Extra pulmonary tuberculosis in Tunisian children referred to tertiary pediatric care hospital: Clinical features, Diagnosis, Management and Outcomes

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Abstract

Background and aims : Tuberculosis (TB) is a public health problem in our country. Extra pulmonary TB (EPTB) is the most common form of TB in children. No Tunisian clinical studies on EPTB in children were published since 2009. This study was conducted to describe clinical features of EPTB in children and to assess management and outcomes.

Patients and methods : All children with EPTB diagnosed from January 2010 to December 2021 in a department of a Tunisian pediatric tertiary referral center, were reviewed.

Results : EPTB represented 79% of all cases of tuberculosis diagnosed during the study period. The mean age at diagnosis was 7.8±4.2 years. The involved sites were peripheral lymph nodes (40%) followed by abdominal TB (30%), osteoarticular TB (17%), central nervous system TB (11%) and disseminated TB (2%). BCG vaccine was given to 96% of patients. Immunodeficiency was reported in 23% of cases. Mean diagnosis delay was 3.3 months. The longer diagnostic delay was reported in abdominal TB cases (p=0.028). Granulomatous inflammation with caseous necrosis was found in 41% of cases. Mycobacterial culture was positive in 15% of cases. Mean duration of antituberculosis treatment was 10.8±4.5 months. Response to first-line antituberculosis drugs was good in all patients. Three patients had sequelae: vertebral deformation (n=1) and neurological sequelae (n=2).

Conclusion : We reported the highest proportion of EPTB in children. The most common site of EPTB was lymph nodes. Vaccination with BCG and screening of children for latent forms of TB are the main measures to control this disease.

Key words: Tuberculosis, children, extrapulmonary, tuberculous meningitis, clinical outcome, antituberculosis therapy

Introduction

Tuberculosis (TB) is a chronic infection caused by Mycobacterium tuberculosis (MTB) also known as Koch's bacillus. Transmission is mainly caused by inhaling respiratory droplets contaminated with MTB [1]. It mainly affects the lungs and can reach all other organs. It remains a public health problem in several countries. In 2021, an estimated 10.6 million people worldwide were affected by TB [2]. Eleven percent of them were children and adolescents aged less than 15 years. Tunisia is an intermediate endemic country with an average incidence of 36/100 000 inhabitants in 2020 [2]. Extra pulmonary TB (EPTB) is the most common form of TB in children, especially under the age of five years [3]. TB in children is characterized by clinical polymorphism, leading to delay in diagnosis and management. No Tunisian clinical study on EPTB in children has been published during the last decade. The aim of this study was to describe epidemiology and clinical features of EPTB in children and to assess management and outcomes.

Methods

This was a retrospective descriptive study of all EPTB cases diagnosed from January 2010 to December 2021 in Pediatric Department C of Bechir Hamza Children's Hospital of Tunis which is a pediatric tertiary referral center.

Study subjects

We included, all children aged between one and 18 years in whom we diagnosed EPTB during the study period. Data were collected from medical records. Demographic characteristics (gender, age, geographic distribution, etc.), medical history, vaccina-

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tion with Bacillus-Calmette-Guerin (BCG) vaccine, contact with a person who has active TB, clinical presentation, time from patient-reported symptom onset, physical examination findings, tuberculine skin test result, results of laboratory tests, radiologic findings, microbiologic data, histological data, treatment regimens and outcomes were recorded from the patient files.

Definition of cases

EPTB was defined as the presence of the infection in organs or tissues outside pulmonary parenchyma. EPTB was classified as lymph node TB, abdominal TB, osteoarticular TB, Central Nervous System (CNS) TB (CNS-TB) and miliary TB. In patients in whom pulmonary TB and EPTB existed simultaneously, the extra pulmonary organs involved were recorded.

Diagnosis

Tuberculin skin test (TST) was performed by injecting 0.1 ml of tuberculine purified protein derivative into the anterior cutaneous surface of forearm. Skin reaction was read 72 hours after injection by a pediatrician trained to read TST results. The diameter of induration was measured in millimeters. TST was considered positive if the induration measured 10 mm or more.
Interferon-γ release assay (QuantiFERON test) was used in some patients.

Diagnosis of lymph node tuberculosis

The diagnosis of lymph node TB was confirmed in children with positive mycobacterial culture of samples obtained by needle puncture-aspiration (fine-needle aspiration (FNA)) or lymph node biopsy. The diagnosis was also confirmed in children with compatible histological findings in lymph node samples and clinical improvement after specific treatment. Compatible histological findings were defined as the presence of epithelioid and gigantocellular granuloma with caseous necrosis.

Diagnosis of abdominal tuberculosis

Abdominal TB includes infection of gastrointestinal tract, peritoneum, abdominal solid organs and abdominal lymph nodes. The diagnosis of abdominal TB was made from a combination of biochemistry data, radiological findings on abdominal ultrasound and contrast-enhanced computed tomography scan (CT-scan) of the abdomen, microbiological results, histological findings and laparoscopic features.

Diagnosis of osteoarticular tuberculosis

The diagnosis of osteoarticular tuberculosis was based on epidemiological and clinical features, imaging data (CT-scan and Magnetic Resonance Imaging (MRI) findings), microbiological and histological examination of samples obtained by biopsy under image guidance or by arthroscopy or during open surgical procedures.

Diagnosis of central nervous system tuberculosis

CNS-TB was defined as intracranial TB which included tuberculous meningitis (TBM), tuberculous encephalopathy, tuberculous vasculopathy, cerebral tuberculoma and tuberculous brain abscess [4]. Spinal TB which included Pott's spine and Pott's paraplegia, was classified as osteoarticular TB.
We assessed the clinic stage of TBM according to Medical Research Council criteria: Stage I: patients with no focal neurological signs and Glasgow Coma Scale (GCS) score of 15; Stage II: children with GCS score of 15 and who presented with focal neurological deficit or patients with GCS score between 10 and 14; Stage III, children with GCS score < 10 [5].
The diagnosis of TBM was confirmed by the detection of MTB in the cerebrospinal fluid (CSF) either by smear examination or by culture or by PCR.

Diagnosis of miliary tuberculosis

Miliary TB was defined as a disseminated TB characterized by a simultaneous involvement of at least two non contiguous organs, or infection of the bone marrow or the liver [6].

Microbiological Techniques

Smear examination: Specimens were used for microscopic examination, to detect acid-fast bacilli (AFB) in stained smears. Ziehl–Neelsen method was used for acid-fast staining.
Mycobacterial culture: Lowenstein-Jensen solid medium was used for culture and isolation of MTB from specimens.
Molecular testing: The Gene Xpert MTB/RIF assay was used. It is based on nucleic acid amplification for detection of MTB DNA and screening for Rifampicin resistance to Rifampicin by real-time polymerase chain reaction (RT-PCR)

Statistical analysis

Statistical analysis was performed by using Statistical Package for the Social Science (SPSS) version 21 software. We used ANOVA test to compare means among groups and chi-square test of Pearson for comparing categorical data in independent groups. A p value < 0.05 was considered statistically significant. The study was approved by the ethical committee of Bechir Hamza Children's Hospital of Tunis. All the data collected was anonymized.

Results

We recorded 53 cases of EPTB which represented 79% of 67 cases of tuberculosis diagnosed during the study period, in our department. EPTB incidence was 1.47/year/1000 children hospitalized in our pediatric department. The mean age at diagnosis was 7.8 ± 4.2 years [1.5-15 years]. The gender ratio was 1.20. Contact with a person who had active TB was reported in 15 children (28%), it was intra familial in nine cases. Two children did not receive

Bacillus-Calmette-Guerin vaccine. They were aged less than 5 years. One of them was born in Germany. Table 1 summarizes epidemiological and clinical characteristics of children with EPTB. Serological tests for the diagnosis of Human immunodeficiency virus (HIV) were performed in 18 children (34%). They were negative in all cases. Immunodeficiency was reported in 12/53 (23%). Causes of immunodeficiency are detailed in Table 1.

Table I : Epidemiological and clinical characteristics of children with extra pulmonary tuberculosis included in the study

Parameters		N	%
Gender	Male	29	55
	Female	24	45
Age groups	1 – 5 years	18	34
	6 – 10 years	16	30
	11 – 15 years	19	36
Geographic distribution	North-West of Tunisia	17	32
	North-East of Tunisia	9	17
	Center-West of Tunisia	11	21
	Southwest of Tunisia	16	30
Residency area	Urban	41	77
	Rural	12	23
Positive close contact history (intra familial)		9	17
Chronic diseases	Diabetes mellitus type 1	4	7
	Alpha-1 antitrypsin deficiency	1	2
	Hypogammaglobulinémie	1	2
Corticosteroid therapy		2	4
Autoimmune disease (immunosuppressive drug)		1*	2
Moderate/ Severe malnutrition		4	9
Growth failure		2	4

*Autoimmune Hepatitis

General symptoms of TB disease were found in 29 children (55%): fever (n=23), weight loss (n=13), weakness (n=11) ans night sweats (n=16). Mean time between symptoms onset and diagnosis was 3.3 ± 2.3 months with extremes ranging from 15 days to 12 months. Tuberculin skin test (TST) was performed for 48/53 (90%) children. It was positive in 33/48 (69%) cases. The most predominant site of infection was lymph nodes (40%) followed by abdominal TB (30%). Figure 1 summarizes distribution pattern of EPTB sites.

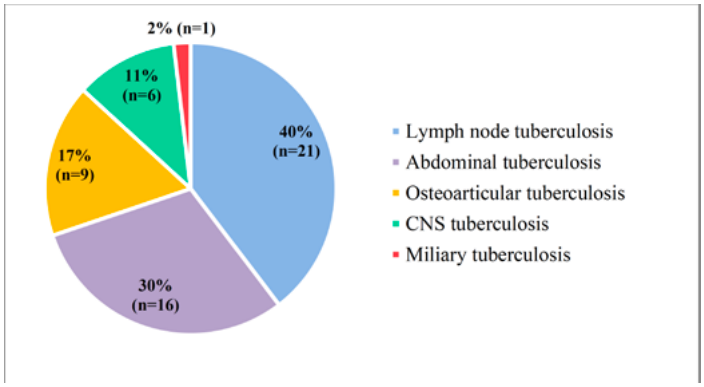

Figure I : Distribution pattern of extra pulmonary tuberculosis sites among 53 Tunisian children

Table 2 summarizes clinical features, laboratory tests findings and microbiological characteristics of children with EPTB according to infection sites. The mean duration of antituberculosis treatment (ATT) was 10.8 ± 4.5 months with extremes ranging from 6 to 22 months. Side effects of ATT were observed in seven cases: hepatic cytolysis (n=6) and cutaneous adverse drug reaction (n=1). Acetylation test was performed in 29 children (58%), 16 (55%) of whom were classified as slow and 13 (46%) as rapid inactivators of Isoniazid. Hepatic cytolysis was observed in three slow Isoniazid inactivators patients.

Lymph node tuberculosis

Lymph node TB was diagnosed in 21 children. Cervical lymph nodes were involved in 20 cases: lateral jugular (n=11), middle jugular (n=7) and submandibular (n=2). Axillary territory was affected in one patient. Neck swelling was found at presentation in 20 cases. Cervical ultrasound was performed in all cases of cervical lymph node TB. Ultrasound showed necrosis and surrounding soft tissue edema respectively in 12/20 and 9/20 cases. Cervical Doppler ultrasound showed vascularity patterns in 13 cases: capsular or peripheral (n=8) and hilar (n=5). Samples were obtained by lymph node biopsy and needle puncture-aspiration respectively in 16/21 and 5/21 children. Lymph node aspirate culture was positive in one patient. Histological examination showed epithelioid and gigantocellular granulomas in all cases. Caseous necrosis was found in 11/21 cases. A chest X-ray was performed for all children with lymph node TB looking for pulmonary location. All patients were given standard regimen of ATT. The fixed-dose combination antituberculosis therapy (2 HRZE/ 4 HR) (H: Isoniazid 75mg/ R: Rifampicin 150mg/ Z: Pyrazinamid 400mg/ E: Ethambutol 257mg) was administered in 17 cases. Only four patients received separate drugs. All patients received following doses: Isoniazid 5mg/ Kg per day; Rifampicin 10mg/Kg per day; Pyrazinamid 25mg/Kg per day and Ethambutol 15mg/ Kg per day. Three patients were lost to follow-up. Side effects of antituberculosis drugs were noted in two patients who presented moderate liver cytolysis. The evolution was uneventful in 17 cases. A six-year-girl presented a relapse and required nine months of treatment.

Abdominal tuberculosis

Abdominal TB was diagnosed in 16 children. Symptoms at presentation were: acute abdominal pain (n=2), recurrent and insidious abdominal pain (n=9), abdominal distension (n=10) (Table 2). Ingestion of unpasteurized milk and milk products was reported in nine patients.

Table II : Epidemiology, clinical features, laboratory tests findings and microbiological characteristics of children with extra pulmonary tuberculosis according to infection sites

	Lymph node TB (n=21)	Abdominal TB (n=16)	Osteoarticular TB (n=9)	CNS-TB (n=6)	p
Mean age at diagnosis (years)	7.1 ± 4 [1.5 – 13]	6.9 ± 4.8 [2 – 15]	9.1 ± 3.8 [2.5 – 14]	10.4 ± 3.5 [4.5 – 14]	0.234
≤ 5 years	6/21	10/16	1/9	1/6	0.030
Male to female ratio	1.33 (12/9)	0.78 (7/9)	2 (6/3)	2 (4/2)	0.642
Immunosuppressive conditions	2/21	8/16	1/9	1/6	0.022
BCG vaccine	21/21	15/16	9/9	5/6	-
History of TB contact	2/21	4/16	5/9	3/6	0.034
Mean time from symptom onset to diagnosis (months)	2.8 ± 2.04 [1 – 9]	4.4 ± 2.9 [1 – 12]	3.7 ± 1.5 [2 – 6]	1.4 ± 0.6 [0.5 – 2]	0.028
Fever (prolonged/ intermittent)	8/21	3/16	7/9	4/6	0.019
Weight loss	2/21	6/16	3/9	2/6	0.206
Weakness	1/21	3/16	4/9	2/6	0.063
Night sweats	5/21	5/16	4/9	1/6	0.613
TST	19/21	16/16	8/9	5/6	-
Positive TST	13/19	11/16	6/8	2/5	0.591
Mean diameter of induration of positive TST (mm)	14.8 ± 2.2 [12.5 – 19]	15.1 ± 2.9 [11 – 21]	16 ± 2.5 [12 – 19]	16.7 ± 2.4 [15 – 18.5]	0.655
Positive QuantiFERON test	1	2	-	1	-
Leukocytosis (>10000/mm³)	14/21	9/16	5/9	4/6	0.890
ESR mm/ 1st hour	30.7 ± 19.2 [8 – 66.7]	38.1 ± 22.8 [9 – 81.3]	55.5 ± 32.2 [8 – 103]	31.9 ± 25.7 [10.8 – 65.8]	0.129
Accelerated ESR (>15 mm/hr)	9/14	8/11	7/9	2/4	0.753
CRP (mg/L)	53.5 ± 23.2 [15 – 96.7]	42.8 ± 29.7 [10.8 – 111.3]	79.7 ± 36.5 [24 – 128.9]	68.2 ± 53.8 [17.9 – 163]	0.046
Increased CRP (>30 mg/L)	17/21	8/16	7/9	4/6	0.216
Anaemia of inflammation	5/21	7/16	4/9	1/6	0.406
Positive mycobacterial culture	0/21	4/16 (biopsy specimens)	3/9 (biopsy specimens)	1/5	-
Epithelioid and gigantocellular granulomas	21/21	14/16	8/9	-	-
Caseous necrosis	11/21	9/16	2/9	-	0.233
Detection of MTB by PCR	-	-	-	3 (CSF)	-
Mean duration of ATT (months)	6.5 ± 1 [6 – 9]	11.2 ± 2.6 [9 – 18]	16.3 ± 3.08 [12 – 21]	15.2 ± 4.6 [12 – 22]	<0.001

Abdominal TB was classified as peritoneal TB (n=11), abdominal Abdominal ultrasound was performed in all cases of abdominal TB. Ultrasound showed diffuse peritoneal thickening in ten cases associated with regular and hypoechoic enlargement of the parietal peritoneum, nodular pattern and striated greater omentum respectively in seven four and two cases. Ascites was found on ultrasound in nine cases with thin fibrinous septations in three cases. Mesenteric lymphadenopathy was found in 12/16 cases. Cecal wall thickening was noted in two cases. Abdominal CT-scan was performed in four children. CT imaging features seen were: nodular thickening of the peritoneum with abnormal peritoneal enhancement (n=2), "cake-like" omentum (n=2), ascites (n=2), hypodense mesenteric lymphadenopathy (n=4) and circumferential wall thickening of terminal ileum and cecum (n=2). Laparoscopy was performed for 14 patients with peritoneal or lymph node biopsy. Laparoscopic findings were thickened peritoneum with diffuse erythema (n=12), whitish nodules or tubercles (n=7), mesenteric lymphadenitis (n=10), fibrous adhesions (n=5) and ascitic fluid (n=12). In two cases, the specimen was taken during open surgery. These two children were operated for suspected appendicitis. lymph node TB (n=3) and ileocecal TB (n=2). All patients had received anti-tuberculosis treatment (ATT). The fixed-dose combination antituberculosis therapy (2 HRZE/ 4 HR) was administered in 13 cases. Only three patients received separate drugs. Side effects of antituberculosis drugs were observed in three patients who presented moderate hepatic cytolysis. The evolution was uneventful in all cases.

Osteoarticular tuberculosis

Out of the 53 children included, nine had osteoarticular TB. Pain was found in all patients, with functional impairment in 7/9 of cases. Joint swelling was noted in 2/9 of cases and joint stiffness in 4/9 of cases. A 13-year-old girl presented with a painful sternal mass. A 2.5-year-old boy presented with inflammatory swelling of the upper extremity of the left lower limb. Painful left lumbar swelling was noted in a 6-year-old boy. Sites involved were: TB of the hip (n=2), TB of the knee (n=2), tuberculous spondylodiscitis (n=2), tuberculous osteomyelitis of proximal tibia (n=1), sternoclavicular joint TB (n=1) and tuberculous sacroiliitis (n=1). Eight children were evaluated by MRI. MRI findings were strongly suggestive of TB disease in all cases. MRI of the spine was performed in two cases. It showed collapse of the vertebral body with marrow edema, paravertebral collection with epidural extension, and psoas abscess in two cases. Tissue samples were obtained by biopsy under image guidance (n=3), by arthroscopic procedure (n=4) and during open surgical procedure (n=2). CT-guided needle biopsy of sacroiliac joint was performed in 8-year-old girl presented with lower back pain and reduced mobility associated with right sacroiliac joint erosions at the CT-scan of the pelvis. Spinal surgery was performed in two cases because of neurological deficit at presentation. Histopathology was suggestive of tuberculosis in seven cases. Mycobacterial culture was positive in two cases. All patients received a standard regimen of ATT. One patient presented skin maculopapular rash few days after treatment onset. Treatment was stopped for a certain period then antibiotics were introduced one by one. Thereafter, the treatment was well tolerated. Vertebral deformation was observed in one case. Three patients with osteoarticular TB were assessed in search of chronic granulomatous disease and interleukin 12-interferon gamma axis defect, without finding of these diseases.

Central nervous system tuberculosis

Out of the 53 children included, six had CNS-TB: TBM (n=5) and cerebral tuberculoma (n=1). All children presented with stage II of TBM. The main characteristics of children with TBM are summarized in table 3.

Table III : Characteristics of children with tuberculous meningitis

Patients	1	2	3	4	5
Age at diagnosis (years)	10.5	14	12.5	8	4.5
Gender	Male	Male	Female	Female	Male
TB contact history	Yes	No	Yes	No	No
BCG vaccin	Yes	Yes	Yes	Yes	Yes
Duration of symptoms at admission	1 month	15 days	1 month	2 months	2 months
TST	Positive	Positive	Negative	Negative	Negative
Symptoms	Slight fever * Vomiting Headache Seizure	Moderate fever ** Vomiting Headache Dizziness Blurred vision in both eyes	Night sweats Vomiting Headache Seizure	Vomiting Headache Dizziness Sub-acute onset of left-sided facial weakness with diplopia	Slight fever Vomiting Headache Weakness Seizure Altered mental status
Clinical findings	Neck stiffness Kernig's sign GCS=13/15	Neck stiffness GCS=13/15 Fundoscopy: papilledema	Hemiparesis GCS=15/15	Neck stiffness GCS=15/15 Sixth cranial nerve palsy	Neck stiffness Kernig's sign GCS=12/15
Interferon- γ release assay (QuantiFERON)	-	-	Positive	-	-
Lumbar puncture (cerebrospinal fluid)					
WBCs count /mm³ Lymphocyte (%) Protein (g/L) Glucose level	68 70 0.96 0.5 blood sugar	380 95 1.35 0.16 blood sugar	- - - -	690 75 1.8 0.42 blood sugar	230 60 3.2 0.38 blood sugar
Cerebral CT-scan	Contrast enhancement of basal cisterns	Leptomeningeal enhancement	Cerebral infarction and diffuse brain edema	Basal meningeal enhancement Pre contrast basal hyperdensity	Contrast enhancement of basal cisterns
Smear examination (AFB stain)	Negative	Negative	-	Negative	Negative
CSF culture	Negative	Negative	-	Positive	Negative
Detection of MTB in CSF using PCR	Positive	Positive	-	-	Positive
Chest X-ray	Normal	Normal	Normal	Normal	Normal
Sputum culture	Negative	Negative	Negative	Negative	Negative
HIV serological test	Negative	Negative	Negative	Negative	Negative
Antitubercular therapy	HRZE***/HR	HRZE***/HR	HRZE***/HR	HRZE***/HR	HRZE***/HR
Duration of ATT	12 months	12 months	18 months	20 months	12 months
Steroid / Duration	Dexamethasone (6 weeks)	Dexamethasone (8 weeks)	Dexamethasone (8 weeks)	Dexamethasone (8 weeks)	Dexamethasone (6 weeks)
Outcome	No neurological sequelae	No neurological sequelae	Epilepsy	Hydrocephalus Ventriculoperitoneal shunting	No neurological sequelae

Cerebral tuberculoma was diagnosed in 13-year old boy who had a 2-month history of weakness, intermittent moderate fever and weight loss. He received BCG vaccine. He had an intra familial TB contact (the father suffered from pulmonary TB). He presented with a 2-week history of vomiting and headaches. Physical examination found hemiparesis and GCS at 13/15. Laboratory tests showed CRP of 163 mg/L. Cerebral CT-scan found hypodense mass lesion in left parietal lobe (3 cm), with ring enhancement and perilesional edema and associated with mass effect and midline shift. The child was immediately transferred to the neurosurgery department. He was not followed up in our department.

Disseminated tuberculosis

Miliary TB was diagnosed in a 9-year-old girl with alpha-1 antitrypsin deficiency and positive history of TB contact, which had a disseminated TB with lymph node TB, cerebral tuberculoma and tuberculous spondylitis. She presented with a left cervical swelling of 4 cm long axis with a 2-month history of moderate fever, weakness and night sweats and recurrent headaches associated with inflammatory lumbar pain. During hospitalization she presented hemicorporal seizure and status epilepticus. She had a BCG scar. TST was positive. Cerebral CT-scan showed ring enhancing mass lesion (4 cm) consistent with cerebral tuberculoma with hydrocephalus. Ventriculoperitoneal shunt was placed. MTB was detected in CSF by RT-PCR. Histological examination of lymph node samples showed epithelioid and gigantocellular granulomas. She received ATT during 26 months with steroids during three months. She presented hepatic cytolysis and cholestasis which were managed with improvement in laboratory tests. She was the patient was assessed in search of chronic granulomatous disease and interleukin 12-interferon gamma axis defect, without positive findings.

Outcomes

No patient died. Three patients had sequelae. A girl with TB spondylodiscitis had a slight dorsal kyphosis. A girl with TBM had epilepsy and seizures were controlled with a single antiepileptic drug. One patient with TBM had hydrocephalus that was managed by insertion of ventriculoperitoneal shunt with good recovery.

Discussion

EPTB is an important cause of morbidity in pediatric population in low-income countries. Pediatric EPTB is still under-diagnosed in our country because symptoms are often non-specific and challenging. Nevertheless, early diagnosis and management of EPTB improve significantly clinical outcomes.

Few Tunisian studies focused on the clinical and diagnostic characteristics and outcomes of EPTB in children. The last one carried on in our pediatric hospital was published in 2009 and recorded 41 cases over a period of 13 years (1995-2007) [7].

Our study described the epidemiology, clinical features, diagnostic challenges and outcomes of EPTB in a Tunisian tertiary pediatric department. EPTB represented 79% of TB cases recorded in our department. To the best of our knowledge this proportion was the highest in the literature. The proportion of EPTB cases was 57.9% in our pediatric hospital between 1995 and 2007 [7]. Our findings can be explained by a patient selection bias. Indeed, children with suspected pulmonary TB are often referred to a tertiary center of phthisiology and pulmonology. Several studies showed that EPTB is more common in children than adults [8-9]. This may be due to high risk of lymphohematogenous spread of the disease in children [8]. About two-thirds of children hospitalized for EPTB in our department were from the northwest or southwest of the country. It was shown in a recent Tunisian epidemiological study that southern Tunisia hosted the highest proportion of TB patients among Tunisian population [10]. Our study showed that older children [6 – 15 years] represented 64% of children with EPTB. An age group distribution almost similar to our study was found in a recent Turkish study [8]. A slight male predominance was found in our study. This result was reported in most studies [11-12]. We found that 96% of patients were vaccinated with BCG. BCG vaccination is mandatory in Tunisia at birth according to the national vaccination schedule. In our series, no patient died and three patients had sequelae that were not seriously disabling. Thus BCG vaccine seems to prevent death and severe and disabling neurological complications. Indeed a recent meta-analysis showed that infant BCG vaccine prevents all tuberculosis and death caused by TB in young children. This study also showed that the protective effect of BCG vaccination decreased in patients aged 5 years or older [13]. These findings may explain the age group distribution of EPTB observed in our study. The results of this meta-analysis suggest that protective immunity against MTB should be boosted after childhood [13]. We found a positive history of contact with TB patient in 28% of cases. A similar result was found in a Turkish study [8]. In our study, medical conditions that weaken the immune system were found in 23% of cases. This finding suggests that the progression from infection to active TB disease may result from the presence of individual factors such as immunosuppressive conditions. Established risk factors are HIV, malnutrition, young age, diabetes, use of immunosuppressive drugs, etc [14]. Lymph node TB was the most common site of EPTB, in our study. This result was found in most of pediatric studies [7-9, 15-17]. However, the proportion of other sites of EPTB varied extremely between studies. This difference may be explained by the study design, the case definition, the diagnostic criteria, the incidence of TB disease in the country, the prevalence of HIV

infection in the population, the BCG vaccination coverage, etc [9]. In this study we found that abdominal TB was the second site of EPTB (17%) and the most common site of EPTB in children under the age of 5 years. However lymphadenitis, CNS-TB and osteoarticular TB were more common in older children. This difference was significant. This result was not found in a previous Tunisian study [7].

Abdominal TB is uncommon in children. It is seen in only 0.3% of pediatric TB [18]. The symptoms of abdominal TB are often non specific, resulting in a diagnosis delay [19]. This is consistent with our results, since we found that time between symptoms onset and diagnosis was significantly longer in children with abdominal TB. We found a mean delay of 4.4 months to establish the diagnosis. A similar result was found in an Indian study [20]. We found that immunosuppressive conditions were significantly more common in children with abdominal TB (p=0.022). Moderate or severe malnutrition was observed in four patients who all had abdominal TB. Admittedly, malnutrition leads to diverse changes in the immune system by repressing immune responses and increases in TB disease risk, but abdominal TB can lead to malnutrition by decrease in food intake due to abdominal pain and gastrointestinal disorders. Thus malnutrition may be a cause or consequence of abdominal TB [21]. Abdominal TB is mainly caused by Mycobacterium bovis and the most common mode of transmission is ingestion of unpasteurized milk and milk products which was reported in more than half of the cases in our series. In developing or low-income countries abdominal TB is still present. Despite the efforts of the health authorities for the slaughter of infected cattle and the pasteurization of milk and dairy products, abdominal TB still exists in our country. Abdominal TB may involve the peritoneum, the gastrointestinal tract, solid viscera or abdominal lymph nodes [22-23]. In our series, diagnosis of abdominal TB was based on radiological, laparoscopic and histological findings. Positive mycobacterial culture of biopsy specimens was positive in four cases. Positivity of laparoscopic biopsy specimens' culture was ranging between 38% and 92% [24]. Among 14 laparoscopies performed, 12 showed suggestive findings of abdominal TB. Typical laparoscopic findings are accurate enough to diagnose abdominal TB with a specificity and sensitivity ranging respectively between 96%-100% and 84%-100% [22, 24]. Characteristic granulomas with central caseous necrosis were found for over half of cases with abdominal TB. Granulomas with caseous necrosis found on laparoscopic biopsy specimens had sensitivity and specificity of 70%-100% and 100%, respectively [24]. All children with abdominal TB in this series showed a response to ATT. Osteoarticular TB represented 17% of EPTB in this series. Osteoarticular involvement represents 4% to 5% of TB infection cases with reports in children of up 7% [25].

The diagnosis of osteoarticular TB is a challenge in children because its clinical presentation is often insidious. Indeed, this study showed a medium duration of symptoms before diagnosis of 3 months with extremes ranging between 2 and 6 months. A medium time of pre-diagnostic symptoms of 8, 7 and 2 months, was reported in Mexican, UK and Taiwan pediatric cohort, respectively [26-28]. Pain was the most common symptom in all patients. This result is consistent with other studies [26].

In this series fever was significantly more common in osteoarticular TB. Mean CRP level was significantly highest in osteoarticular TB. Sites involved were the hip (n=2), the knee (n=2), the vertebral column (n=2), proximal tibia (n=1), sternoclavicular joint (n=1) and sacroiliac joint (n=1). Conventional sites of osteoarticular TB in children are vertebral, hip, femur and knee [26]. Conventional sites were observed in tow thirds of cases in our series. Microbiological confirmation was poor in this study. One third of children with osteoarticular TB had positive culture of biopsy specimens. The main diagnostic method was histological examination. It was shown that tissue specimens yield the best results. Samples can be obtained by biopsy under image guidance or by arthroscopic procedures or during open surgical procedures [29]. Mycobacterial culture remains the gold standard in the diagnosis of osteoarticular TB [29]. In Tunisia where TB is endemic and since it is not always possible to identify MTB, early management should be considered in children with clinical, radiological and histological findings suggesting TB.

The most severe form of EPTB is CNS-TB and miliary TB [8]. It has been reported that these two forms of EPTB occurs mostly in children aged between six months and four years [8]. We diagnosed TBM in five patients. TBM was confirmed by detection of MTB in CSF using PCR in three cases. A recent diagnostic test introduced in our microbiology laboratory is Xpert MTB/ Rifampicin which is a rapid nucleic acid amplification test to detect MTB and Rifampicin resistance simultaneously. This molecular method was useful for the diagnosis of TBM in our patients. However, the role of Xpert MTB/ RIF in the diagnosis of TBM, remains controversial. Even though a positive result confirms the diagnosis of TBM but negative result cannot rule out TBM [30]. Xpert MTB/ RIF assay is a definitive diagnostic test of TBM with a sensitivity and specificity of 67%-85% and 94%-98% respectively [31]. CSF findings were suggestive of TBM in all cases. However, CSF findings are not specific for TBM and can be seen in other conditions such as bacterial, viral or fungal meningitis [30]. In the present study, two-fifths of children with TBM had poor outcomes. Neurological sequelae in children with TBM were reported from 14.3% to 28.1% of cases in African studies [32, 33]. Disseminated TB is a severe form of TB that results from massive lymphohematogenous dissemination of MTB. This form occurs most commonly in children infected with HIV [34]. Miliary TB in the current study represented 2% of extrapulmonary

sites. Our patient was immuno-competent and was an older child. Response to first-line antituberculosis drugs was good in all patients and drug-induced hepatotoxicity was the most common side effect of ATT, in our study. The limitations of the study were the low number of patients included, the retrospective design and the low rate of cases with positive mycobacterial culture. However, we think that our study is interesting and relevant since it will contribute to the Tunisian national data on tuberculosis in children and especially that the last clinical study on pediatric EPTB dates back to 2009. Our study found that histological findings, granulomatous inflammation with caseous necrosis, were the main diagnostic criteria. Clinical and radiologic findings, history of close contact with TB cases, positive skin tuberculin test, and good response to treatment were used in several cases to establish diagnosis of EPTB. However this study showed an improvement in diagnostic laboratory tests such as the PCR technique which allowed the detection of MTB.

Conclusion

This study showed an improvement in the diagnosis and management of EPTB in children. However, the emergence of the HIV infection in our country and the widespread use of immunosuppressive drugs in pediatric population, suggest that the diagnosis of TB should be considered at the slightest sign in children. BCG vaccine is still recommended in areas with intermediate incidence of tuberculosis like Tunisia.

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