all specimen types ranged from 93-100%[16]. In a study done at the National Institute of Health in New Orleans, specimen samples were obtained from sputum (25%), gastric aspirate (25%) and non-pulmonary (50%) sites.[13] The WHO recommends the use of TB PCR in the following specimens: processed or unprocessed sputum, gastric lavage or aspirate, CSF, lymph node and other tissues[16]. This suggests that no specimen type is superior.

The sensitivity, specificity, PPV and NPV of TB PCR, using TB culture as the gold standard were 90%, 91.6%, 78.3%, and 96.5% respectively. In a meta-analysis, sensitivity and specificity of TB PCR for TB detection were 62% and 98%, respectively[12]. In a more recent meta-analysis, sensitivity and specificity of TB PCR compared to TB culture were 62% and 98%, respectively with use of sputum samples, and 66% and 98%, respectively, with the use of gastric lavage samples[12]. With these good results, TB PCR has been shown to be a valuable test that can produce rapid results that will be useful in children suspected to have TB disease, where resources are available. In situations where the sample volume is low, or additional specimen cannot be obtained, TB PCR can be helpful because its accuracy is comparable to that of TB culture[16].

Rifampicin resistance for TB PCR-positive and TB culture-positive children were 2% and 8%, respectively. Rifampicin resistance can be used to suggest multi-drug resistance since rifampicin mono-resistance is uncommon and most isolates that are rifampicin-resistant are also isoniazid-resistant[17]. In this study, TB PCR underestimated the real rifampicin resistance rate when compared to conventional culture, consistent with findings from previous studies[1]. TB PCR can detect DNA from both viable and non- viable bacilli and is not recommended for monitoring the treatment response of patients[7]. This suggests that conventional culture is still needed to monitor treatment response; it is also necessary if data on resistance to drugs other than rifampicin is desired.

The sensitivity, specificity, PPV and NPV of TB PCR rifampicin resistance detection, using TB culture susceptibility as the gold standard, were 33%, 100%, 100% and 95%, respectively. In a meta-analysis, sensitivity and specificity of TB PCR rifampicin resistance detection were 86% and 98%, respectively[12]. In a study done in Geneva, rifampicin resistance showed sensitivity and specificity of 83.3% and 99.1% respectively[16]. TB PCR rifampicin resistance in this study showed that it is a method with high specificity and positive predictive value. The sensitivity in this study was low in relation to the above reported results. The paucibacillary nature of childhood TB may not be blamed for this low sensitivity, as the sensitivity of TB PCR versus culture as shown above is a high 90%, so it is unclear why the PCR rifampicin resistance sensitivity is low at 33%. The false positive results, on the other hand, may be explained by the detection of non-viable MTB that would not be detected on culture. For reliable results a good quality of specimen collection is very important[1].

The following were demographic factors found to be significant predictors for a positive TB culture: older age, known TB exposure, a chest radiograph compatible with TB disease; presence of fever, weight loss, pleuritic or retrosternal pain; a positive TST and a positive TB quantiferon test.

For every unit increase in age, the odds of a positive TB culture increases by 16.6%. In a study done at PGH and RITM, majority were 11-15 years of age (33% were 1-5 years old, 22% were 11-15 years old, 16.5% were less than 1 year old and 15% were 16-18 years old) [13]. Age is the most important risk factor that determines the progression to disease following primary infection among immune-competent children[18].

Patients with active TB exposure were 3.94 times more likely to have a positive TB culture. In the PGH and RITM study, 56.7% of patients had a history of TB exposure[13]. According to the WHO, after prolonged exposure with a sputum smear-positive source, 60-80% of children become infected. When the household contact is smear-negative, 30-40% of children become infected. Children with history of contact exposure are 2.5 times more likely to develop TB disease than in children without known exposure[18]. Young children are most vulnerable among household members who are exposed to an adult or adolescent source case. These children are at greater risk of developing infection, disease and its complications, with dissemination or even death[19].

A chest radiograph compatible with TB disease was a significant predictor for a positive TB culture. Children with a chest radiograph indicating TB disease were 6.5 times more likely to have a positive TB culture. Radiologic examination is often equivocal, needing consensus among radiologists. A chest radiograph is the most basic and widely used radiologic investigation for TB. There are no pathognomonic radiograph findings but the most common findings are lymphadenopathy, parenchymal abnormalities and millet seeds. In the PGH and RITM study, hazy densities were the most frequently seen chest x-ray finding at 23.6%, followed by cystic lucencies at 21.8%[13]. In a cross-sectional study done among Filipino children 6 months to 18 years old at the Philippine Heart Center, 64% of patients showed lymphadenopathies as part of Ghon focus in 64% and 7% had normal radiographs[13].

The presence of fever, weight loss and pleuritic or retrosternal pain were significant predictors for a positive TB culture. Weight loss can be used as a red flag in TB disease case-finding[19]. In a study done in PGH and RITM, the most frequently seen symptoms were fever in 89.6%, cough in 76.1%, weight loss in 50.7%, anorexia in 44.8% and difficulty in breathing 28.4%. On physical examination, cervical lymphadenopathy was found in 62.7% followed by hepatomegaly at 37.3%[13].

A positive TST and a positive serum TB quantiferon test were significant predictors for a positive TB culture. Children with positive TST results were 25.96 times more likely to have a positive TB culture. In a study done in PGH and RITM, of the subjects who tested positive for TST, 28% had pulmonary TB while 57.1% had disseminated TB[13]. TST has become the standard method in demonstrating TB infection. Tuberculin reactivity provides a general measure of a person's cellular immune responsiveness[20]. The tuberculin skin test reaction should always be correlated with history of exposure to an infectious TB source, presence of clinical signs and symptoms suggestive of TB and chest radiograph findings in order to diagnose TB infection and disease.

In clinical practice, TB PCR is an invaluable tool that can provide rapid diagnosis of TB disease and detect possible drug resistance, thereby allowing a more prompt and confident start of treatment. In childhood TB in particular, the paucibacillary nature of TB causes a low initial AFB smear-positive rate.

Limitations of the study

This was a single-site study done at an urban tertiary care hospital with a predominantly middle class to affluent market, so that the results may not be applicable to children in other settings. TB disease affects the poor and malnourished

individuals in the community,[21] so the results herewith may potentially underestimate the rifampicin resistance rate.

CONCLUSION

The accuracy of TB PCR in detecting TB disease is 91.2% versus conventional TB culture, and the accuracy of TB PCR in detecting rifampicin resistance is 95% versus conventional TB susceptibility testing. The findings in our study suggest that TB PCR plays an important role in rapid diagnosis, but clinical and radiological assessment and contact tracing are still essential in the diagnosis of childhood TB. This assay allows patients to be treated promptly and to identify those who need second-line drug treatment. However, conventional culture is still needed to monitor treatment and to detect resistance to drugs other than rifampicin.

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ORIGINAL ARTICLE

Association of Factors with Successful Treatment Outcome of Childhood Tuberculosis in Barangay Commonwealth, Quezon City, Philippines: A Two-Year Retrospective Study

Christine N. Pecson , MD*
Ana Liza H. Duran, MD*

*East Avenue Medical Center, Philippines

Correspondence:
Dr. Christine N. Pecson;
Email: cnpecson@yahoo.com.ph

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: Tuberculosis remains a public health concern worldwide. Reports on the association of factors of childhood tuberculosis with treatment outcome are limited.

Objectives: To determine the epidemiology and association of factors of childhood tuberculosis with successful treatment outcome in some of the barangays of Quezon City.

Methodology: This is a retrospective cohort study done at Barangay Commonwealth Health Centers including children 0-14 years old with tuberculosis registered and treated from January 1, 2013 to July 15, 2015. Socio-demographic and clinical data were obtained. Patient profile data, treatment cards and medical records were the data sources.

Results: A total of 267 new cases of childhood TB were analyzed. The treatment success rate was 98% (97% completed treatment, 1% cured). The rate of poor treatment outcome including default cases was 2%. There were no reported deaths or treatment failure. On univariate analysis, patients with weight gain (p=0.001) had an odds ratio of 8.085 (95% CI:1.310-49.900) to have a successful treatment outcome. On multivariate analysis, weight gain was significantly associated with treatment success (p=0.042; OR=12.5, 95% CI: 1.091, 143.244). None of the socio-economic and clinical factors studied was associated with successful treatment outcome.

Conclusion: Weight gain is a factor of a successful treatment in childhood tuberculosis. Children who gained weight after treatment are more likely to have a successful treatment outcome.

KEYWORDS:

Childhood tuberculosis, treatment outcome, weight gain

INTRODUCTION

Tuberculosis (TB) continues to be a public health concern not only in the Philippines but throughout every region in the world. It ranks as the world's second leading cause of death from a communicable disease.[1] As stated in the Global Tuberculosis Report 2014 of the World Health Organization (WHO), an estimated 9.0 million people developed TB and 1.5 million died from the disease in 2013. Childhood TB contributes 6%, equivalent to 550,000 of the total new cases and 7%, equivalent to 80,000 of the total TB deaths from HIV-negative people in the same year.

The Philippines remains one of the 22 highest TB-burden countries worldwide and has one of the highest problems of multidrug resistant TB.[2] TB in children in our country forms part of the TB burden. The Philippine Health Statistics of 2010 of the Department of Health shows that TB in all forms tops the list of the leading cause of mortality among the immunizable diseases in 0-14 years old.[3]

TB is a significant cause of morbidity and mortality among children [4,5,6] and yet there are limited data on the epidemiology of childhood tuberculosis.[6] Few studies from Asia have also been published.[7] The World Health Organization has recently expressed the urgent need to address the lack of epidemiological data on pediatric tuberculosis in high-burden countries.[6]

A surveillance report on TB profile of the Philippines from 2003 to 2011 stated that 1% of the new cases were children 0 – 14 years old.[2] The proportion of their treatment outcome and the factors associated with it, however, were not emphasized.

In a study on the treatment outcomes of childhood TB in Thailand, 200 (72%) out of the 279 (2% of the national burden) cases completed treatment or were cured; 17(6%) died, 3(1%) failed, 39(14%) defaulted and 20(7%) transferred out.[7] A 5-year retrospective study in Addis Ababa on TB revealed that the percentage of children with TB was 6.6%. Treatment outcomes were documented for 95.2% of children with treatment success rate of 85.5%. Mortality rate was 3.3% and defaulting was 3.8%.[8] The data collected in a review of pediatric TB cases in Taiwan from 2002 to 2009 showed that a relatively small number of children ranging from 0.72% to 1.24% were diagnosed with TB.[9] The nationwide study of TB in Malawi revealed that 11.9% were children from the 22,982 cases registered. Death rate was high at 17%. Forty five percent completed treatment; 13% defaulted and 21% with unknown outcome.[10]

The above studies showed that treatment outcomes and incidence of childhood TB vary from one country or region to another even amongst endemic areas. Grange, et al discussed the changing epidemiology of tuberculosis which may result from a complex interplay between social, political, economic, genetic, cultural and environmental factors and the possibility of natural selection of an immune population.[11] As presented by Sivanandan, et al, the factors associated with treatment failure in childhood tuberculosis included AFB positivity at diagnosis, non-receipt of Bacille Calmette-Guerin (BCG) vaccination and extrapulmonary tuberculosis (EPTB).[12] The study done in Southern Ethiopia indicated that males, extremes of ages and patients on retreatment were those with poor outcome; smear negative patients had the lowest rate of successful treatment outcome.[13] Marais, et al pointed out in an article that the determinants of the burden of childhood TB could be extrapolated from community exposure which includes

number and duration of infectiousness and crowding; and community vulnerability which comprises immune compromise, immune stimulation and local defenses.[14] Aside from crowding the other risk factors on childhood TB were identified as parental education and annual household income.[6] Successful treatment outcome in children was higher in older age group,[9,11,15] smear-positive and HIV-negative patients.[11,16]

Childhood TB is a neglected aspect of the TB epidemic because it is usually smear-negative and considered to contribute little to the propagation of the disease.[17,18,19] However, pediatric cases are important because they provide valuable epidemiologic perspective since they reflect on-going transmission within communities.[20]

This study determined and investigated the successful treatment outcomes of TB in children and identified the factors affecting them. The results may serve as monitoring tool and may contribute in the modification of existing guidelines, strategies or policies in the management of TB in children to improve the outcome particularly in the community level.

This study aimed to determine the association of factors of childhood tuberculosis with successful treatment outcome in Barangay Commonwealth, Quezon City from January 2013 to July 2015.

We also determined the socio-demographic, anthropometric and clinical profile of childhood TB patients and the prevalence rates of childhood TB with successful and poor treatment outcomes. The association of socio-demographic, anthropometric and clinical characteristics of childhood TB with successful treatment outcome was studied.

METHODOLOGY

This is a retrospective cohort study that utilized odds ratio to determine association between various socio-demographic, anthropometric and clinical data and treatment outcome of children with TB.

The study was conducted in three health centers of Barangay Commonwealth, the biggest barangay in terms of population size, accounting for 5.6 percent (120,569) of the total population of Quezon City, Philippines [21] and located in the second district of the city which is administratively divided into seven units.[22] The three health centers namely: Commonwealth Health Center (HC), Dona Nicasia HC and National Government Center (NGC) HC are also designated Directly Observed Therapy Short Course (DOTS) facilities under the management and supervision of the Quezon City Health Department (QCHD).

The patients included in the study were children aged zero to fourteen years old diagnosed with tuberculosis based on the NTP standard guidelines and treated from January 1, 2013 to July 15, 2015.

Sample Size

All cases of childhood tuberculosis equivalent to 267 were included in the study.

Inclusion and Exclusion criteria

Patients aged zero to fourteen years old diagnosed with tuberculosis and treated in the above-mentioned centers were included. All patients transferred out were excluded from the study because the outcomes of treatment were indeterminate.

Operational Definition of terms

(as defined in the Manual of Procedures of the National Tuberculosis Control Program 5th ed., 2014 DOH)[23]

Children - individuals with age ranging from 0 to 14 years old.

Treatment outcome - the condition of the patient after the prescribed treatment period:

Completed treatment - anti-tuberculous drugs taken and completed during the prescribed course.

Cured - the condition of the patient in which he/she has initially a smear -positive sputum microscopy that turned out to be negative in the last month of treatment and on at least one previous occasion in the continuation phase.

Relapse patient - those previously treated patients for TB and declared cured or treatment completed at the end of the recent course of treatment and are now TB symptomatic with any one of the following: progressive deterioration or worsening of chest radiograph findings, smear positive or culture positive.[24]

Failed - an initially smear positive who remains or becomes smear positive on the 5th month of treatment or a newly diagnosed TB patient whose TB symptoms persisted and has failed to gain weight after six months of treatment.[24]

Defaulted - one who has interrupted treatment for two months; lost to follow up.

Retreatment - previously treated case of TB who is started on a treatment regimen after previous treatment has failed or a patient treated for TB who returns to treatment having defaulted; or a patient who was previously declared cured or treatment completed and is diagnosed with bacteriologically positive T5.[25]

Successful treatment outcome - refers to patients considered as cured or completed treatment; good treatment outcome; treatment success.

Poor treatment outcome - refers to patients considered to have defaulted, failed in the treatment and died during the treatment period; unsuccessful treatment.

Smear positive PTB - PTB diagnosed through DSSM with two or more initial sputum smear examination for acid-fast bacilli; or one sputum smear examination positive for acid-fast bacilli plus chest radiograph abnormalities consistent with active TB as determined by a clinician; or one sputum smear examination positive for acid-fast bacilli plus sputum culture positive for M. tuberculosis; bacteriologically-confirmed case of TB.[24]

Smear negative PTB - PTB diagnosed through DSSM in 10-14 years old or younger with at least three smear-negative for acid-fast bacilli; and radiologic abnormalities consistent with active pulmonary TB; and no response to a course of broad spectrum antibiotics; and decision by a physician and/or TB Diagnostic Committee to treat the patient with a full course of anti-TB chemotherapy; or a negative DSSM or PTB diagnosed through other diagnostic tests other than DSSM in 0-9 years old who cannot expectorate with any three of the following: TB symptomatic, positive exposure to an adult TB patient, positive tuberculin skin test, abnormal chest radiograph suggestive of TB, laboratory findings suggestive or indicative of TB; clinically-diagnosed case of TB.[24]

Poverty threshold - the minimum income required for a family/individual to meet the basic food and non-food requirements which is PhP 8,778.00 monthly for a family of five.[26,27]

Directly observed treatment short course (DOTS) - a treatment strategy wherein a TB patient takes the anti-TB drugs in the presence of a caregiver whether he be a doctor, a nurse, a midwife, a community health worker or any volunteer who stands as treatment partner of the patient.

Malnutrition – undernutrition in children which is manifested as underweight, wasted or stunted based on the Preventive Pediatric Health Care Handbook 2014[28] as follows:

Wasted - children with body mass index (BMI) for age z-score of below -2 to below -3 and weight for length/ height z-score of below -2 to below -3.

Stunted - children with height for age z-score below -2 and below -3.

Underweight - children with weight for age z-score of below -2 to below -3.

Data and information were extracted from the National Tuberculosis Program (NTP) TB registry, treatment cards and the health center patient profile and medical records. The following data were collected: socio-demographic such as age, sex, educational attainment of parents, employment status and occupation of parents, family income, and family size; anthropometric data: weight, BMI and height; and clinical information as to the classification of TB cases, category of patients, close TB contact, BCG vaccination, Tuberculin Skin Test (TST), chest radiograph findings, co-morbid conditions, exposure to cigarette smoke and treatment outcomes. Pre-treatment and post treatment weight were taken to determine the presence of weight gain, average weight gain and percentage of weight gain from baseline. Post treatment height was unavailable; hence, post treatment BMI was not calculated. The presence of malnutrition in every patient was determined by getting the height/length for age, BMI for age, weight for age, and weight for height/length. Z-scores of the anthropometric record of each patient were taken using the WHO Z-score charts. Data from the treatment cards were rechecked in the TB registry. Missing information on the patient profile and medical records were verified by the community health workers who stood as treatment partners of the patients. Hence, the TB registration number, the names, addresses and telephone numbers were initially gathered for this purpose but disregarded in the final tally of data prior to analysis to ensure confidentiality. Data were listed in a data extraction form and saved using EXCEL

Data from all evaluable subjects who satisfy the inclusion/exclusion criteria were included in the analysis. Missing values were not replaced or estimated during the statistical analysis of outcome variables. Summary statistics were presented in tables and reported as n (%). Column percentages were computed relative to total data excluding missing values. Checks for homogeneity of sample population was done. Yates' chi-square test was used to compare proportions. Univariate analysis was performed to determine independent significant associations of sociodemographic, anthropometric and clinical characteristics with success of treatment outcome. Significant variables from the univariate analysis were included in the multivariate logistic regression analysis to determine significant associations considering effects of other independent characteristics. Odds-ratios and 95% confidence intervals were estimated. Statistical significance was based on p-values ≤ 0.05. Statistical Package for the Social Sciences version 20 (SPSS v20) was used in data processing and analysis.

ETHICAL CONSIDERATIONS

A waiver of consent for the conduct of this study was given by the East Avenue Medical Center Institutional Ethics Review Board (EAMC IERB). An approval from the QCHD was obtained prior to the initiation of the study.

RESULTS

A. Socio-demographic, Anthropometric and Clinical Profile

Data from 267—eligible subjects were included in the analysis. Most of the children were 4 years or younger with majority of the parents either finished grade school or high school, most had both or either parent employed and belonged to families with 2-5 members Socio-demographic characteristics are summarized in Table 1.

Table 1. Socio-demographic Profile of Children with TB in Barangay Commonwealth, Quezon City, 2013 – 2015

	Successful Treatment Outcome		Poor Treatment Outcome	Total	*p*-value
	Cured n = 3	Completed n = 259	Defaulted n = 5	n = 267	
Age in years, n (%)					
0 – 4	-	152 (56%)	5 (100%)	157 (59%)	0.000*
5 – 9	-	85 (33%)	-	85 (32%)	
10-14	3 (100%)	22 (8%)	-	25 (9%)	
Gender, n (%)					
Male	-	131 (51%)	4 (80%)	135 (51%)	0.665
Female	3 (100%)	128 (49%)	1 (20%)	132 (49%)	
Educational Attainment of Parents, n (%)					
Grade School/ High School	2 (67%)	158 (65%)	5 (100%)	165 (66%)	0.000*
Vocational/ College	1 (33%)	86 (35%)	-	87 (34%)	
Employment of Parents, n (%)					
Employed	2 (67%)	239 (98%)	5 (100%)	246 (98%)	0.000*
Unemployed	1 (33%)	5 (2%)	-	6 (2%)	
Family size, n (%)					
2-5 members	3 (100%)	174 (71%)	3 (60%)	180 (71%)	0.000*
≥ 6 members	-	70 (29%)	2 (40%)	72 (29%)	
Economic status, n (%)					
Equal/ below poverty threshold**	3 (100%)	127 (52%)	5 (100%)	135 (54%)	0.609
Above poverty threshold	-	116 (48%)	-	116 (46%)	

Non-homogeneity of sample population: significant at 5% level

*** Approximately PhP8,000.00 to PhP9,000.00 estimate of average monthly income based on 2014 National Statistical Coordination Board Poverty threshold equivalent to PhP8,778.00 monthly income for a family of five*

---The total number of cases in some parameters was less than 267 due to missing data

The median weights of cured patients before and after treatment were 37kg and 40kg, respectively. Patients who completed treatment and defaulted both had a median weight of 14kg prior to treatment. The median weight after treatment among those with complete treatment was 15kg. No weight change was seen among those who defaulted. The BMI of patients with successful treatment outcome and poor treatment outcome was comparable prior to treatment. Among those who completed treatment, 50 (50/262) were stunted (Z-score below -2 to Z-score below -3) and 64 (64/262) were wasted (Z-score below -2 to Z-score below -3). Among those with poor treatment outcome, only 1 (1/5) was wasted. All cured patients had gained weight with a median percentage of 7.53% from baseline. Eighty four percent among those who completed treatment gained weight of 5.71% from baseline. Two patients who defaulted had a weight gain of 4.16%. Anthropometric characteristics are summarized in Tables 2 and 3.

Table 2. Anthropometric Profile of Children with TB in Barangay Commonwealth, Quezon City, 2013 – 2015

	Successful Treatment Outcome		Poor Treatment Outcome	Total	*p*-value
	Cured n = 3	Completed n = 259	Defaulted n = 5	n = 267	
Weight (kg), median (range)	37 (34-37)	14 (6-52)	14 (8-15)	14 (6-52)	0.009*
Height (cm), median (range)	160 (158-162)	102 (57-155)	99 (75-109)	102 (57-162)	0.008*
Height for age before treatment, n (%)					
Z-score above 3	-	6 (2%)	1 (20%)	7 (3%)	0.000*
Z-score above 2	-	7 (3%)	-	7 (3%)	
Z-score above 1	-	2 (1%)	-	2 (1%)	
Z-score 0	3 (100%)	170 (66%)	4 (80%)	177 (66%)	
Z-score below -1	-	22 (8%)	-	22 (8%)	
Z-score below -2	-	30 (12%)	-	30 (11%)	
Z-score below -3	-	20 (8%)	-	20 (8%)	
BMI (kg/m²), median (range)	14 (13-15)	14 (6-23)	15 (13-15)	14 (6-23)	0.820
BMI for age before treatment, n (%)					
Z-score above 3	-	2 (1%)	-	2 (1%)	0.000*
Z-score above 2	-	10 (4%)	-	10 (4%)	
Z-score above 1	-	22 (8%)	-	22 (8%)	
Z-score 0	-	96 (37%)	1 (20%)	97 (36%)	
Z-score below -1	-	68 (26%)	3 (60%)	71 (26%)	
Z-score below -2	2 (67%)	31 (12%)	1 (20%)	34 (13%)	
Z-score below -3	1 (33%)	30 (12%)	-	31 (12%)	

Non-homogeneity of sample population: significant at 5% level

Table 3. Anthropometric Data After Treatment of Children with TB in Barangay Commonwealth, Quezon City, 2013 – 2015

	Successful Treatment Outcome		Poor Treatment Outcome	Total	*p*-value
	Cured n = 3	Completed n = 259	Defaulted n = 5	n = 267	
Weight (kg), median (range)	40 (37-40)	15 (6-52)	14 (8-16)	15 (5 -52)	0.006*
Weight gain, n (%)	3 (100%)	218 (84%)	2 (40%)	223 (84%)	0.000*
Weight gain in kg, median (range)	2.8 (2.5-3.0)	0.8 (0.10-7.80)	0.5 (0.3-0.7)	0.8 (0.10-7.80)	0.009*
% weight gain relative to baseline weight, median (range)	7.53 (7.25-8.11)	5.71 (0.30-35.21)	4.16 (3.66-4.67)	5.71 (0.30-35.21)	0.443

Non-homogeneity of sample population: significant at 5% level

All children were new cases of childhood tuberculosis and classified as pulmonary TB. Of the 267 cases, two children had both pulmonary and extrapulmonary types of TB. One had scrofula and the other, TB peritonitis. There were no cases of extrapulmonary TB alone. Two hundred sixty-four (99%) are smear-negative or clinically diagnosed TB. Comparable results were seen in children exposed (126/262, successful treatment; 3/5, poor treatment) and not exposed (109/262, successful treatment; 2/5, poor treatment) to a known source case of TB. Majority received BCG vaccination and most of the children (163/262, successful treatment; 4/5, poor treatment) had a positive skin test or TST size of equal to or more than 10mm. Most common comorbidity reported was malnutrition (3/3, cured; 108/262, completed; 1/5, defaulted). Clinical characteristics are summarized in Table 4.

Table 4. Clinical Profile of Children with TB in Barangay Commonwealth, Quezon City, 2013 – 2015

	Successful Treatment Outcome Cured n = 3	Completed n = 259	Poor Treatment Outcome Defaulted n = 5	Total n = 267	*p*-value
Category of Patients, n (%)					
New	3 (100%)	259 (100%)	5 (100%)	267 (100%)	-
Classification of TB, n (%)					
PTB Smear +/ BC[a]	3 (100%)	-	-	3 (1%)	-
PTB Smear -/ CD[aa]	-	259 (100%)	5 (100%)	264 (99%)	
Close TB contact, n (%)					
Negative	3 (100%)	106 (41%)	2 (40%)	111 (42%)	0.199
Positive	-	126 (49%)	3 (60%)	129 (48%)	
BCG Vaccination, n (%)					
Positive	2 (67%)	240 (95%)	5 (100%)	247 (95%)	0.000*
Negative	1 (33%)	11 (4%)	-	12 (5%)	
Tuberculin Skin Test size (mm), n (%)					
< 10	-	51 (24%)	1 (20%)	52 (24%)	0.000*
≥ 10	-	163 (76%)	4 (80%)	167 (76%)	
Chest X-ray, n (%)					
Without findings	3 (100%)	121 (47%)	4 (80%)	128 (48%)	0.341
With findings	-	138 (53%)	1 (20%)	139 (52%)	
Cigarette smoke exposure, n (%)					
Yes	-	97 (40%)	2 (40%)	99 (39%)	0.000*
No	3 (100%)	147 (60%)	3 (60%)	153 (61%)	
Comorbidity, n (%)					
Without	-	145 (56%)	3 (60%)	148 (55%)	0.019*
With	3 (100%)	114 (44%)	2 (40%)	119 (45%)	
Malnutrition, n (%)					
Without	-	151 (58%)	4 (80%)	155 (58%)	0.076
With	3 (100%)	108 (42%)	1 (20%)	112 (42%)	
Asthma, n (%)					
Without	3 (100%)	240 (93%)	5 (100%)	248 (93%)	0.000*
With	-	19 (7%)	-	19 (7%)	
Recurrent URTI[aaa], n (%)					
Without	3 (100%)	237 (92%)	5 (100%)	245 (92%)	0.000*
With	-	22 (8%)	-	22 (8.2%)	
Pneumonia, n (%)					
Without	3 (100%)	232 (90%)	5 (100%)	240 (90%)	0.000*
With	-	27 (10%)	-	27 (10%)	
Acute tonsillopharyngitis, n (%)					
Without	3 (100%)	257 (99%)	5 (100%)	265 (99%)	0.000*
With	-	2 (1%)	-	2 (1%)	

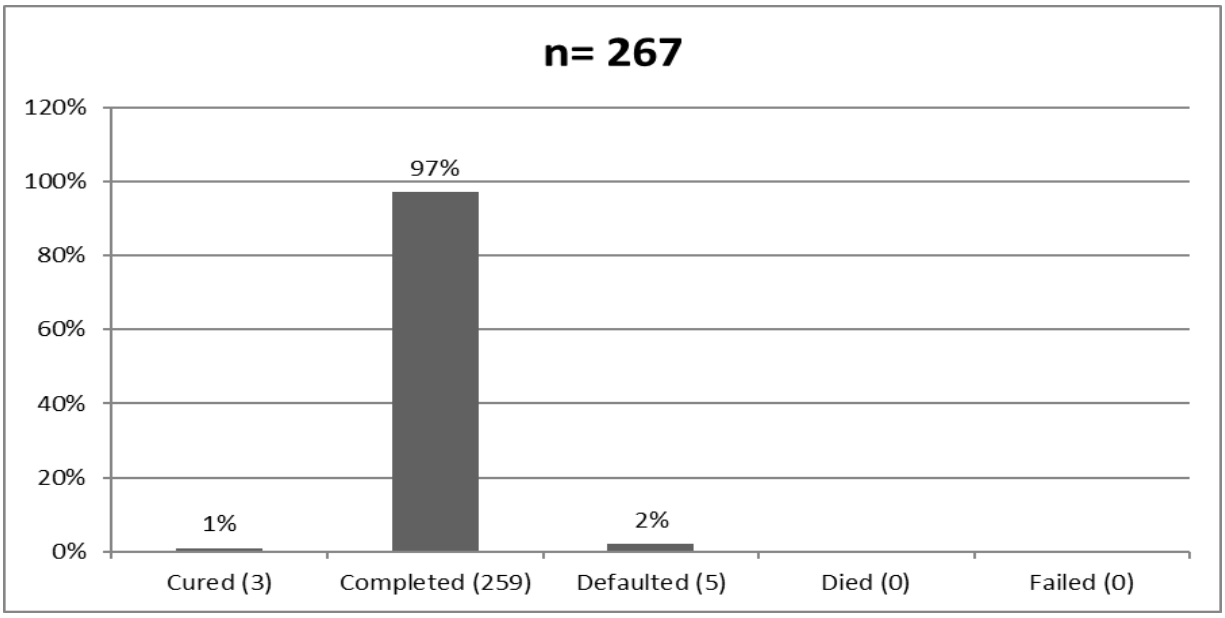
	Successful Treatment Outcome Cured n = 3	Completed n = 259	Poor Treatment Outcome Defaulted n = 5	Total n = 267	*p*-value
Scabies, n (%)					
Without	3 (100%)	257 (99%)	5 (100%)	265 (99%)	0.000*
With	-	2 (1%)	-	2 (1%)	
Otitis, n (%)					
Without	3 (100%)	256 (99%)	5 (100%)	264 (99%)	0.000*
With	-	3 (1%)	-	3 (1%)	
Parasitism, n (%)					
Without	3 (100%)	259 (100%)	4 (80%)	266 (99.6%)	0.000*
With	-	-	1 (20%)	1 (0.4%)	
Hearing defect, n (%)					
Without	3 (100%)	258 (99.6%)	5 (100%)	266 (99.6%)	0.000*
With	-	1 (0.4%)	-	1 (0.4%)	
Brain cyst, n (%)					
Without	3 (100%)	258 (99.6%)	5 (100%)	266 (99.6%)	0.000*
With	-	1 (0.4%)	-	1 (0.4%)	

**Non-homogeneity of sample population: significant at 5% level---The total number of cases in some parameters was less than 267 due to missing data*
[a]Bacteriologically confirmed *[aaa]Upper Respiratory Tract Infection*
[aa]Clinically diagnosed

B. Treatment Outcome

Majority of children with tuberculosis in this study had a successful treatment outcome. Two hundred fifty-nine (97%) completed treatment and three (1%) were cured. A negligible number had unsuccessful treatment outcome (5, 2%). All of those with poor outcome defaulted. There were no reported cases of death or treatment failure (Figure 1).

Figure 1. Rates of Outcome of Treatment in 267 Children with Tuberculosis



C. Factors Associated with Successful Treatment Outcome

On univariate analysis (Table 5), the successful treatment outcome was 8.085-fold (95% CI, 1.310-49.000) higher in

children with weight gain (p=0.001). The percent weight increase (p=0.422) of patients with successful treatment outcome (5.73%) was not significant compared to the percent weight increase of those with poor treatment outcome (4.16%). The absence of comorbid conditions namely: acute tonsillopharyngitis (p=0.015), scabies (p=0.015), parasitism (p=0.019), hearing defect (p=0.000) and brain cyst (p=0.000) was a factor independently related with the treatment outcome among children with tuberculosis. On multivariate analysis (Table 5), the successful treatment outcome was 12.5-fold (95% CI, 1.091-143.244) higher in patients with weight gain (p=0.042).

Table 5. Univariate and Multivariate Association of Sociodemographic, Anthropometric and Clinical Characteristics with the Treatment Outcome of Childhood TB in Barangay Commonwealth, Quezon City, 2013 – 2015

	Successful Treatment Outcome n = 262	Poor Treatment Outcome n = 5	*p*-value (Univariate Analysis)	Odds Ratio (95% CI**) (Univariate Analysis)	*p*-value (Multivariate Analysis)	Odds Ratio (95% CI**) (Multivariate Analysis)
Age in years, n (%)						
0 – 4	152 (58%)	5 (100%)	0.447	-	-	-
5 – 9	85 (32%)	-				
10-14	25 (10%)	-				
Gender, n (%)						
Male	131 (50%)	4 (80%)	0.380	0.250 (0.028,2.267)	-	-
Female	131 (50%)	1 (20%)				
Educational Attainment of Parents, n (%)						
Grade School/ High School	160 (65%)	5 (100%)	0.224	-	-	-
Vocational/ College	87 (35%)	-				
Employment of Parents, n (%)						
Employed	241 (98%)	5 (100%)	0.259	-	-	-
Unemployed	6 (2%)	-				
Family size, n (%)						
2-5 members	177 (72%)	3 (60%)	0.944	1.686 (0.276,10.305)	-	-
≥6 members	70 (28%)	2 (40%)				
Economic status, n (%)						
Below/equal to poverty threshold	130 (53%)	5 (100%)	0.101	-	-	-
Above poverty threshold	116 (47%)	-				
Weight (kg), median (range)						
Before treatment	14 (6-52)	14 (8-15)	0.307	-	-	-
After treatment	15 (6-52)	14 (8-16)	0.160	-	-	-
Weight gain, n (%)						
With	221 (84%)	2 (40%)	0.001*	8.085 (1.310,49.900)	0.042*	12.5 (1.091, 143.244)
Without	41 (16%)	3 (60%)				
Weight gain in kg, median(range)	0.8 (0.10-7.80)	0.5 (0.3-0.7)	0.204	-	-	-
% weight gain relative to baseline weight, median (range)	5.73 (0.30-35.21)	4.16 (3.66-4.67)	0.422	-	-	-
Height for age before treatment, n (%)						

	Successful Treatment Outcome n = 262	Poor Treatment Outcome n = 5	*p*-value (Univariate Analysis)	Odds Ratio (95% CI**) (Univariate Analysis)	*p*-value (Multivariate Analysis)	Odds Ratio (95% CI**) (Multivariate Analysis)
Z-score above 3	6 (2%)	1 (20%)	0.243	-	-	-
Z-score above 2	7 (3%)	-				
Z-score above 1	2 (1%)	-				
Z-score 0	173 (66%)	4 (80%)				
Z-score below -1	22 (8%)	-				
Z-score below -2	30 (12%)	-				
Z-score below -3	20 (8%)	-				
BMI (kg/m^2), median (range)	14 (6-23)	15 (13-15)	0.569	-	-	-
BMI for age before treatment, n (%)						
Z-score above 3	2 (1%)	-	0.682	-	-	-
Z-score above 2	10 (4%)	-				
Z-score above 1	22 (8%)	-				
Z-score 0	96 (37%)	1 (20%)				
Z-score below -1	68 (26%)	3 (60%)				
Z-score below -2	33 (13%)	1 (20%)				
Z-score below -3	31 (12%)	-				
Category of Patients, n (%)						
New	262 (100%)	5 (100%)	-	-	-	-
Classification of TB, n (%)						
PTB Smear +/ BC[a]	3 (1%)	-	0.057	-	-	-
PTB Smear -/ CD[aa]	259 (99%)	5 (100%)				
Close TB contact, n (%)						
Negative	109 (46%)	2 (40%)	0.865	1.298 (0.213,7.909)	-	-
Positive	126 (54%)	3 (60%)				
BCG Vaccination						
Positive	242 (95%)	5 (100%)	0.564	-	-	-
Negative	12 (5%)	-				
Tuberculin Skin Test size (mm), n (%)						
< 10	51 (24%)	1 (20%)	0.739	1.252 (0.137,11.452)	-	-
≥ 10	163 (76%)	4 (80%0				
Chest X-ray, n (%)						
Without findings	124 (47%)	4 (80%)	0.319	0.225 (0.025,2.037)	-	-
With findings	138 (53%)	1 (20%)				
Cigarette smoke exposure, n (%)						
No	150 (61%)	3 (60%)	0.668	1.031 (0.169,6.283)	-	-
Yes	97 (39%)	2 (40%)				
Co-morbid condition, n (%)						
Without	145 (55%)	3 (60%)	0.805	0.826 (0.136,5.027)	-	-
With	117 (45%)	2 (40%)				
Malnutrition, n (%)						
Without	198 (76%)	4 (80%)	0.749	0.790 (0.087,7.195)	-	-
With	64 (24%)	1 (20%)				
Asthma, n (%)						
Without	243 (93%)	5 (100%)	0.879	-	-	-
With	19 (7%)	-				
Recurrent URTI[aaa], n (%)						
Without	240 (92%)	5 (100%)	0.885	-	-	-
With	22 (9%)	-				

	Successful Treatment Outcome n = 262	Poor Treatment Outcome n = 5	*p*-value (Univariate Analysis)	Odds Ratio (95% CI**) (Univariate Analysis)	*p*-value (Multivariate Analysis)	Odds Ratio (95% CI**) (Multivariate Analysis)
Pneumonia, n (%)						
Without	235 (89%)	5 (100%)	1.000	-	-	-
With	27 (10%)	-				
Acute tonsillopharyngitis, n (%)						
Without	260 (99%)	5 (100%)	0.015*	-	-	-
With	2 (1%)	-				
Scabies, n (%)						
Without	260 (99%)	5 (100%)	0.015*	-	-	-
With	2 (1%)	-				
Otitis, n (%)						
Without	259 (99%)	5 (100%)	0.057	-	-	-
With	3 (1%)	-				
Parasitism, n (%)						
Without	262 (100%)	4 (80%)	0.019*	-	-	-
With	-	1 (20%)				
Hearing defect, n (%)						
Without	261 (99.6%)	5 (100%)	0.000*	-	-	-
With	1 (0.4%)	-				
Brain cyst, n (%)						
Without	261 (99.6%)	5 (100%)	0.000*		-	-
With	1 (0.4%)	-				

DISCUSSION

Tuberculosis is an infection that leads to wasting caused by loss of appetite and body weight, nutrient malabsorption, micronutrient malabsorption and altered metabolism as a response to the infectious process in which a complex interaction between the host and the virulence of the organism modulates the overall metabolic response and the various degrees of tissue breakdown.[29,30] The presence of weight gain after therapy indicates a satisfactory response to treatment.[31,32] wherein the virulence of mycobacteria has been successfully targeted by the anti-tuberculosis drugs.

As seen in our study, weight gain has a significant association with successful treatment outcome based on univariate and multivariate analyses. Children with TB who gained weight after treatment have an 8.085-fold to 12.5-fold probability of having a successful treatment outcome. However, the median weight gain of 0.8kg or 5.73 % weight increase seen among those with successful treatment in this study is not significant compared to the 0.5kg weight gain or 4.16% weight increase among those with poor outcome.

This study shows that the socio-demographic and clinical factors such as age, gender, educational attainment and employment of parents, family size, economic status, patient category, TB classification, TST size, chest x-ray, cigarette smoke exposure and co morbid conditions namely malnutrition, asthma, recurrent URTI and pneumonia have no significant association with successful treatment outcome.

Several studies have demonstrated an association between age and gender and successful treatment outcome such as those done in Addis Ababa[8] and southern region of Ethiopia.[13,15] Fifty nine percent of patients in this study are children 0-4 years old. Age plays one of the most significant

roles in determining which children will progress to disease.[18] Young children under 2-3 years of age in whom the immune system is still immature are likely susceptible to developing disease following the primary Mycobacterium tuberculosis infection.[7,14] This study parallels the research done in Cape Town, South Africa where children <3 years old have the most number of cases (52%),[33] in contrast to the research done in Thailand where the least number of cases belongs to the under 4 years of age (26%).[8] There is no significant difference in the distribution of cases across genders in this study which is different from the data at national level which show a male to female ratio of 1.8 in 2014.[34]

Majority (98%) of the parents are employed but more than half (54%) of them still belong to the poverty threshold or below threshold, 68% acquired a low level of education and 72% with successful treatment belong to families with few members. No association between parental education, socio-economic background and crowding to treatment success of patients is created with these data found in the present study. Previous literatures show that there is a higher incidence of childhood tuberculosis found among parents with lower level of education and low annual household income such as those found in a cross-sectional study in South Africa[6] and a hospital-based study in Pakistan.[35] The odds ratio of successful treatment outcome is only 1.686-fold higher in families with 2-5 members in contrast to a previous study where crowding is a factor for unsuccessful treatment outcome.[5]

All cases of childhood tuberculosis in this study are newly diagnosed, which matches the study done in Malawi where 99% of the childhood TB patients were new cases.[10] The studies conducted in Thailand and Addis Ababa had 78% and 88% as new cases, respectively. Almost all are PTB smear-negative or clinically diagnosed, opposing other studies where sputum smear-negativity ranges from 29%-66% of all childhood TB cases evaluated.[7,8,36] Only 1% is PTB smear-positive or bacteriologically confirmed belonging to the 10-14-year age group. This finding is congruent to the study done in Malawi where 5% of the studied population had sputum smear-positive belonging to the 5-14 year age group as compared to the studies done in Congo and Thailand which has a higher percentage of 14% and 20%, respectively.[7,8,36] Adolescence is associated with an increased risk of the development of TB, which usually presents as adult-type pulmonary disease and is often sputum smear-positive.[7] Most of the patients in the present study belong to the 0-4 age group, therefore, expectoration is not expected and the collection of good quality sputum in the 5-9 year age group is hard. The association of TB classification and patient category with successful treatment outcome is not established in this study. Some researches show that successful treatment outcome is lower in smear-negative children16 and in re-treatment adult patients.[13, 37]

The diagnosis of TB infection supported by a positive TST was seen in 76% and chest radiograph findings were remarkable in one half of the study population. Eighty three percent of children assessed in a study in Congo had a pathologic chest radiograph results and is associated with treatment outcome.[36] Positive Tuberculin skin test was observed in 52% of children with TB studied in Rio de Janeiro and 59% in Cape Town, South Africa.[38,39] This study showed that chest radiograph findings and TST size have no association with the treatment outcome.

Almost one half of our study population (48%) was exposed to a source case. The odds ratio of a successful treatment is only 1.298-fold higher among patients with no exposure as found in this study and not significant. Children in household or other close contact with an adult with pulmonary tuberculosis especially smear-positive or culture-positive pulmonary TB are at higher risk of getting infected.[7] The result of a study done by Singh, et al, suggests that there is a high prevalence of infection among children in household contact with adult cases and that the risk is higher for contacts of smear-positive patients but is significant for sputum-negative patients.[40] Singh also stated that there is higher incidence of transmission of infection with exposure to environmental tobacco smoke. This study showed that 39% were exposed to cigarette smoke and has the odds ratio of successful treatment of only 1.031-fold higher than the non-exposed. In a meta-analysis study done by Patra, J., et al, second-hand smoke exposure is associated with an increase in the relative risk of latent TB infection and active TB after controlling for age, biofuel mass use, and contact with a TB patient.[41] Cigarette smoke impairs pulmonary defense mechanisms, making airways more susceptible to infection.[40]

Several medical conditions are risk factors for TB and for poor TB treatment results, while TB can complicate the disease course of some diseases.[42] Forty five percent of the children in this study have medical conditions other than TB. The co-morbid conditions present were as malnutrition, bronchial asthma, recurrent upper respiratory tract infection, pneumonia and otitis media and all these did not show any association on the success of treatment outcome. The other comorbidities found in the study population are as follows: acute tonsillopharyngitis (p=0.015), scabies (p=0.015), parasitism (p=0.019), hearing defect (p=0.000) and brain cyst (p=0.000); and their absence based on univariate analysis reveals an independent relationship with the treatment outcome.

Malnutrition is the most prevalent co-morbidity in this study. The WHO states that malnutrition is a significant risk factor for childhood tuberculosis[7] and is associated with worse outcomes. Although the mechanisms underlying its association with TB remain unclear, some evidences suggest that it affects genetic expression and immune function that predisposes children to tuberculosis progression that results in a disease and inflammatory response that further worsens the nutritional state. [43]

Only two patients were found to have extrapulmonary TB (EPTB) namely scrofula and TB peritonitis concomitant with pulmonary TB. The WHO states that extrapulmonary TB occurs in approximately 20–30% of all cases in children. In this study, the high coverage of almost 100% BCG vaccination among the study population can be a possible explanation for the low rate of EPTB. BCG vaccine has been shown to prevent about 60% to 90% of cases of the more severe forms of TB such as meningeal TB and disseminated TB in young children.[44] Another most likely explanation is that EPTB are generally more severe in terms of signs and symptoms and would usually be referred to or seen immediately in hospitals or referral center instead of being diagnosed and managed in DOTS facilities. As mentioned in the literature, non-receipt of BCG during infancy and EPTB are factors associated with poor treatment outcome. In this study, however, BCG is not associated with successful treatment outcome.

This study showed that children 0-14 years with tuberculosis comprise 23%[45] from the total TB cases both in adult and children which is two-fold higher than the 2014 national estimate of 12% for the same age group.[34] In a study by Marais, et al, a global estimate of 15% occurs in children <15 years of age in low income countries.[33] The treatment success rate in this study is 98%. This has contributed in the high treatment success rate of the entire city which is 91%[46] in 2014 exceeding the national and WHO targets of 90%[47] and 87%[48], respectively for the Millennium Development Goal 2015. The high treatment success rate can be attributed to the efforts of the local health officials to improve case holding through various NTP strategies such as the administration of DOTS in workplaces, homes and other acceptable venues in the community other than the health facility involving community volunteers as treatment partners.[2]

CONCLUSION

Weight gain in general is the single factor of a successful treatment in childhood tuberculosis established in this study. However, the median percentage weight increase of those with successful treatment outcome is not significant compared to the weight increase seen among patients with poor treatment outcome.

The socio-demographic and clinical factors such as patient category, TB classification, TST size, chest x-ray, cigarette smoke exposure and co morbid conditions namely malnutrition, asthma, recurrent URTI and pneumonia have no significant association with successful treatment outcome.

The prevalence rates of successful and poor treatment outcome in this study were 98% and 2%, respectively.

Follow-up on patients after treatment is a vital strategy in achieving and sustaining a TB-free community.

LIMITATIONS AND RECOMMENDATIONS

The limitation of this study is that it was done retrospectively. A prospective study that focuses on the other aspects of childhood tuberculosis such as co-infection with HIV, drug resistance and the factors that affect poor treatment outcome such as defaulting, failure and death is recommended. A larger population is also suggested by doing a multi-center study composed of more than 5 institutions or multi-barangay setting and longer study period of 5 years or more. Studies on weight gain in relation to TB are mostly done among adult patients. Further prospective research on weight and body mass index in childhood tuberculosis with emphasis on the percentage of monthly weight gain is, likewise, recommended. Some variables are found to be missing in the course of data collection. A complete patient profile and medical record should be obtained and recorded electronically to avoid missing data and result to easy access of a more reliable and valid information for future research studies.

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CASE REPORT

Pediatric Sellar-Suprasellar Tubercular Abscess: A Case Report and Literature Review

Virgi Lea Claudine C. Esquivel-Aguas, MD*

* University of the Philippines – Philippine General Hospital

Correspondence:
Dr. Virgi Lea Claudine C. Esquivel-Aguas
Email: vlccesquivel@gmail.com

The author declares 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

Sellar-suprasellar tuberculoma represents 1% of all intracranial tuberculomas, which can convert into a pituitary abscess.

Objectives: This paper aims to present a case of a common lesion in an uncommon site, discuss the challenges in diagnosis in terms of clinical manifestations, imaging and histologic findings, discuss a holistic approach to treatment, and enumerate identified clinical outcomes of reported cases in literature.

Methodology: This paper presents a case report of a sellar-suprasellar tubercular abscess, and reviews similar cases reported in literature.

Result: This is a case of a 16-year old female, Filipino, presenting with a chronic history of intermittent headache, fever, blurring of peripheral vision, polyuria, and increased sleeping time. On neurologic examination, the patient had bitemporal hemianopsia and decreased visual acuity on the right eye. Neuroimaging revealed a hypodense lesion at the sellar-suprasellar area with rim-enhancement on CT and MRI, and laboratory findings suggestive of panhypopituitarism. She underwent Right Pterional Craniotomy and intraoperatively there was note of a firm, yellowish capsule with intracapsular yellowish viscous fluid, which was positive for acid fast bacilli. Marsupialization of abscess was performed and hormonal replacement and anti-tubercular medications were given.

Conclusion: Tuberculoma in the sellar-suprasellar area, can impinge on the optic chiasm, producing bitemporal hemianopsia and pituitary dysfunction. It presents like other sellar-suprasellar masses with non-specific symptoms and these masses share similar features on cranial CT scan. Due to the complexity of the disease, treatment of sellar-suprasellar TB requires integrated management of an infectious disease expert, neurologist, neurosurgeon, endocrinologist, and adolescent medicine specialist. Outcomes of four other cases found in literature were generally good after aspiration or drainage of the abscess followed by TB treatment for 15 to 18 months with resulting improvement in vision, marked reduction in the size or complete resolution of the mass, but with one case having loss of pituitary function.

KEYWORDS: *sellar-suprasellar mass, tubercular abscess, pituitary abscess, pediatric sellar abscess*

INTRODUCTION

Pituitary abscess is a rare potentially life-threatening disease, occurring in all age groups, and is estimated to account for less than 1% of clinically apparent pituitary diseases.[1] It can have a chronic course, mimicking a slow-growing tumor that produces non-specific symptoms due to mass effect, such as headache, panhypopituitarism, and visual field defects. While neuroimaging plays a crucial role in confirming the location and in characterizing the lesion, it can also mislead clinicians because other disease processes can also present similarly as cystic masses on the sellar area.

This case was initially diagnosed as craniopharyngioma but was later on found to be an abscess intraoperatively. On further work-up, the abscess was positive for acid fast bacilli. This case report aims to present a case of a common lesion in an uncommon site; discuss the challenges in diagnosis in terms of clinical manifestations, imaging, and histologic findings; discuss the holistic approach to the treatment of such a disease; and enumerate identified clinical outcomes of similar reported cases in literature.

This case report not only presents as a rare presentation of a common disease, it also highlights the importance of a high index of suspicion, timely intervention, and holistic approach to management as these can improve the prognosis of patients with tubercular abscess.

CASE

A 16-year old female presented with a 3-month history of intermittent headache, episodic esotropia, and "clumsiness" described as frequent bumping of bilateral shoulders onto walls when walking. She was subsequently noted to have increased sleeping time with accompanying polyuria, prompting consultation at a local hospital in Gerona, Tarlac, where cranial CT scan was done with note of a hypodense lesion about 3x3 cm in the sellar-suprasellar area.

Cranial MRI done at the same institution showed a lobulated heterogeneous suprasellar mass with rim enhancement measuring 3.0x2.9x.3.5 cm with no parenchymal signal abnormalities. Hormonal work-up showed the following results: FSH 0.59 mIU/mL (NV 3.5-12.5mIU/mL), LH <0.100 mIU/mL (NV 2.4-12.6mIU/mL), cortisol 54.53nmol/L (NV 171-536nmol/L). She was then referred to our institution for further management.

Upon initial consultation, she was drowsy with the following vital signs: blood pressure 100/70 mmHg, heart rate 89 beats per minute, respiratory rate 19 cycles per minute, temperature 36.5^0 Celsius. On further physical examination, sexual maturity rating of breasts is at 3, and genitalia at 2. The rest of the physical examination was normal. On neurologic exam, patient was drowsy, followed commands with prodding, pupils were 3mm equally and briskly reactive to light with primary gaze at midline. There was decreased visual threat bitemporally. No cranial nerve deficits were noted. She was normoreflexive, with supple neck, no nystagmus. Assessment was Sellar-suprasellar mass probably Craniopharyngioma vs Pituitary macroadenoma. Other hormonal work-ups included TSH 0.20 mIU/mL (NV 0.3-3.8 mIU/mL), FT4 5.7 pM (NV 11-24 pM), cortisol 86.6 nmol/L (NV 138-690 nmol/L), prolactin 59.5 mIU/mL (NV 92-868 mIU/mL). Due to findings of panhypopituitarism, she was started on hormonal replacement with Hydrocortisone and Levothyroxine. There was subsequent improvement in sensorium—and later on became awake and was able to follow commands. Visual field testing showed bitemporal hemianopsia. The plan of management was craniotomy with excision of tumor. While securing funds for surgery, she was discharged improved on Hydrocortisone 20mg/tab 2 tabs TID and Levothyroxine 50mcg/tab 1 tab OD.

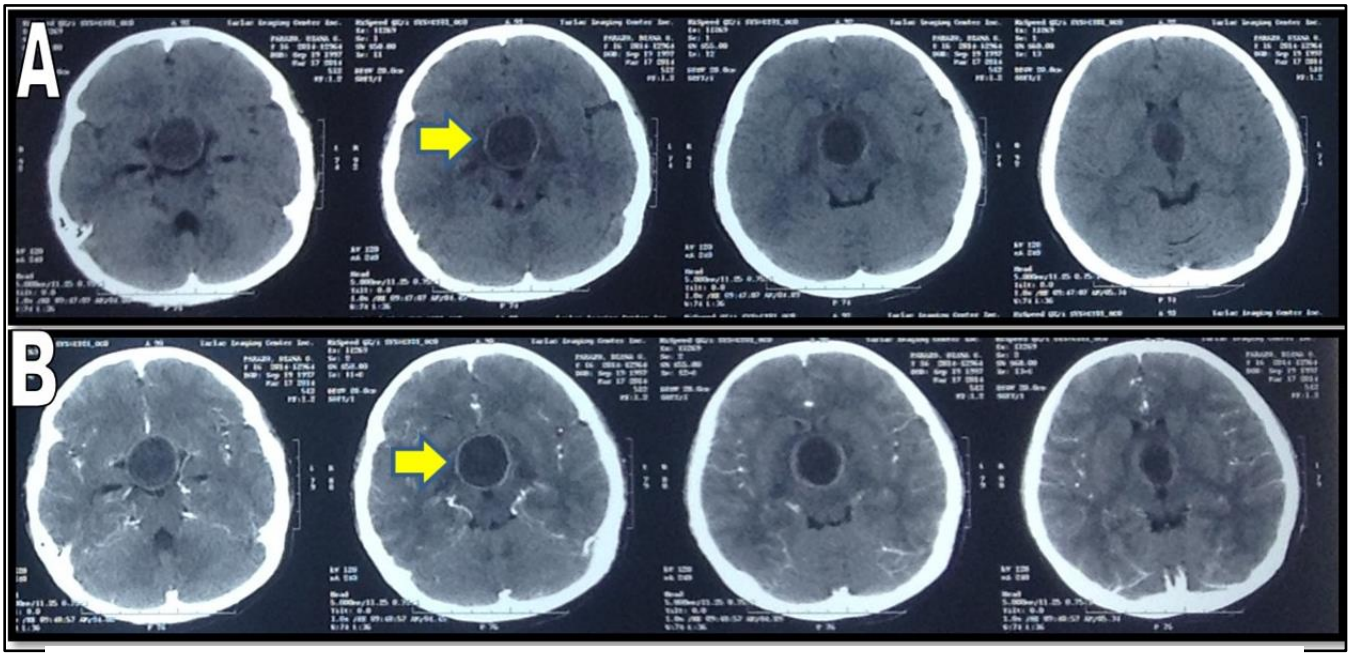

Figure 1. A) Plain cranial CT scan showing hypodense lesion (yellow arrow) measuring 3x3cm at the sellar-suprasellar area. B) Contrast study showing marginal enhancement of the lesion.

She was on regular follow-up with her neurologist, endocrinologist, neurosurgeon, with good compliance to medications.

In the interim, she was apparently well until three days prior to admission, when she developed high-grade fever. This was accompanied by increased sleeping time, prompting her second admission at our institution two months after the first admission. She was seen at the emergency room awake, conversant, not in cardiorespiratory distress with stable vital signs. Optic nerve examination showed no evidence of papilledema. There was bitemporal hemianopsia elicited on confrontational visual field testing. No other cranial nerve or sensorimotor deficits were noted. At the ward, she had episodes of headache, fever, and blood pressure spikes as high as 130/80. Fluid balance was negative. Serial serum electrolytes with simultaneous urine electrolytes were determined. The patient consistently had hypernatremia and hypokalemia with urine specific gravity ranging from 1.001 to 1.003. Oral fluids were given *ad libitum* and hydrocortisone as well as levothyroxine were continued. Desmopressin (Minirin) was eventually started and free water deficit correction was done. The neurosurgical plan was to proceed with contemplated procedure.

She had intermittent low-grade fever with occasional spikes reaching 39^0C. Blood count showed leukocytosis with neutrophilic predominance. Cefuroxime was started for urinary tract infection. Due to persistence of fever, Cefuroxime was shifted to Ceftazidime and Amikacin for a possible nosocomial infection. Acute phase reactants were elevated, but blood cultures were negative. The patient was cleared for surgery after 10 days of IV Ceftazidime.

On her 13^{th} hospital day, she underwent Right pterional craniotomy. Intraoperative finding was a firm yellowish capsule at the sellar-suprasellar area with intracapsular yellowish viscous fluid. On frozen section, the specimen was consistent with fibrocollagenous tissue in acute inflammation. Marsupialization of abscess was done. Cerebrospinal fluid studies were sent for analysis revealing leukocytosis with lymphocytic

predominance, with increased levels of glucose and total protein. On Gram stain, no organisms were seen.

Post-operatively, the patient reported improved peripheral vision. There were no recurrences of headache, blurring of vision, episodes of vomiting, or nausea. However, the patient still had febrile episodes despite nine days of antibiotics. Abscess AFB smear revealed +2/30 fields. Further TB work-up showed an unremarkable chest x-ray but sputum AFB was +1. The patient was started on quadruple anti-TB medications. On the 4th day of treatment, the fever began to lyse.

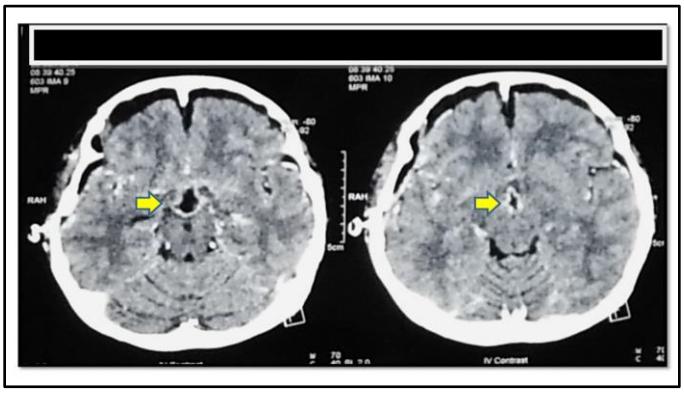

Figure 2. Post-operative cranial CT scan with contrast showing a decreased size of the mass.

Repeat CT scan showed a decrease in the size of the previously described predominantly fluid-attenuating mass lesion with well-defined hyperdense enhancing borders and a punctate internal calcification in the sellar-suprasellar region. It now measured approximately 2.8 x 2.2 x 1.7cm from a previous 4.3 x 2.7 x 3.0cm. The patient was discharged within a week after initiating anti-TB medications. The final diagnosis was Disseminated Tuberculosis (sellar-suprasellar tubercular abscess, PTB) with Panhypopituitarism (hypocortisolism, hypoprolactinemia, hypothyroidism, diabetes insipidus) S/P Pterional Craniotomy, Right; Marsupialization of Abscess.

DISCUSSION

The pituitary gland is situated in the sella turcica which is a depression within the sphenoid bone. It is connected to the hypothalamus by the infundibulum or pituitary stalk, which closely lies posterior to the optic chiasm. A disease process localized at the sellar-suprasellar area may exert a mass effect and impinge on the optic chiasm, producing bitemporal hemianopsia. The same mass effect will also produce pituitary dysfunction.

There is a multitude of conditions that can exert a mass effect and produce the clinical manifestations seen in our patient hence, performing imaging studies is of paramount importance to confirm the location of the lesion as well as to gain clues to the type of the disease process involved. In our patient, imaging revealed a hypodense mass with rim-enhancement, which can be any of the following: craniopharyngioma, Rathke's cleft cyst, or pituitary abscess.[1]

Craniopharyngiomas are benign tumors that grow near the pituitary gland. They can be solid tumors or cysts. Approximately 10-15% of pituitary tumors are craniopharyngiomas. They are most commonly found in children, teenagers, and adults older than 50. The MR appearance of craniopharyngiomas depends on the proportion of the solid and cystic components, the content of the cyst(s), and the amount of calcification.[2] The solid portions of the tumor appear as iso- or hypointense relative to the brain on pre-contrast T1-weighted images, but can also have a mottled appearance owing to calcific regions. They are usually of mixed hypo- or hyperintensity on T2-weighted sequences, and heterogeneously enhance following Gd administration.[3,4]

Rathke's cleft cysts are non-neoplastic cysts arising along the craniopharyngeal duct from the remnant of squamous epithelium of Rathke's pouch. They consist of a single layer of cuboidal or columnar epithelial cells with mucoid, cellular or serous components in the cyst fluid. They are often

discovered incidentally, but may become symptomatic in a minority (5-9% of all surgically-resected sellar lesions) when intracystic bleeding or infection occurs, leading to symptoms similar to those of our patient. On MRI, Rathke's cleft cysts appear well-circumscribed, centrally located spherical or ovoid, non-calcified cyst lesions of the sellar region. The lesion is fairly isointense to CSF.

Pituitary abscess is a rare potentially life-threatening disease, occurring in all age groups, and is estimated to account for less than 1% of clinically apparent pituitary diseases.[1] The typical MR features of an abscess are the presence of a round cystic or partially cystic sellar mass that appears as hypo- or isointense on T1 and hyper- or isointense on T2, with an enhanced rim after Gd injection and a central cavity that is isointense to the brain.[5,6] The sella may be enlarged and, occasionally, extensively eroded.

Only 200 cases of primary pituitary abscesses have been reported in literature, primarily in adults. Diagnosis may be difficult, as symptoms can be nonspecific, and without signs of an infectious process. Median time from the onset of symptoms to diagnosis is 6 months.[2] Most patients present with a chronic and indolent course with few manifestations thus mimicking a pituitary tumor.[5] The most common symptoms are neurological (headache, visual impairment and cranial nerve palsy), but manifestations of hypopituitarism are frequent. Diabetes insipidus and headache are the most common presenting complaint (70%)[7] and over half of the patients complain of visual disturbances. Most patients (85%) have partial or total hypopituitarism (including prolactin deficiency). The following are the identified etiologic agents of pituitary abscesses: Gram-positive cocci, fungi, and other organisms including *Mycobacterium tuberculosis, Toxoplasma, Clostridium difficile, and Pseudomonas aeruginosa.* In our patient, the abscess was positive for acid-fast bacilli.

Sellar-suprasellar tuberculosis may present as a tuberculoma,[8] which are inflammatory granuloma cells surrounded by a rich network of collagen and reticulin. Sellar-suprasellar tuberculoma represents 1% of all intracranial tuberculoma. The tuberculoma can undergo caseation resulting in a pituitary abscess. A TB abscess is an encapsulated collection of pus containing viable tubercle bacilli and without typical tubercular granuloma and epithelioid cells. A review of literature on pituitary or sellar tubercular abscess yielded only five cases. [9,10,11,12,13]

The first report of a TB abscess by Dutta[9] and colleagues was in 2006, on a 13-year old Indian boy who presented with meningitis, deteriorating vision and panhypopituitarism. Cranial MRI showed a solid-cystic lesion with suprasellar extension. The patient underwent stereotactic aspiration and biopsy of abscess which was positive for AFB. He was treated with anti-TB medications and steroids. The patient had improved vision after 2 weeks, and follow-up imaging showed a marked reduction in the size of the lesion, 6 months into treatment. This patient, however, was lost to follow-up.

The second case was reported in 2008[10] on a 45-year old man from India with holocranial headache for 6 months, A sellar mass with peripheral rim enhancement was seen on cranial MRI. Trans-sphenoidal excision was done and the specimen was positive on mycobacterial culture. He was given anti-TB medications and hormonal replacement. The patient eventually had complete loss of pituitary function and required permanent hormonal replacement therapy.

The third report in 2011[11] presented similarly: a 27-year old from India with progressive headache, occasional vomiting, hypothyroidism, and hyperprolactinemia. Cranial MRI revealed a cystic sellar lesion with suprasellar extension. Drainage and decompression of the cyst was done. The cyst cavity contained creamy pus which was positive for mycobacterial colonies after six weeks. She was also given anti-TB medications. The patient

had no residual cyst on post-operative imaging, had normal thyroid function after three months with pituitary hormone status recovered to normal after six months, and as of the time of writing of the report, was doing well at 12 months.

The fourth report[12] in 2012 was a case of a 50-year old Filipina, diabetic with gradual loss of bitemporal vision, headache, polyuria and polydipsia. Trans-sphenoidal surgery was done which yielded AFB from the abscess. She was treated with anti-TB medications, vancomycin and cefepime. Outcomes reported only included improved vision and subsequent development of central diabetes insipidus.

Finally, the last report[13] in 2016 was on a 44-year old Indian female, a known case of tuberculous meningitis for one year who now presented with behavioral changes and increased frequency of micturition. Cranial MRI revealed a hypointense lesion on T1 images in the hypothalamic region, iso-intense on T2, and restricted diffusion on diffusion-weighed images. The lesion was rim-enhancing on contrast study. Pterional craniotomy and sylvian fissure opening were performed with total excision of the lesion. Post-surgery, the patient had diabetes insipidus which eventually resolved.

Abscesses resulting from hematogenous spread can localize in any part of the brain, but most commonly occur in the distribution of the middle cerebral artery at the junction of the gray and white matter of the cerebral hemispheres. In contrast, abscesses derived from contiguous sources tend to be superficial and close to the infected bone or dura.

Visual loss is a common presenting complaint due to the proximity of the lesion to the optic nerves, chiasm and optic tracts. For our patient, this was manifested as bitemporal hemianopsia. Involvement of the cavernous sinus produces symptoms and signs related to affectation of the cranial nerves (3rd, 4th, and 6th, as well as 1st and 2nd divisions of the 5th cranial nerve) that run in the cavernous sinus. Our patient had episodes of esotropia. Headache develops either as a consequence of increased intracranial pressure, distortion of the diaphragm or irritation of the parasellar dura.[14]

Both tuberculoma and abscess do not present with hypersecretory syndromes but rather with hypopituitarism or symptoms of mass effect due to compression of nearby vital surrounding structures, the severity of which depends on the location, size and growth potential of the lesion[6]. Owing to their compressive effects, varying degrees of anterior pituitary dysfunction can develop later with or without central diabetes insipidus. Hypopituitarism with hyperprolactinemia occurs, that causes galactorrhea and amenorrhea in females and decreased libido in males.[15,16] In the case of our patient, hypothyroidism and hypocortisolism were noted.

Diagnostic Tests to be done in such cases include neuroimaging to confirm the location of the lesion; endocrine work-up and hormone level determination to distinguish functioning from non-functioning masses; tuberculosis work-up since we are in a TB-endemic setting

The role of neuroimaging in this case cannot be overemphasized. Further differentiating tuberculoma from a TB abscess is important because of differences in management. They may be distinguished through MRI where the stages of of tuberculoma evolution are better appreciated, except in cases where central liquefaction has taken place, when the two may become indistinguishable from one another. Sellar tuberculoma may occasionally appear hyperintense on T1-weighted images owing to their high protein content. On T2, they can be hypo or hyperintense. With contrast, the tuberculomas characteristically appear as conglomerate ring-enhancing nodules. On the other hand, sellar tubercular abscess on MRI shows cystic sellar lesion with ring enhancement on contrast. On T2, there is a hyperintense signal in the cyst cavity.[17,18,19]

Whitner has established the following diagnostic criteria for intracranial TB abscess.[20] There has to be (1) macroscopic evidence of a true abscess formation within the brain as confirmed during surgery or autopsy; (2) histological proof of presence of inflammatory cells in the abscess wall and (3) demonstration of Acid Fast bacilli in the pus or abscess wall in immunocompromised patients with or without HIV infection or in an immunocompetent patient from an endemic region with a pulmonary focus of infection. The following are the risk factors for the development of tuberculous brain abscess: immunocompromised condition, endemicity, and a pulmonary focus of infection.

Distinguishing between tuberculoma and a TB abscess is crucial since a tuberculoma would usually resolve with anti-TB medications. In fact, some authors recommend starting anti-TB medications in patients suspected to have sellar tuberculoma by imaging even without histologic diagnosis, especially in endemic areas. On the other hand, a TB abscess needs to be aspirated due to the impenetrability of the abscess wall to drugs.

The procedure of choice is the trans-sphenoidal approach as it allows local cure, provides a histopathological diagnosis, and avoids CSF contamination. Radical excision is not necessary. Based on literature, a four-drug regimen consisting of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol for 18 months has been given to patients with both tuberculoma and TB abscess. However, there is still no definite consensus as to the duration of treatment for this condition.

As in our patient, hormonal replacement should be initiated if indicated. Family members should also be worked up for TB. Lastly, the patient and her family should be educated on the importance of compliance to therapy and follow-up.

CONCLUSION

Tuberculoma in the sellar-suprasellar area, can impinge on the optic chiasm, producing bitemporal hemianopsia and pituitary dysfunction. It presents like other sellar-suprasellar masses with non-specific symptoms and these masses share similar features on cranial CT scan—hypodense lesions with rim-enhancement. Due to the complexity of the disease, treatment of sellar-suprasellar TB requires integrated management of an infectious disease expert, neurologist, neurosurgeon, endocrinologist, and adolescent medicine specialist. Outcomes of four other cases found in literature were generally good after aspiration or drainage of the abscess followed by TB treatment for 15 to 18 months with resulting improvement in vision, marked reduction in the size or complete resolution of the mass, but with one case having loss of pituitary function.

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I would like to express my gratitude to our patient who willingly gave consent for this clinical material to be written as a case report.

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CASE REPORT

Hansen's Disease in an Adolescent: A Case Report

Patricia Carla N. Asuncion, MD*
Rhanee Lota-Salvado, MD*

*Department of Pediatrics
University of the Philippines,
College of Medicine - Philippine General Hospital

Correspondence:
Dr. Rhanee Lota-Salvado
Email: rhaneesalvado@gmail.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

Leprosy is a chronic communicable disease that remains to be endemic worldwide and children and adolescents are most vulnerable to infection. A 17-year-old Filipina presented with a 4-year history of multiple skin lesions evolving into various forms, associated with pain and deformity of extremities. She was diagnosed with Hansen's disease, lepromatous type, in severe erythema nodosum leprosum. She was started on multi-drug therapy with Rifampicin, Clofazimine and Clarithromycin. There was remarkable improvement with arrested progression of skin lesions, conversion of wounds into granulation tissue, significant decrease in painful sensation, and gradual ability to move the extremities. Early recognition of leprosy and prompt initiation of treatment will ultimately prevent complications and disabilities in afflicted patients. A holistic approach is key in the management of children and adolescents with leprosy.

KEYWORDS:
Hansen's Disease, Leprosy, Adolescent, Philippines

INTRODUCTION

Leprosy, or Hansen's disease, is a chronic, communicable disease caused by *Mycobacterium leprae*. It affects the skin, peripheral nerves, upper respiratory tract mucosa, and eyes. Leprosy remains endemic in many countries, despite having been eliminated as a public health problem globally more than 15 years ago. The World Health Organization reported 210,758 new cases of leprosy worldwide in 2015.[1] The proportion of children among these new cases was 8.9%.[1] Children and adolescents are most vulnerable to infection with leprosy.[2-4] This study depicts the case of an adolescent female with multibacillary, lepromatous leprosy presenting with a 4-year history of multiple skin ulcerations associated with gradually progressing neuritis. A timeline of the patient's medical history and course of care is detailed in Figure 1.

PATIENT INFORMATION

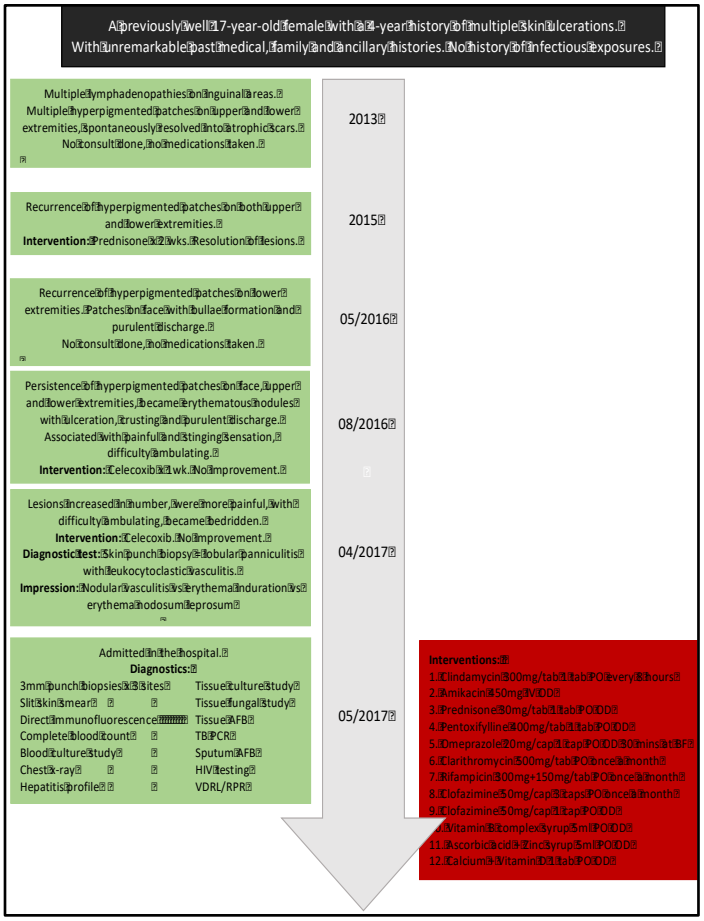
A 17-year-old Filipino female was admitted in our institution in May 2017 due to skin lesions of 4 years duration. She presented with recurrent, multiple hyperpigmented patches which evolved into varying lesions: erosions, ulcerations, bullae formation, erythematous nodules, appearing on her face, hips, and both her upper and lower extremities. Due to neglect, the lesions became secondarily infected, with purulent discharge. She also reported painful sensations on her lesions as well as difficulty in ambulation, eventually rendering her bedridden.

Patient was previously well prior to the onset of her symptoms. Her past medical, family, and personal-social histories were unremarkable. No infectious contacts were identified at initial presentation.

CLINICAL FINDINGS

Physical examination revealed a cachectic patient with multiple, well-defined, irregularly-shaped hypo- and hyperpigmented patches and plaques with erosions and ulcerations on the face, ears, back, and extremities. Her skin was pale, xerotic and atrophic. An enlarged ulnar nerve was noted on the left arm. She had deformed feet, with marked edema on the left extremity.

Figure 1. Patients Timeline



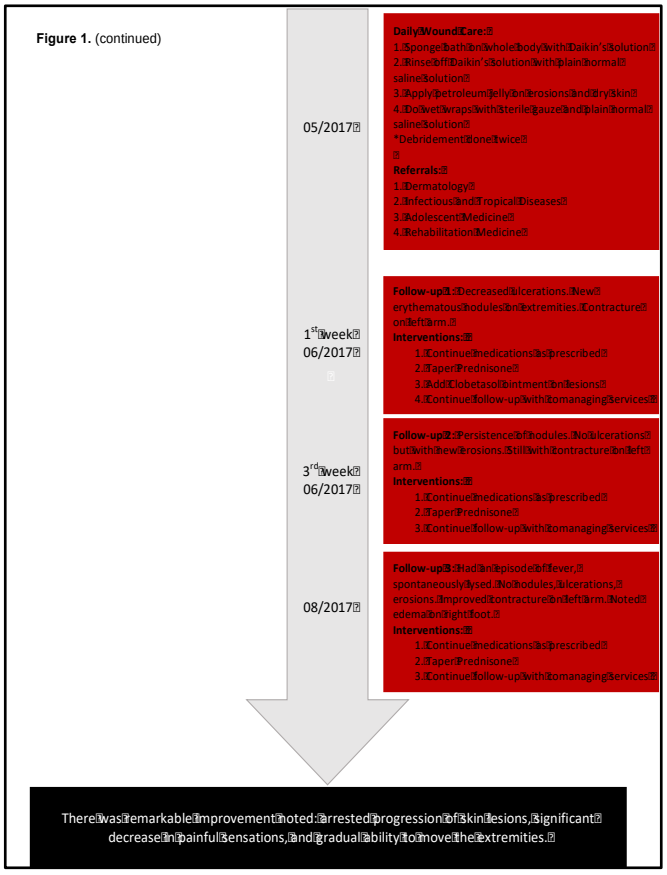


Figure 2. Lesions on the upper and lower extremities on admission.

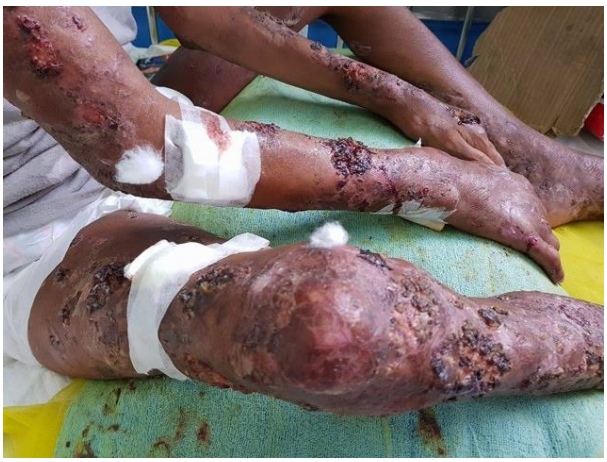
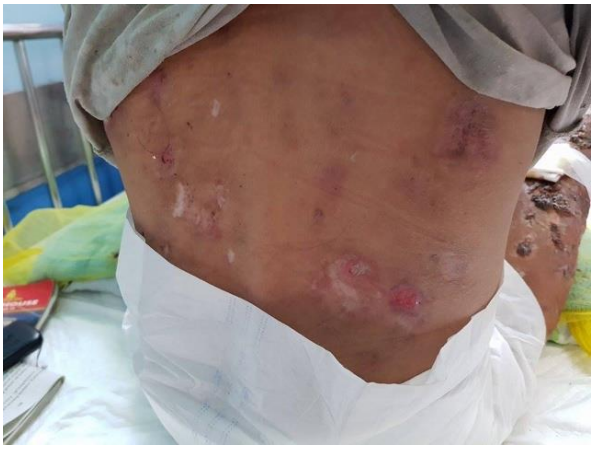


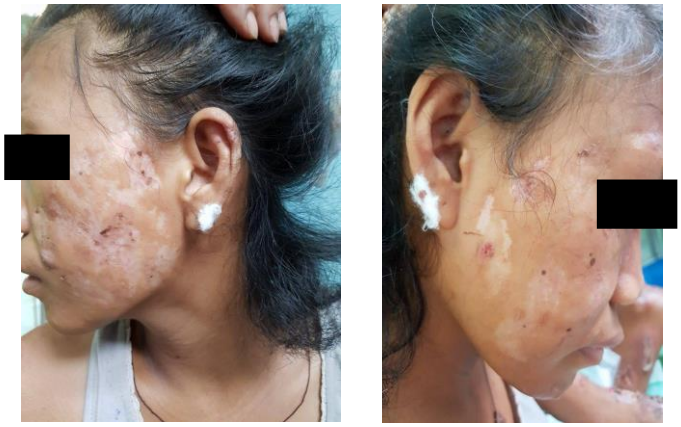
Figure 3. Lesions on the back on admission.



DIAGNOSTIC ASSESSMENT

The initial impression for this patient was Lepromatous leprosy, type 2 lepra reaction, with superimposed bacterial infection. Other disease entities considered were cutaneous lupus erythematosus, impetigo, and cutaneous tuberculosis.

Figure 4. Lesions on the face and ears on admission.



Complete blood count showed anemia, leukocytosis and thrombocytosis. Direct immunofluorescence was negative for anti-nuclear antibodies. There was no growth on cultures of blood and tissue samples. Wound discharge culture showed moderate growth of Methicillin-resistant *Staphylococcus*

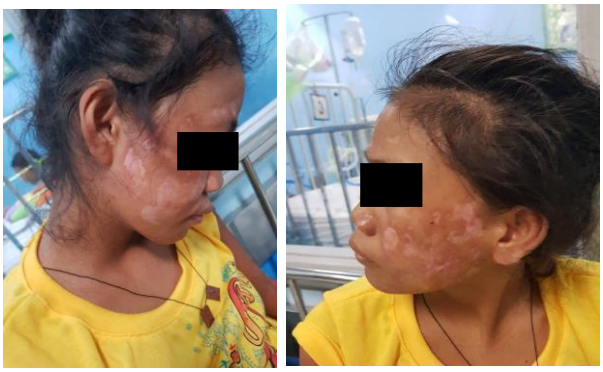
aureus (MRSA). Tuberculosis polymerase chain reaction (TB PCR) was negative. HIV screening was negative as well. Slit skin smears signified a bacillary index of 2. Skin punch biopsies revealed lobular panniculitis with leukocytoclastic vasculitis.

After extensive work-up and evaluation, the patient was diagnosed with Hansen's disease, lepromatous, in severe erythema nodosum leprosum, with superimposed MRSA infection; severe acute malnutrition.

THERAPEUTIC INTERVENTION

The patient was given Clindamycin (30mg/kg/day) 300mg/tab 1 tablet per orem every 8 hours and Amikacin (15mg/kg/day) 450mg intravenously once a day to treat the MRSA infection. A skin care regimen, comprising of petroleum jelly, plain saline solution and Daikin's solution, was used for cleaning and dressing her lesions. Initially, she was given Prednisone (1mkday) 30mg/tab 1 tablet per orem once a day and Pentoxifylline 400mg/tab, 1 tablet per orem once a day to control the erythema nodosum leprosum reaction. Pentoxifylline was given in lieu of Thalidomide, a teratogenic drug, since the patient is of reproductive age. For leprosy, she was started on multi-drug therapy (MDT) multibacillary treatment, based on the WHO recommended MDT regimen[5]: Rifampicin 450 mg, Clofazimine 150 mg and Clarithromycin 500 mg once a month, and daily Clofazimine 50 mg for 12 months. Since that the patient had anemia, Clarithromycin was substituted for Dapsone (a drug known to cause hemolytic anemia). Other medications given were Omeprazole, Vitamin B complex, Ascorbic acid + Zinc, and Calcium + Vitamin D. Debridement procedures were done by the dermatology service. The rehabilitation medicine service took care of splinting her extremities.

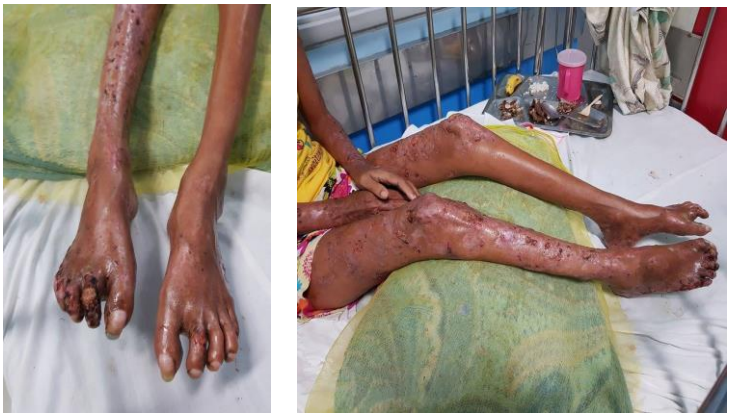
Figure 5. Lesions on the face on discharge, after one week of treatment.



The patient tolerated the procedures well. She did not experience any untoward reactions with the medications given. She exhibited remarkable improvement, with significant decrease in pain sensation on her extremities, arrested progression of her skin lesions, conversion of her previously active wounds into dry areas with granulation tissue formation, and gradual ability to move her lower extremities. She was discharged well after 11 days in the hospital.

Figure 6. Lesions on the lower extremities on discharge.

With noted improvement in lesions after one week of treatment.

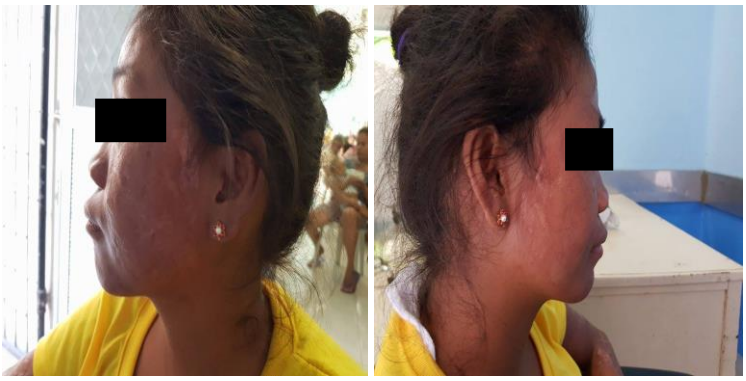


FOLLOW-UP AND OUTCOMES

On the patient's initial visit two weeks after discharge (June 2017), the skin ulcerations further improved and decreased in number. However, there was note of new erythematous nodules on the extremities, and contracture on her left arm. She was instructed to continue her medications and continue with daily wound care regimen. Clobetasol ointment was advised for her lesions.

On her second visit two weeks after the first (June 2017), the ulcerations reported earlier had healed but there were new skin erosions. There was still persistence of the nodules on the extremities, and left arm contracture. She was advised to continue her medications.

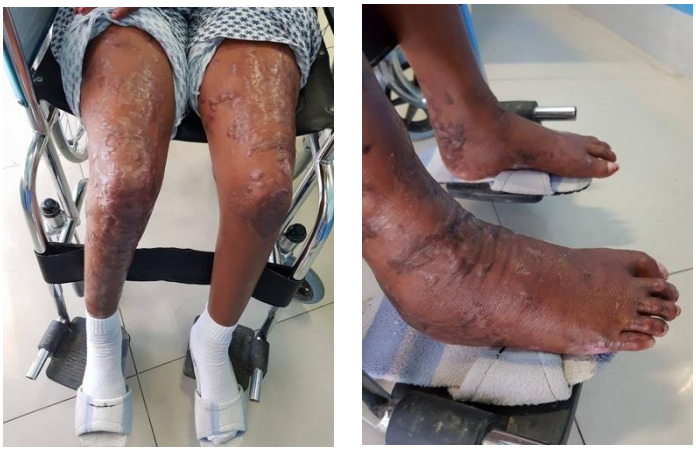
Figure 7. Lesions on the face on her third visit, after 3 months of treatment.



On her third visit (August 2017), she reported an episode of undocumented fever which spontaneously lysed. The skin erosions and nodules previously noted had resolved. The contracture on her left arm had improved. There was note of edema on the right foot. Her medications were advised to be continued.

Figure 8. Lesions on the upper extremities, after 3 months of treatment.

Figure 9. Lesions on the lower extremities, after 3 months of treatment. Noted edema on right foot.



DISCUSSION

Leprosy continues to be one of the important neglected tropical diseases worldwide. Global strategies have long been implemented to strengthen efforts for leprosy control. Despite achievements in decreasing the global disease burden, there still remain pockets of high endemicity in some areas of many countries.[6] The World Health

Organization reported that 203,600 (96%) of new leprosy cases came from 22 high-burden countries.[6] The Philippines, being one of these, contributed the highest number of cases in the Western Pacific Region, with mostly multi-bacillary cases (92.21%).[1] In 2015, there were 1,617 new cases of leprosy detected in the Philippines.[1] Out of these, 131 cases (8.1%) were among children.[1] Childhood leprosy correlates with active disease transmission in the community.[1,3,4]

Leprosy, a chronic systemic granulomatous disease, exhibits 3 cardinal symptoms, all of which were present in our patient: multiple nodular skin lesions, peripheral nerve damage, and positive slit skin smear and biopsy.

Spontaneous immunologic phenomena called lepra reactions indicate sudden increase in disease activity. These reactions, which are often precipitated by infection, stress, surgery, pregnancy and vaccination, complicate the course of disease in 40% to 50% of patients.[7] Two distinct leprosy reactions occur: type 1 (reversal type) and type 2 (erythema nodosum leprosum). Manifestations of erythema nodosum leprosum were seen in the patient: neuritis – a painful enlarged left ulnar nerve, loss of function on both feet, joint pains, and generalized tender skin nodules with ulceration.

The treatment goals for this patient included (1) treating the *Mycobacterium leprae* and superimposed MRSA infections, (2) managing the complications: neuritis and deformities, and (3) addressing her psychosocial concerns. The patient responded well to treatment while admitted in the hospital and reported good compliance with her home medications. As recommended by WHO, MDT regimen is continued for 12 months.[5] She and her caretakers were advised regarding the importance of completing the MDT regimen and the possible repercussions of discontinuing therapy. A study by Kar and Bob which focused on the burden of deformities in children with leprosy, determined various factors that contributed significantly to the deformities: increasing age of children, delay in accessing health care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and reaction at the time of presentation to the hospital.[8] Prednisone, an oral corticosteroid given to control the neuritis and erythema nodosum leprosum reaction, was gradually tapered in this patient. Medical management, with concurrent supportive rehabilitation practices, aided in her marked improvement. As in the study of Govindharaj et al, it is important to deal with child and adolescent issues related to health and stigma.[3] The psychosocial aspect of the disease was addressed with counselling by the Adolescent Medicine service and the hospital chaplain.

LIMITATIONS

The treatment response seen in our patient thus far may not necessarily apply to other patients in general, given the modified therapeutic regimen accorded to her. Since the patient has only been on the first few months of a year-long therapy, the utmost effects of treatment and signs of significant recovery are yet to be observed. Continuous follow-up and evaluation is therefore emphasized.

CONCLUSION

Leprosy remains an important endemic disease worldwide. This report illustrated the case of an adolescent with a protracted history of multiple skin lesions and resultant deformities. Multi-drug therapy is effective in treating leprosy. Early recognition of the disease and prompt initiation of treatment will ultimately prevent complications and

disabilities in the afflicted patients. A holistic approach in the management of children and adolescents with leprosy is recommended.

CONSENT

Written consent was obtained from her parents and verbal consent was given by the patient for publication of this article.

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