Childhood tuberculosis: A descriptive study in a pneumo-pediatrics department in Tunisia

Tuberculose de l'enfant: une étude descriptive dans un service de pneumo-pédiatrie en Tunisie

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RÉSUMÉ

Objectif: Le but de cette étude était de déterminer les différentes localisations de la tuberculose (TB) chez des enfants hospitalisés dans un service de pneumo-pédiatrie en Tunisie et de décrire les moyens diagnostiques étant donné que la confirmation diagnostique de la TB chez l'enfant est entravée par la nature pauci bacillaire de la maladie et de la difficulté d'obtenir de bons prélèvements.

Méthodes: Quarante-six cas d'enfants atteints de TB ont été étudiés entre 2008 et 2013. L'histoire de la maladie, l'examen clinique et la radiographie thoraciques ont été rapportés. On a eu recours à plusieurs examens complémentaires pour confirmer le diagnostic de la TB, tels que: test cutané à la tuberculine (IDR), recherche du Mycobacterium tuberculosis (MT) à l'examen direct et à la culture des différents prélèvements, la ponction et la biopsie pleurale, biopsie ganglionnaire et la fibroscopie bronchique. Le traitement anti-tuberculeux a été prescrit selon les recommandations du guide national de lutte anti-tuberculeuse.

Résultats: La toux et l'altération de l'état général étaient les symptômes les plus constants (47,8% et de 43,7%). Le reste des enfants ont consulté pour une tuméfaction cervicale (19,5%), des douleurs thoraciques (17,4%) ou une hémoptysie (4,3%). Des anomalies ont été trouvées à la radiographie thoracique dans 35 cas (76%). L'IDR à la tuberculine était positive dans 73% des cas. Le diagnostic de la TB a été confirmé dans 56,6% des cas après isolement du MT et / ou par biopsie. Le diagnostic a été fait sur des arguments de présomption dans 20 cas (43,4%), basé sur la notion d'un contage tuberculeux, des symptômes cliniques évocateurs et une IDR positive. Une biopsie chirurgicale était nécessaire pour le diagnostic dans 17 cas (nasopharynx, os, ganglions cervicaux, médiastinaux ou mésentériques). Cinquante-deux pourcent des cas avaient une localisation pulmonaire. Deux enfants avaient une tuberculose disséminée. Tous les enfants ont été traités selon les recommandations du guide national de lutte anti-tuberculeuse sans effets secondaires majeurs. La guérison sans séquelles a été obtenue dans 91% des cas.

Conclusion: Les enfants constituent une population à risque élevé de TB surtout en cas de contage familial avec une fréquence plus élevée des formes multifocales par rapport aux adultes. Les difficultés du diagnostic de la TB chez l'enfant peuvent en partie expliquer le retard du diagnostic, néanmoins, des efforts restent à faire pour améliorer le dépistage et le diagnostic de la maladie dans notre pays. .

Mots-clés

Tuberculose, enfant, diagnostic.

SUMMARY

Objective: The objectives of this study were to assess the different localizations of tuberculosis (TB) in children in a pneumopediatric department in Tunisia and to describe its diagnosis tools since clinical investigations of childhood TB are challenged by the paucibacillary nature of the disease and the difficulties in obtaining specimens.

Methods: Forty-six cases of TB in children were studied between 2008 and 2013. Clinical history, examination and chest radiography were reported. Several investigations have been conducted to confirm the diagnosis of TB such as: tuberculin skin test (TST), bacteriological and histological investigations. Anti-tuberculosis treatment was prescribed according to the national guidelines.

Results: Cough and deterioration in general condition were the most frequent symptoms (47.8% and 43.7%). The other children presented cervical swelling (19.5%), chest pain (17.4%) and hemoptysis (4.3%). Abnormalities have been found in chest radiography in 35 cases (76%). TST was positive in 73% of cases. Diagnosis of TB was confirmed in 56.6% of cases by Mycobacterium tuberculosis (MT) isolation and/or biopsy. The diagnosis was made on presumptive arguments in 20 cases (43.4%) based on a history of TB contact, suggestive symptoms and a positive TST. A surgical biopsy was necessary for diagnosis in 17 cases (nasopharynx, bone, cervical, mediastinal and mesenteric lymph nodes). Pulmonary TB was diagnosed in 52% of cases. Two children were diagnosed with disseminated TB. A diagnosis delay was noted with an average of 20 days and a contact history was found in 52% of the children. All children were treated according to the national guidelines without major side effects. Healing without sequelae was achieved in 91% of cases.

Conclusion: Children represent a population at high risk for TB especially after a household contact with a higher frequency of multifocal forms compared to adults. The difficulty of the diagnosis in children may explain partially the diagnosis delay, but efforts must be done to improve prevention and diagnosis in our country.

Key-words

Tuberculosis, children, diagnosis.

In 2010, an estimated 8.8 million new tuberculosis (TB) cases occurred in the world (equivalent to 128 cases per 100,000 inhabitants) and one third of the world's population is infected with Mycobacterium tuberculosis (MT) complex. Each year, 1.1 million person die from TB and at least 10-15% of deaths occur in children under 15 years of age [1]. Incidence rates start to rise in adolescents and precede a peak in adulthood in developing countries [2]. However, the exact extent of childhood TB is unknown. The main challenge for the diagnosis of TB in children is the difficulty in isolating MT. The lack of a standardized definition, the wide range of clinical presentation of the disease, difficulties in diagnosing extra pulmonary or atypical pulmonary manifestations, especially military TB and tuberculous meningitis are provided daunting challenges. In addition, the lack of priority of childhood TB in the national control programs makes this task even more difficult [1,3].
The objectives of this study were to describe its clinical presentations and diagnostic tools.

METHODS

Study Population

From January 2008 to June 2013, data on TB cases in children below the age of 18 years were obtained from the pediatric respiratory diseases department B at Abderrahman Mami hospital in Ariana-Tunisia. The patients' medical records were studied and demographic data, medical history, clinical presentation at admission, radiological and microbiological data, treatment and outcome were reviewed. Patients who were diagnosed with TB and treated with a standard anti-tuberculosis regimen were included in the study. TB in children was grouped into pulmonary (lung parenchyma, intra thoracic lymph nodes even if associated with an extra pulmonary location [3]) and extra-thoracic (pleural, extra thoracic lymph nodes, bones and joints, gastrointestinal…) according to the clinician's assessment. Diagnosis was performed according to the national guidelines: (1) clinical presentation (symptoms or signs); (2) contact history (family, close contact); (3) Tuberculin skin test (TST); (4) chest radiography; (5) bacteriologic examination (of sputum, pleural effusion, bronchial fluid, gastric aspirates, cerebro-spinal fluid, and peritoneal fluid) and in some cases other diagnosis methods (computed tomography scan, bronchoscopy and biopsy). The gold standard diagnosis of TB is made when MT is isolated or on typical histological findings. Anti-tuberculosis treatment was prescribed according to the recommendations of our national guidelines.

RESULTS

Demographic characteristics:

Between January 2008 and June 2013, 46 children with TB were enrolled in the study. Mean age was 7.5 years [range 16 months-16 years]. Demographic data are described in Table 1.

Table 1 : Demographic data

Characteristic	N (%)	TB Household contact
Age groups (year)		
1-4	13 (28.3%)	9 (64%)
5-9	13 (28.3%)	6 (40%)
10-14	14 (30.4%)	7 (54%)
15-17	6 (13%)	2 (33%)
Gender		
Female	35 (76%)	
Male	11 (24%)	

All but one child were vaccinated by BCG. Two children were immune-compromised and another one suffered from bilateral bronchiectasis. TB household contact was found in 52.2% of cases, but only 1/4 was seen for TB screening. The mean age of these children with TB contact was 7 years. The index was one of the parents or siblings in 79% cases and a relative in 21%. Seven children were sleeping in the same room of the index and 2 of them in the same bed.
Among the patients, 24 (52%) were diagnosed with PTB and 22 (48%) with EPTB. Patients with PTB had TB infection in 5 cases (21%) and isolated pulmonary localization in 9 cases (37.5%). PTB was associated with other localizations: mediastinal lymph node (2 cases), meningeal (1 case), urinary (1case), pleural (2 cases) and peritoneal (1 case). Two children had disseminated TB (one patient with leukemia). Patients with EPTB had extra thoracic lymph node involvement among them cervical lymph node TB (10 cases) and mesenteric lymph node TB (2 cases). Figures 1 and 2 summarize these different localizations.

Figure 1: Pulmonary tuberculosis localizations

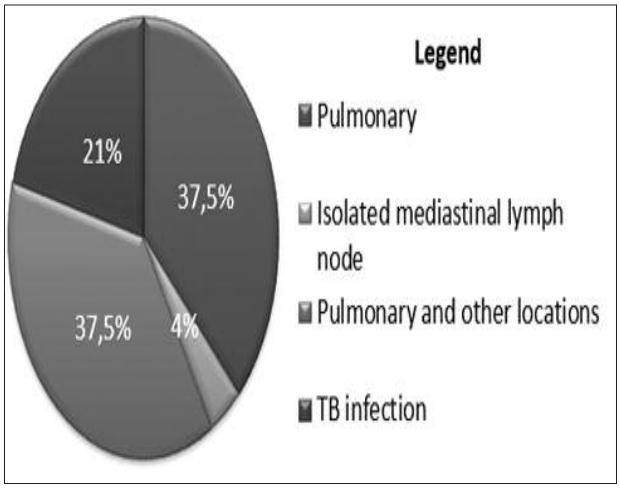
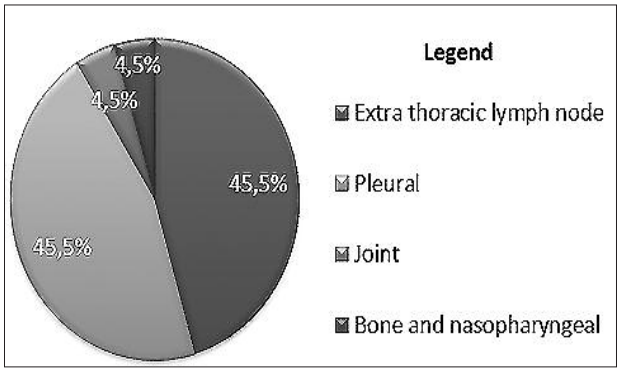


Figure 2: Extra pulmonary tuberculosis localizations



In children between 15 and 17 years, as in adults, PTB was more frequent than EPTB. However, in those between 10 and 14 years, EPTB was the most frequent presentation with pleural involvement in 66.6% of cases. In young children there were as many cases of PTB as EPTB. TB localizations by age groups are detailed in Table 2.

Table 2 : TB localizations by age groups

	Localization	1-4 years	5-9 years	10-14 years	15-17 years
PTB	TB infection	4 (50%)	1 (14%)	0	0
	Pulmonary	1 (12.5%)	3 (43%)	3 (75%)	2 (40%)
	Pulmonary+other	3 (37.5%)	3 (43%)	1 (25%)	3 (60%)
	Total	8(57%)	7(54%)	4(31%)	5(83%)
EPTB	Pleural	2 (33.3%)	1(16.6%)	5 (55.5%)	1 (100%)
	Lymph node	3(50%)	4 (66.6%)	4 (44.5%)	0
	Bone	1 (16.6%)	1(16.6%)	0	0
	Total	6(43%)	6(46%)	9(69%)	1(17%)

There was an important diagnosis delay with a median of 20 days [range 4-730]. The majority were diagnosed with TB within one month (71.8%). (Table 3)

Table 3 : Diagnostic delay

Days before diagnosis	N (%)
0–30	33 (71.8%)
31–60	6 (13%)
61–90	1 (2.2%)
≥90	6 (13%)

Clinical data

Cough and deterioration in general condition were the most frequent symptoms (47.8% and 43.7%). The other children consulted for cervical swelling (19.5%), chest pain (17.4%) and hemoptysis (4.3%). Other nonspecific signs were reported as dyspnea (8.5%), purulent rhinorrhea (2%), joint swelling (2%) and abdominal pain or diarrhea (4%).

Cough (58.3%) and fever (33.3%) were the most predominant symptoms in PTB and cervical swelling (36.5%) in EPTB. Deterioration in general condition was reported in only 41% of cases of EPTB. The table 4 summarizes the different general signs in every age group according to TB localization.

Table 4 : Different general signs in every age group according to TB localization

	Symptoms	1-4 years	5-9 years	10-14 years	15-17 years
PTB	Deterioration in general condition	0	2 (28.6%)	3 (75%)	3 (60%)
	Weight loss	0	1 (14.3%)	2 (50%)	4 (80%)
	Fever	1 (12.5%)	1 (14.3%)	1 (25%)	5 (100%)
	Night sweats	1 (12.5%)	1 (14.3%)	4 (100%)	1 (20%)
	Total general signs	**2(25%)**	**2(28.6%)**	**4(100%)**	**5(100%)**
EPTB	Deterioration in general condition	1 (16.6%)	2 (33.3%)	5 (55.5%)	1 (100%)
	Weight loss	2 (33.3%)	2 (33.3%)	3 (33.3%)	0
	Fever	3 (50%)	2 (33.3%)	5 (55.5%)	1 (100%)
	Night sweats	2 (33.3%)	1 (16.6%)	2 (22.2%)	1 (100%)
	Total general signs	**4(66.6%)**	**3(50%)**	**6(66.6%)**	**1(100%)**
Total general signs in all cases		6(43%)	5(33.3%)	10(77%)	6(100%)

Paraclinical tests

TST was performed in 30 children and 22 (73%) were found positive. The Quantiferon-TB test for MT was performed in 3 children aged of 2, 6 and 7 years. Blood count cell revealed anemia in 34 children (73.9%) and leukocytosis in 14 cases (30.4%). Chest X ray performed in all children was abnormal in 74% of them. It showed micro nodules (41%), pulmonary consolidation (26.5%), pleural effusion (38%), cavitary lesions (1%) and mediastinal enlargement (1%). MT was isolated in 35% of all cases and in 56.5% of lung parenchymal infection. Smear microscopy for MT was done in all children with suspected PTB on expectorated sputum in 16 children (66.6%) whose ages ranged from 4 to 16 years, on gastric liquid aspiratesin 9 children (37.5%) whose ages ranged from 1 to 10 years and on induced sputum in a girl of 16 months (4%). Other more invasive tests were needed to have bacteriological confirmation (flexible bronchoscopy, thoracocentesis, paracentesis, and lymph node biopsy). MT was isolated in 13 cases on smear microscopy: on sputum in 8 cases, on bronchial fluid in 2 cases, on lymph node biopsy in 2 cases and on ascites in 1 case. Cultures for MT were positive in lymph node biopsy (2 cases),

pleural fluid (1 case) and pleural biopsy (1 case). Otherwise, it was positive in 3 cases with negative smear microscopy. Flexible bronchoscopy was performed in 9 patients with chest X-ray abnormalities and negative bacteriology in sputum. It showed endobronchial tuberculosis in 2 cases and bronchial narrowing due to compressive mediastinal lymph nodes in one case.

TB was histologically confirmed in 19 cases (50% of all extra-pulmonary localizations): pleural biopsy in 7 cases (58% of pleural TB), cervical lymph node biopsy in 9 cases (75% of cervical lymph node TB), cavum biopsy in one case, mediastinal lymph node biopsy in one case (25% of mediastinal lymph node TB) and peritoneal biopsy in one case (25% of mesenteric lymph node TB).

Finally diagnosis was confirmed in 26 cases (56.6%) and 20 children (43.4%) were treated for TB on presumptive arguments based on contact history, suggestive symptoms and positive TST.

All children were treated according to the national guidelines. One child had a left lower lobectomy and a pleural decortication at 4 months of TB treatment. Only minor cutaneous and digestive side effects were observed in 6 children (11%). One child presented vomiting during the first 2 weeks of treatment which required hospitalization. All children were cured. Six children (13%) had pleural or pulmonary sequelae. One child with disseminated TB initially had relapsed 1 year after the end of anti tuberculous treatment.

DISCUSSION

Although this study is not representative of the general population, our results showed that the frequency of EPTB is approximately equal to that of PTB in children as in adults. In fact, according to figures from the national guide for TB management in Tunisia, PTB represents 43% of all localizations of TB in the general population.

Tunisia is at intermediate endemicity for TB with a reported incidence of 30/100,000 inhabitants in 2012. In 2014 and according to figures from the Primary Health Care Directorate (PHCD) in Tunisia, the incidence of TB in the age group 0-14 years was 7.34/100,000 inhabitants for boys and 8.61/100,000 inhabitants for girls. In the 22 countries with the highest burden of TB, 4,452,860 new cases were reported in 2010 and only 157,135 (3.5%: range 0.1 to 15) were in children. Best estimates suggest that over 332,000 cases of tuberculosis in children were undiagnosed or unreported in these countries [4]. This problem is illustrated by the low number of cases of childhood tuberculosis reported in four countries with a high disease burden, where the expected rate would be beyond 10% (Russia: 0.8%; India: 1.1%; Nigeria: 1.4% and Brazil: 3.5%) [1]. In North America and Western Europe which are countries with low endemicity, a smaller proportion of children is affected and most cases of childhood TB occur in immigrant populations [5,6]. Furthermore, in developing countries, especially in rural areas, TB incidence is much higher than that of cities; these differences among various countries could be due to different levels of economic development and the difference of financial input on TB diagnosis and treatment [7].

In our study, a contact history at home was found in 52% of cases among them only ¼ was seen for screening. House contact was most predominant in the age group 1-4 years (64%) who are not yet attending school. These findings incite us to focus on the following issues: screening of contacts, isolation of infectious patients and early treatment to limit the contagion around the index case. But limits are raised like that described in a cohort study in China in 2013 [8]. There was no simple way to identify a TB patient in the population, so certainty of contact was weakened to some extent.

EPTB represents 48% of all cases in our study and lymph node disease was diagnosed in approximately one third of the cases with or without other localizations and it was cervical lymph node in 78%. Lymph node TB was predominant in the age group 5-9 years while pleural TB was predominant after the age of 10 years. Indeed, over the past decade, the incidence of EPTB appears to be increasing [9] and its relative frequency in children was assessed differently depending on the authors. It varied from 2% to 63% in an Indian study [9-13]. The most common EPTB localization is lymph node [14-17] particularly cervical about 70% to 87% of cases [18,19]. This lymph node involvement may be explained in part by Mycobacterium bovis infection caused by consumption of unpasteurized milk. In Tunisia, frequency of lymph node tuberculosis is raising as in the developing countries reaching 8/100000 inhabitants in 2012 [1].

The clinical presentation of TB depends largely on the age of infection with MT. Infants are more likely to develop miliary TB, while lymph node and meningeal TB are more prevalent in small preschooler and finally, pleural and bone disease in older children [10,12]. Moreover, abdominal localization complicates 6 to 38% of untreated pulmonary TB [20]. In our study, PTB and uncomplicated forms of the disease were the most frequent because severe forms without pulmonary involvement are generally not managed in our department. Furthermore, in the age group 1-4 years there are as many cases of TB infection as pulmonary TB whereas after the age of 5 years pulmonary TB is predominant.

Diagnosis of TB may be difficult in some cases because of atypical symptoms which may cause a delay in its diagnosis. In fact, although the endemicity of childhood TB is important, the incidence of the disease may be underestimated in our country. As reported in the literature, the most predominant symptoms in PTB were cough and fever [13,14,21-23]. In our study, in PTB, general symptoms were frequent after the age of 10 years and in EPTB, these symptoms were reported in more than

50% of all age groups. Nevertheless, impaired general condition is rare in lymph node TB as it has been reported in the literature [24]. Indeed, deterioration in general condition and weight loss were reported in only 41% of cases of EPTB in our study. Otherwise, bacteriological confirmation remains the gold standard for the diagnosis of TB. In our study, MT was isolated in 35% of all cases and in 56.5% of lung parenchymal infection despite the efforts to have good quality of samples by gastric aspiration or induced sputum. In 2009, only 19% of childhood TB cases were culture confirmed in the European Union/European Economic Area [21]. The main reason for this is the paucibacillary nature of the disease in children. Young children only expectorate small amounts of sputum, and sample collection is unpleasant and often requires hospitalization.

In EPTB, pathological examination is the most effective method to confirm TB and especially for pleural TB because pleural fluid is rarely bacillary and culture is only positive in 20-40% of cases [25]. In our study, TB was histologically confirmed in 19 cases (50% of all extra-pulmonary localizations) and compared to lymph node TB which is confirmed histologically in 75% of cases, pleural TB is confirmed only in 58% of cases.

While TST is an essential part of the diagnosis of TB in children, it can be falsely negative in 10% of cases of authentic culture-positive TB [26]. It has also weaknesses which are firstly its limited sensitivity in immune-compromised individuals with active TB infection and secondarily, the lack of specificity due to the cross-reaction after BCG vaccination which is generalized at birth in our country. Some centers use Interferon gamma releasing assays (IGRA) as a diagnostic tool of TB. However, the sensitivity of these tests in children is lower than in adults and the probability of indeterminate results increases with young age [27]. To date, the WHO did not recommend using IGRAs in TB diagnosis in high burden countries [28].

In high-incidence countries, treatment is generally initiated on the basis of the combination of clinical presentation, known TB exposure, positive TST and an abnormal chest X-ray [20,29,30]. And that was the case for 43% of our patients who were treated on arguments of presumption since all bacteriological investigations were inconclusive. However, TB is not highly endemic in our country, so we think that TB treatment should be initiated only after exhausting all invasive methods to try to confirm infection with MT. In fact, some TB-control programs did not allow initiating treatment without bacteriologic confirmation, because the risk of adverse events of treatment [31].

New vaccines with genetically modified living mycobacterial could replace BCG in newborns so they allow better protection and efficacy against latent forms [32]. In fact, new TB vaccines are being developed as part of the strategy to combat TB and adolescents are a proposed target for such vaccines [33].

Finally, childhood TB is a good indicator of the effectiveness of the National Program for TB control and especially the quality of screening.

CONCLUSION

This study showed that as in adults, EPTB is frequent in children and TB may have an unspecific clinical appearance. Obtaining specimens for microbiological tests in children is invasive and requires hospitalization in most cases. Due to the paucibacillary nature of the disease in children, the diagnosis is mainly based on compatible clinical symptoms and signs, radiological findings suggestive of TB, a positive TST and a history of exposure. We lack new diagnostic tools which quickly and with a high level of sensitivity can determine whether a patient is infected with MT and which differentiates between latent and active disease. We think that efforts have to be made in screening of children with household contact of TB in our country.

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