

EXTRA-PULMONARY TUBERCULOSIS IN CHILDREN: A STUDY OF 41 CASES.

Faten Tinsa, Leila Essaddam, Zohra Fitouri, Faouzi Nouira, Wiem Douira, Saida Ben Becher, Khadija Boussetta, Souad Bousnina.

*Department of pediatrics B of the Children's Hospital of Tunis
Department of Pediatric Radiology, Children hospital of Tunis
Department of Pediatric surgery of the Children's Hospital of Tunis*

F.Tinsa, L.Essaddam, Z.Fitouri, F.Nouira, W.Douira, S.Ben Becher, K.Boussetta, S.Bousnina.

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TUBERCULOSE EXTRA-PULMONAIRE CHEZ L'ENFANT:
ÉTUDE DE 41 CAS

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R É S U M É

Pré-requis: la tuberculose extra-pulmonaire représente le 1/3 des cas de tuberculose. L'enfant a une prédisposition à présenter la forme extra-pulmonaire de tuberculose

But : rapporter les aspects cliniques de la tuberculose extra-pulmonaire chez l'enfant

Méthodes : 41 enfants présentant une tuberculose extra-pulmonaire colligés à l'hôpital d'enfants de Tunis ont été inclus dans cette étude

Résultats : la tuberculose extra-pulmonaire représente 57.6% de tous les cas de tuberculose. Le sex-ratio était de 0.7 et l'âge moyen était de 7 ans et demi. La tuberculose ganglionnaire était la plus fréquente des localisations extra-pulmonaire (11 cas) suivie par la localisation abdominale (11 cas), cérébro-méningée (7 cas), ostéoarticulaire (5 cas) puis multifocale (4 cas). Une histoire familiale de tuberculose a été retrouvée dans 22.5% des cas. Le délai du diagnostic était de 4.7 mois. Les séquelles observées durant le suivi étaient neurosensorielles dans 5 cas et à type de déformation vertébrale dans 1 cas.

Conclusion: La tuberculose extrapulmonaire représente une fraction importante dans notre série. La localisation la plus fréquente est ganglionnaire suivie par la localisation cérébro-méningée. Les séquelles neurosensorielles sont fréquentes au cours de la tuberculose du système nerveux central.

S U M M A R Y

Background: Extrapulmonary tuberculosis accounts for up to one third of all cases of tuberculosis and children show a higher predisposition to the development of extra-pulmonary tuberculosis

Aim: To review the clinical features of the extrapulmonary tuberculosis in children.

Methods: forty one children with extrapulmonary tuberculosis followed in the Children Hospital of Tunis between January 1995 and December 2007 were reviewed.

Results: Extrapulmonary tuberculosis constitutes 57.9 % of all cases of tuberculosis. Male to female ratio was 0.7 and the mean age was 7.5 years. The most commonly involved sites were the peripheral lymphadenitis (14 cases) followed by abdominal (11 cases), central nervous system (7 cases), osteoarticular (5 cases) and multifocal (4 cases). A positive family history of active tuberculosis was detected in 22.5% of the cases. Diagnosis delay was 4.7 months. Sequelae observed during the follow up were: neurosensory in 5 cases, and vertebral deformation in 1 case.

Conclusion: extrapulmonary tuberculosis represents an important fraction of tuberculosis in our study. The most common form is lymph nodes localization followed by abdominal and central system nervous forms. Neurosensory sequelae were frequent in central system nervous tuberculosis.

M O T S - C L É S

Tuberculose, extra-pulmonaire, enfant

K E Y - W O R D S

Tuberculosis, extrapulmonary, child

Tuberculosis constitutes the main infectious cause of death worldwide. An estimated 1.3 million cases of tuberculosis and 450 000 associated deaths occur annually in children [1]. Tuberculosis is a serious problem in developing countries. Tunisia is a country situated in North Africa with an intermediary epidemiologic situation of tuberculosis. The incidence among child was 11.02/ 100 000 population in 1979 and declined to 4.39/100 000 population in 1999 [2]. Extrapulmonary tuberculosis accounts for up to one third of all cases [3,4]. Children show a higher predisposition to the development of extra-pulmonary tuberculosis [5,6]. In the current study, we present our 12 years' experience with extrapulmonary tuberculosis in children, with emphasis on epidemiological and clinical features, and outcome.

PATIENTS AND METHODS

A retrospective study was conducted over a 12-year period between January 2005 and December 2007. We investigate the results of clinical, radiological, microbiological and histopathological findings of children with extrapulmonary tuberculosis admitted in the Children's Hospital of Tunis. Treatment modalities and outcome were also analyzed in all patients.

Extrapulmonary tuberculosis was defined as identification of mycobacterium tuberculosis through Ziehl-Neelsen acid fast stain and culture in loewenstein-jensen in a tissue or specimen from a site other than lung parenchyma, in association with clinical and/or imaging findings compatible with infection locally. In case of negative culture, extrapulmonary tuberculosis was defined as clinical, laboratory, imaging and/or histopathological finding compatible with tuberculosis in a site other than hilar lymph nodes or lung parenchyma, in association with a positive tuberculin skin test and/or history of exposure to tuberculosis and a good response to antituberculous medications. Tuberculin skin test was interpreted at 48–72 hours following intracutaneous injection of 5 tuberculin units of purified protein derivative, and was considered positive when the local induration was more than 10 mm. However, cases with active tuberculosis of lung parenchyma or patients who had lung parenchyma involvement in addition to extrapulmonary region were diagnosed having pulmonary tuberculosis and were excluded from the study.

The data were expressed as mean \pm SD and percentage.

RESULTS

During the study period, 41 children (24 female, 17 male) were admitted with extra-pulmonary tuberculosis in our department. The mean age was 7.5 years. Overall, extra-pulmonary tuberculosis accounted for 57.9% of the total 69 cases of tuberculosis admitted in our department during the study period. BCG vaccine is the routine vaccine in Tunisia; 39 patients received BCG vaccine and two patients did not because they were born in Italy. Tuberculin skin test was positive in 47.5 % of cases. Contact history with tuberculosis cases was elicited in 9 cases (22.5%). Seven cases (17%) of extra-pulmonary

tuberculosis had bacterial confirmation.

Peripheral lymph nodes tuberculosis

A total of 14 patients (35%) were admitted with tuberculous peripheral lymphadenitis. Cervical lymph nodes were the most frequently involved node observed in 11 patients; axillary and inguinal lymph nodes were involved respectively in 2 patients and 1 patient. Lymph node enlargement was unilateral in nine cases and bilateral in five cases. Fever, a general condition deterioration and weight loss were noted in 6 patients (42.8%). The mean duration of the symptoms before admission was 88 days \pm 51.6. Chest radiographs were normal in all patients. Tuberculin skin test was positive in 10 patients (71%). 7 patients had phlyctenular tuberculin skin test. the history of exposure to tuberculosis was found in 4 cases: mother, sister, cousine and aunt in each one of cases.

Lymph nodes biopsies were performed in all cases and histopathological examination revealed granuloma with caseous compatible with tuberculosis. Distinction from non-tuberculous mycobacterial lymphadenitis was based on a positive tuberculin skin test reaction, and/or a history of exposure to tuberculosis and favourable response to treatment. Treatment consisted of a two month course of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 7 month course of isoniazid and rifampicin. The outcome was favourable in all cases.

Meningitis

7 patients had central system nervous tuberculosis. Out of the patients with tuberculous meningitis, five were vaccinated. Fever was present in 6 patients, vomiting in all patients, and diarrhoea in 4 patients. Neurological signs: seizures and/or drowsiness and/or nuchal rigidity and/or bulging anterior fontanel were present in 4 patients. The mean age of the patients was 2.6 \pm 1.3 years (3 months-11 years). Male to female ratio was 0.5. The mean duration of the symptoms before admission was 10 \pm 5.9 days (3-21days) and the diagnosis delay was 33 \pm 13.4 days (22-62 days). Tuberculin skin test was negative in all patients. The history of exposure to tuberculosis was found in two patients. Chest radiographs were normal in all cases. Computed tomography and/or magnetic resonance examinations were performed in all the patients and were abnormal in three. Findings included hydrocephalus and arachnoiditis in three patients and in association with tuberculomas in two patients (figure 1, 2). Lumbar puncture was performed in all patients and showed pleocytosis with median range of 248 cells/mm³, hypoglycorachia and hyperalbuminorachia .Overall, cerebrospinal fluid (CSF) cultures were positive in two patients ; gastric fluid cultures were attempted all patients and were negative. Biopsy of tuberculoma was performed in one patient and histopathological examination was compatible with tuberculosis treated. Treatment for tuberculous meningitis consisted of isoniazid and rifampicin for a median of 19 months (12 months -28 months) in association with streptomycin and ethambutol during the first two months, daily. Adjunctive steroid treatment was administered to 3 patients for a four week

Figure 1: RMI of the brain showing parietal tuberculoma**Figure 2:** RMI of the brain showing arachnoiditis and obstruction of the sylvian aqueduct

Skeletal tuberculosis

Five patients developed skeletal tuberculosis. The following sites were affected: hip-femoral joint (two patients), knee joint (two), elbow (one), shoulder (one) and thoracic spine (one). The mean duration of the symptoms before admission was 15 months and diagnostic delay was 16 months (3 months-65months). General condition deterioration, weight loss and

anorexia were found in two patients. Fever was present in only one patient. Knee arthritis was found in two patients, limping was found in two patients and a paravertebral mass with a dorsal gibbosity were found in one patient. Male to female ratio was 1.5 and the mean age of the patients was 6.6 years (2-13 years). Skin tuberculin test was negative in all patients and the exposure tuberculosis history was found in one patient. Radiographs showed bone lacuna in four cases. Computed Tomography Scan and/or Magnetic Resonance Imaging were performed in 4 patients and showed better bone and/or synovial involvement (figure 3,4). Isotope scanning showed increased radionuclide uptake from the involved sites. Chest X ray showed military and mediastinal widening in one case. Cultures of sputum and of the para-vertebral collection puncture, were positive to mycobacterium tuberculosis in one patient. Bone and/or synovial biopsies were performed in four patients and were compatible with the diagnosis of tuberculosis. Synovial fluid culture was performed in one patient with knee tuberculosis and was negative. Treatment consisted of isoniazid, rifampicin, pyrazinamide, and streptomycin for two months, followed by isoniazid and rifampicin for a total of 12 months. Complete clinical and imaging restoration was achieved in four patients. However, one patient maintained spinal deformation.

Abdominal tuberculosis

11 patients (2 male, 9 female) developed abdominal tuberculosis: peritoneal tuberculosis in 10 patients with mesenteric lymphadenitis involvement in 4 cases and cecum involvement in one case. One patient had mesenteric lymphadenitis without peritoneal involvement. Male to female ratio was 0.2. All patients were older than 7 years and the mean age was 10 years (7-14 years). The main clinical features were: asthenia and anorexia in 5 patients, abdominal pain in 9 patients, mimicking appendicitis in one patient, abdominal distension in 8 patients and abdominal mass in 1 patient. The mean duration of the symptoms before admission was 3 months and the diagnosis delay was 3 months and half (14 days- 1 year). The history of exposure to tuberculosis was found in only 1 case. Tuberculin skin test was positive in 7 patients. Abdominal ultrasonography demonstrated mesenteric lymph nodes in 4 cases, abdominal Computed Tomography Scan showed adenopathy with hypodense center suggestive of necrotic adenopathy in 4 cases. Ascitis puncture was performed in 8 patients and the culture of mycobacterium tuberculosis was positive in two cases. Histological findings were compatible with tuberculosis in 4 cases. Patients received a 12 month course of isoniazid plus rifampicin in association with pyrazinamid and ethambutol for two months. The outcome was favourable in all cases.

Multifocal tuberculosis

Multifocal tuberculosis was defined as the presence of at least two extrapulmonary sites. Four patients had multifocal tuberculosis (9.7%). Their characteristics features and tuberculous sites involved are shown in table 1. Tuberculin skin test was positive in three patients. The tuberculosis exposure

Figure 3: RMI of the knee showing metaphysical-epiphyseal collections



Figure 4: Spinal RMI showing dorsal spondylodiscitis with paravertebral abscesses



history was noted in one patient. The mean duration of symptoms before admission was 7 months and half (3 months-12 months). *Mycobacterium tuberculosis* was found in sputum culture in one case, and on direct examination of liver puncture biopsy in another case. Histological examination of lymphadenitis, cecum and synovial biopsies were compatible with the diagnosis of tuberculosis in three cases. Patients received 12 month course of isoniazid plus rifampicin in association with pyrazinamid and ethambutol for two months. The outcome was favourable in two patients without sequelae; and two patients, who had central system nervous involvement, developed neurosensory sequelae.

DISCUSSION

In Tunisia, tuberculous incidence in children represent 10-15% of the global incidence of this infection [2]. Extra-pulmonary tuberculosis accounts for up to one third of all cases [3,4]. In our study, extrapulmonary tuberculosis was more frequent than pulmonary involvement (57.9%).

Several factors have been involved in the current resurgence of tuberculosis, including the Acquired Immunodeficiency Syndrome (AIDS) epidemic, the emergence of multiple drug resistant *M tuberculosis* strains, poverty, immigration, homelessness, and inadequate tuberculosis control programmes [1,5,7]. The significance of these factors is further intensified during early childhood, not only because of the immature immune responses of infants and young children, but also as a result of the economic and social dependence of this group of patients. However, in the present study, there were no cases of AIDS, and there were excellent clinical responses to the standard antituberculous regimens observed in all other patients.

Superficial lymphadenitis constituted the predominant manifestation of extra-pulmonary tuberculosis among the patients studied [3]. However, infants are more susceptible to undergo severe forms of tuberculosis [6,8]. In this study, superficial lymphadenitis predominated in preschool and older children; however, in the literature, it usually appeared at younger age [3]. In this study, meningitis predominated in infants, skeletal and abdominal tuberculosis in older children, confirming age dependent changes in host-pathogen interactions, described by others [3,5,8].

Tuberculous meningitis remains the most serious form of extra-pulmonary tuberculosis. In the present study, long term complications occurred in patients. Younger age and delay in the introduction of appropriate therapeutic agents have made these children vulnerable targets for the development of serious complications. Similar findings have been reported from other studies [5,6,9-11]. In our study, five of the seven patients had received BCG vaccine, yet this did not avoid meningitis tuberculosis and no patient died. Only one patient developed sequelae; BCG vaccine which is generalized in our country, appears to prevent death and severe neurological complications. Abdominal tuberculosis is caused majorly by mycobacterium bovis and the main route of transmission is the ingestion of infected milk or milk products. It is estimated that TBP occurs

in 0.1%-3.5 % of all patients with pulmonary TB and represents 4%-10% of all extrapulmonary TB [12,13]. Most of the cases are in their 30's or 40's and it is rarely seen in children [14,15]. In the pediatric literature, abdominal tuberculosis has been described infrequently 2 of 1000 and 5 of 1700 in industrialized countries [15-17]; this is attributable to the eradication of mycobacterium bovis by slaughter of infected cattle and the availability of pasteurized milk. However, in developing countries this form of tuberculosis is still present. Abdominal tuberculosis may involve the gastrointestinal tract, peritoneum, lymph nodes or solid viscera; however, peritoneum and abdominal lymph nodes are the most common sites [15-17]. The mean age of presentation in our study (6.4 years) was similar to the reported common age group (6-11 years) [18,19]. In the series of Basu et al abdominal TB could only be confirmed in 38 (33.04%) children (16 were bacteria-positive and 22 were confirmed on histopathology). Majority (52.17%) of the patients were diagnosed by suggestive radiological examinations and clinical improvement within three months of starting antituberculous therapy [17]. In our study abdominal tuberculosis was confirmed by bacteriology and/or histopathology in 6 cases; in the other patients, the diagnosis was based on clinical, radiological findings and the response to antituberculous treatment.

Osteoarticular Tuberculosis is an unusual form of the disease, accounting for 1-5% of all cases of all cases of tuberculous disease and 10-18% of extrapulmonary involvement [20-24]. Signs and symptoms are frequently non specific and easily misdiagnosed. The delay in diagnosis may range from months to years [20-22,25]. In the present study, five patients had this form of tuberculosis and one of them had multifocal osteoarticular tuberculosis. Diagnosis delay was 16 months and ranged from 3 months to 65 months. The most common form involves the vertebral column, followed by the hip, knee, sacroiliac, joint, shoulder, elbow and ankle in order of frequency [26]. However, in our study, knee was involved in two cases, hip in two cases, elbow in one case, shoulder in one case and vertebral column in only one case.

Identification of M tuberculosis is essential for the defined diagnosis of osteoarticular tuberculosis, however the detection varies between 19 and 94% [27]. In this study, cultures of the aspiration material materials were positive in only one case and the diagnosis in the other patients, was based on histopathological findings, history of exposure, imaging findings and the response to treatment. Magnetic Resonance Imaging is particularly valuable in the diagnosis procedure and in demonstrating the extent of the involvement. In developing countries where tuberculosis is endemic, and since it is not always possible to identify M. tuberculosis, early treatment should be considered in patients with clinical, radiological and histopathological findings suggesting tuberculosis.

Multifocal tuberculosis is rare. There were few reports on multifocal tuberculosis in children and it occurs most commonly in children coinfectd with Human Immunodeficiency Virus [28]. Multifocal tuberculosis in the current study represented 10% of a total of extrapulmonary sites. All our patients were immuno-competent and three of

them were older children. It is surprising to note the low noise evolution of the disease despite disseminated and important visceral injuries. One of the patients had spleen and liver involvement; these localizations are exceedingly rare in the literature.

The main limitation of this study was low percentage of cases for which a culture result was available. Low percentage of culture-positive cases (17%) stems from the following: 1) difficulty in obtaining culture material from extrapulmonary sites; 2) material typically being sent to pathology but rarely to the microbiology laboratory; 3) lack of adequate laboratory facilities, and 4) inherently low positive culture rate even for pulmonary TB. As a result, we used other diagnostic criteria such as granulomatous inflammation with caseification necrosis by node excision synovial and/or bone biopsies, clinical and radiologic data, history of close contact with tuberculosis cases, positive skin tuberculin test, and favourable response to treatment to establish diagnosis of EPTB in the majority of cases.

Childhood tuberculosis reflects the insufficiency of the Public Health System in to control and come over the transmission of infection in the community. Prompt and efficient identification of the source of transmission and application of effective environmental measures are intimately linked to the control of childhood tuberculosis; BCG vaccine is recommended in areas with intermediate or high incidence of tuberculosis.

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