Challenges in diagnosing tuberculosis in children

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ABSTRACT

INTRODUCTION: Clinical investigations of childhood tuberculosis (TB) are challenged by the paucibacillary nature of the disease and the difficulties in obtaining specimens. We investigated the challenges in diagnosing TB in children in a low-incidence country.

MATERIAL AND METHODS: The data were retrieved retrospectively from the paediatric departments at Danish university hospitals from April 2004 to March 2009 using the diagnosis code A15.0-A19.9 in children below the age of 15 years.

RESULTS: A total of 54 children were identified of whom 13 were native Danes. The remaining immigrants were from a range of countries, the majority from Somalia. In all, 44 children had pulmonary TB and the proportion of extrapulmonary TB was higher among immigrants than among Danes. The cardinal symptoms were fever, weight loss and cough. In 41 (76%) cases, a combination of a positive tuberculin skin test, an abnormal chest X-ray and the clinical presentation led to initiation of treatment. TB diagnosis was confirmed later by culture in 29 cases. The median number of days from contact to the healthcare system to treatment initiation was two days for 23 children who were part of contact tracing and seven days for the remaining children. All children but one completed treatment, and three patients were retreated due to relapse. Side effects to treatment were observed in 20 cases. None of the patients died.

CONCLUSION: The majority of the children affected with TB were foreign-born with a higher proportion of extrapulmonary TB. The microbiological confirmation was low. A rapid onset of treatment was closely related to known, recent exposure.

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Of the estimated nine million annual cases of tuberculosis (TB), at least 10-15% occur in children under 15 years of age. The majority of these cases occur in countries with a high TB burden. It has been estimated that one third of the world's population is infected with *Mycobacterium tuberculosis* complex; however, the exact extent of childhood TB is unknown. The main drawback with regard to the diagnosis of TB is the inherent difficulties in isolating the causative microorganism for reasons that are not fully understood. The lack of a standard case definition, the wide clinical spectrum of disease, difficulties in diagnosing extrapulmonary manifestations, especially miliary TB and tuberculous meningitis are imminent challenges as is the lack of priority from national control programmes [1, 2].

Western European countries have registered an increased incidence in TB among both adults and children during the past two decades due to immigration from high-incidence areas. Childhood TB constitutes 4-7% of all TB cases in Western Europe, with the highest incidence rates being > $40/10^5$ among immigrants in some settings where reliable data are available [3-5]. Denmark has a low TB incidence of $6.5/10^5$, and the notification rate of childhood TB has decreased from 42 cases in 2000 to 20 cases in 2010 [6, 7].

In 2009, only 19% of childhood TB cases were culture-confirmed in the European Union/European Economic Area [8]. 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 hospitalisation. The clinical presentation of TB in children is unspecific due to the fact that TB progresses rapidly, is often spread to many different organs and may mimic other infectious diseases [9]. In low-incidence countries, treatment is generally initiated on the basis of the combination of clinical presentation, known TB exposure, positive tuberculin skin test (TST) and an abnormal chest X-ray [9-11].

The clinical presentation of tuberculosis in children is unspecific and the diagnosis of tuberculosis in a low-incidence, industrialized country like Denmark remains a challenge.

ORIGINAL ARTICLE

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TABLE 1

Characteristics of the study population. The values are n (%).

	Danes (N = 13 (24))	Immigrants (N = 41 (76))
Gender		
Male	5 (38)	17 (42)
Female	8 (62)	24 (58)
Age		
0-4	5 (39)	16 (39)
5-9	6 (46)	10 (24)
10-14	2 (15)	15 (37)
Site of disease		
Pulmonary TB	12 (92)	32 (78)
Extrapulmonary TB	1 (8)	9 (22)
Household exposure	8 (62)	15 (37)
Outcome		
Treatment completed	13 (100)	40 (98)
Treatment discontinuation	0	1 (2)
Died	0	0
Lost to follow-up	0	0

TB = tuberculosis.

We aimed at describing the challenges in diagnosing TB in children in Denmark, which is a low-incidence country. Furthermore, we investigated what symptoms and paraclinical tests led to the diagnosis and recorded the time from first contact to the healthcare system to treatment initiation.

MATERIAL AND METHODS

From April 2004 to March 2009, data on TB cases in children below the age of 15 years were obtained from the paediatric departments at three Danish university hospitals: Copenhagen, Odense and Aarhus. The data were retrieved from hospital systems using the diagnosis code as defined in the International Classification of Diseases (ICD) A15.0-A19.9. 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 antituberculous regime were included in the study.

The results were described in a data collection chart using Microsoft Access 2000 (Microsoft Corporation). Defined as immigrants were children whose parents had been born abroad, including Greenland, as well as children born in Greenland, but living in Denmark.

Trial registration: not relevant.

RESULTS

Ninety cases were identified during the initial search. After the case review, 36 children were excluded; 17 due to missing patient records, the remaining due to rejection of the diagnosis or diagnosis of atypical mycobacteria.

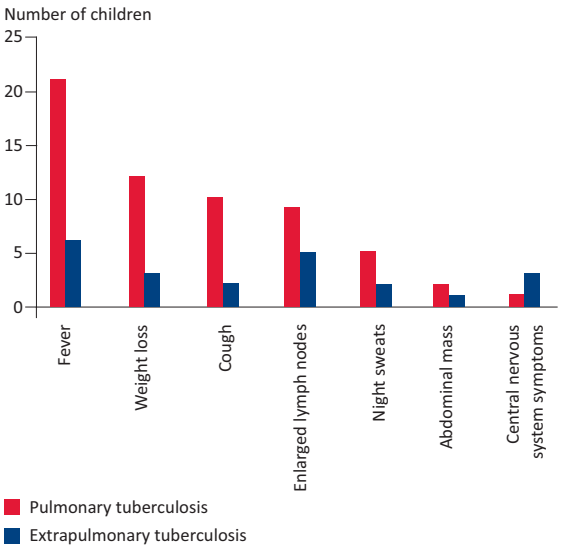
Demographic characteristics

A total of 13 (24%) children were native Danes and the remaining were immigrants from a range of countries. **Table 1** shows the characteristics of the study population. Children from Somalia constituted the majority of immigrants (n = 23, 43%) followed by Greenland (n = 4), Turkey (n = 3), Afghanistan (n = 2), Thailand (n = 2), Kosovo-Albania (n = 2), The Philippines (n = 1), Pakistan (n = 1), Croatia (n = 1), Lebanon (n = 1) and one was of Arabic origin, not further specified. Twenty-one (39%) children were below five years of age. Recent household exposure was identified in 23 (43%) children. Three patients had received Bacillus Calmette-Guérin (BCG) vaccination, but data on BCG vaccination for the remaining children were not available.

In all, 44 (82%) children were coded as having pulmonary TB (PTB), and the remaining had extrapulmonary TB (EPTB). The proportion of EPTB was 22% among immigrants and 8% among Danes. The extrapulmonary localizations were TB in the lymph nodes (n = 5), followed by TB in the central nervous system, meningitis (n = 2) and tuberculoma (n = 2) and miliary TB (n = 1). Among the 44 children coded in the hospital system as having PTB, nine had enlarged peripheral lymph nodes, indicating that they also had extrapulmonary manifestations.

FIGURE 1

Symptoms and clinical findings in children with pulmonary and extrapulmonary tuberculosis.



Symptoms and clinical findings

Symptoms and cardinal clinical findings in patients with PTB and EPTB are shown in **Figure 1**. For children diagnosed with PTB, the most prominent symptoms were fever, weight loss and cough. For the children diagnosed with EPTB, fever and enlarged lymph nodes were predominant. Besides suffering from TB, six children also suffered from wheezing bronchitis. In addition to this, two also suffered from social deprivation (i.e. parents with substance abuse) and two were born prematurely.

Paraclinical tests

Fourteen (26%) children were tested for HIV and all tested negative. TST was performed in 49 children, and 46 were found positive. The Quantiferon-TB test for *M. tuberculosis* was performed in six children, and all cases tested positive. A total of 50 patients were investigated with chest X-ray, and 40 were described as abnormal. Computed tomography (CT) of lungs, cerebrum or peripheral lymph nodes was performed in ten patients, and the results obtained supported TB suspicion in eight cases. Magnetic-resonance imaging (MRI) of the neck, cerebrum, chest or column was done in five cases and found abnormal in four. Combining the results of CT and MRI, the tests showed the following; mediastinal lymphadenopathy (n = 5), tuberculoma (n = 2), enlarged ventricles (n = 1), inhomogeneous process in the neck area (n = 1), epidural abscess (n = 1), pleural effusion (n = 1) and atelectasis (n = 1).

Furthermore, ultrasound was performed in nine cases, including echocardiography, ultrasound of the abdomen, neck, peripheral lymph nodes or transthoracic ultrasound. In seven cases, the findings supported the TB diagnosis.

Specimens were collected for microbiological tests in 48 (89%) children. In 14 (29%) cases, smears were positive for acid fast bacilli (AFB), in 15 (31%) cases *M. tuberculosis* DNA was detected by polymerase chain reaction (PCR) and in 29 (60%) cases TB was confirmed by culture (**Table 2**).

Time to diagnosis

The median number of days from the initial contact to the healthcare system (both general practitioner and hospital) to treatment initiation was seven days (range 1-700 days) for the 31 children who were not in investigation as part of contact tracing. For 28 of these children, the initial contact to the healthcare system to treatment initiation ranged from 1-47 days, but for the remaining three children, who were all immigrants, the range was 300-700 days. A 14-year-old girl was referred to the hospital with fever, weight loss and fatigue. The child was initially investigated for leukaemia. The antituberculous treatment was initiated based on chest X-ray and persistent symptoms 700 days later. A nine-year-old girl who was investigated for pulmonary TB and for whom the initial microbiological results remained negative, the treatment was delayed 300 days. The last case was a two-year-old boy who had an extra-thoracic, enlarged lymph node and in whom nontuberculosous mycobacteriosis was initially suspected. Due to clinical progression, a biopsy was taken one year later, and *M. tuberculosis* was cultured.

For the 23 children found by contact tracing, the median time was two days (range 0-142 days) from initial contact to treatment initiation.

In 41 cases, initiation of treatment was based on the combination of a positive TST, a positive history of exposure, an abnormal chest X-ray and clinical findings. Nine patients started treatment based on a positive PCR and smear for AFB. Treatment was started due to a positive culture in only four cases.

TABLE 2

Microbiological results for the 48 children from whom specimens were taken. The values are n (%).

	Positive smear for AFB	Positive PCR for Mycobacterium tuberculosis complex	Positive culture for Mycobacterium tuberculosis complex
Pulmonary TB[a] (N = 39)	10 (25.6)	12 (30.7)	20 (51.2)
Extrapulmonary TB[b] (N = 9)	4 (44)	3 (33.3)	9 (100)

AFB = acid fast bacilli; PCR = polymerase chain reaction; TB = tuberculosis.
a) The following tests were performed: 32 gastric washing, 9 tracheal secretion, 3 sputum, 5 tissue biopsy, 3 urine, 1 cerebrospinal fluid, 8 other (pleural fluid, faeces, blood).
b) The following tests were performed: 5 gastric washing, 4 broncho-alveolar lavage, 3 sputum, 2 tracheal secretion, 3 urine, 4 biopsy, 4 cerobrospinal fluid, 2 other (faeces, blood).

Treatment, resistance data and outcome

A total of 52 (96%) children received standard treatment of six months' duration (combination of rifampicin, isoniazid, ethambutol and pyrazinamid for the first two months and rifampicin and isoniazid for four months). Four of these patients received additional treatment: three due to relapse (two treatments prolonged for three months and one treatment prolonged for six months) and one due to poor compliance (treatment prolonged for six months). Two children received nine months of treatment. One patient had isoniazid-resistant TB. A total of 20 (37%) patients had side effects from treatment: nausea (n = 14), elevated liver enzymes (n = 5), failure to thrive (n = 4), elevated serum urate level (n = 2) and neurological complications (n = 1). In all, 53 (98%) patients completed treatment, and one stopped treatment prematurely due to side effects.

DISCUSSION

Although the incidence of TB among children in Denmark has declined during the past decade, 20 children

registered with TB in 2010 [6]. This study describes some clinical and microbiological characteristics in children diagnosed with TB in Denmark.

The majority of the children diagnosed with TB were immigrants among whom the main group was from Somalia and only 24% were native Danes. The proportion of children with EPTB differed between native Danes and immigrants, the latter having a higher proportion (22%) than the Danes (8%). These data were consistent with data from the national epidemiological survey system, which showed that 20-30% of childhood TB cases in Denmark were found among Danes within this time period [12]. Earlier studies by Andersen and colleagues [13] found comparable distributions in childhood TB in Danes and immigrants from 1990-1999. TB in children, especially below the age of five years, suggests recent transmission from an infectious adult, and the paediatric patient is therefore an important indicator in respect to national TB control [1]. This age-group constituted 39% of the total population in the present study. To reduce TB in this age group, focus on contact tracing is essential. Children at high risk should be screened and treated for latent TB.

Fever, weight loss, coughing and enlarged lymph nodes were predominant symptoms and clinical findings within the population. Previous studies have shown that the most frequent signs in children with TB were persistent cough, fever of unknown origin and weigh loss [9, 14]. This study underlines the unspecific nature of TB in children where the disease may mimic several common childhood diseases, including pneumonia and bacterial and viral infections which may complicate its diagnosis. The risk of developing active TB is higher in children below the age of five years who may be facing risk factors such as immunosuppression and malnutrition [15, 16]. Six children in the present study had co-morbidities like wheezing bronchitis and social deprivation, none of which are associated with an increased risk of developing active TB. However, the risk for TB exposure among socially deprived individuals is known to be high in low-incidence countries such as Denmark [17].

The majority of the children (89%) had specimens taken for microbiological testing. 60% were positive in culture, which is in line with prior studies which have shown a positive result in culture in 30-50% of children with probable TB. Previous studies have shown that PCR and smear have a low sensitivity, 50% and 10-15%, respectively [10, 11, 18]. Comparable results were found in the present study: 29% tested positive by PCR and 27% tested positive by microscopy. The reason for the low sensitivity of bacteriological tests is primarily the paucibacillary nature of TB in children. Although bacteriological confirmation of TB is not always feasible, it remains the golden standard and should be sought whenever possible [1]. The high rate of false negative tests can make the diagnosis of TB difficult and may delay treatment. This seemed not to be the case in general in the present study. Treatment was initiated based on a positive culture in only four cases. Furthermore, the median time from contact to the healthcare system to treatment initiation was short. One possible explanation for this may be that the paediatric centres included in the study were highly specialized departments. This study cannot clarify whether this is representative for cases diagnosed in other departments. Reducing delay is important to relieve morbidity and improve clinical outcome.

The proportion of children completing treatment reached 98%, and only one had documented isoniazid-resistant TB and no children died as a result of TB.

In line with the WHO [1], the national TB guidelines [19, 20] recommend that all TB cases should be tested for HIV. Only 14 children in the present study were tested for HIV, which suggests that the recommendations are not being followed.

The study had some limitations. It was a retrospective design of limited size. In the study period, the national epidemiological survey system reported 145 cases of childhood TB in Denmark [12] of which only 54 were included in the present study. The size of the population was limited due to the fact that the study did not include all hospitals in Denmark and because a large number of cases had to be excluded. The quality of the data was limited by inaccurate data registration in the hospital systems, e.g. data on BCG vaccination, height and weight, and indication of failure to thrive was missing in many records. However, owing to the review of patient records, the present study was able to present clinical data otherwise not available in surveillance studies.

CONCLUSION

TB has been called “the great imitator” because it can be located in many organs and may have an unspecific clinical appearance that often mimics other common paediatric diseases. Obtaining specimens for microbiological tests in children is invasive and requires hospitalization in most cases hospital. 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. Despite the lack of reliable diagnostic tests, the diagnosis was not delayed and nobody died from TB. We lack new diagnostic tools which quickly and with a high level of sensitivity can determine whether a patient is infected with *M. tuberculosis* complex and which differentiates between latent and active disease. Furthermore, an increased focus on contact tracing is necessary.

The diagnosis of TB in childhood still suffers from

considerable uncertainty. This study emphasises that TB remains a clinical diagnosis.

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