Improving early diagnosis of tuberculous meningitis in children

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3.3 Chest radiograph findings in children with tuberculous meningitis

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ABSTRACT

BACKGROUND: Tuberculous meningitis (TBM) is diagnosed based on a combination of clinical, laboratory, and radiological findings, including signs suggestive of tuberculosis (TB) on a standard chest radiograph.

METHODS: We describe the radiological features suggestive of intra-thoracic TB in children diagnosed with TBM during a prospective evaluation of meningitis suspects seen at Tygerberg Children's Hospital, Cape Town, South Africa.

RESULTS: Of 84 children treated for TBM, 31 (37%) had 'definite' TBM, 45 (55%) 'probable' TBM and 8 (9%) 'possible' TBM. In total, 37 (44%) TBM patients had chest radiograph findings suggestive of TB; 9 (11%) with disseminated (miliary) TB. Only 1 in 4.39 children ≤3 years of age with TBM had suggestive chest radiograph findings. The presence of complicated intra-thoracic lymph node disease was significantly higher in children ≤3 years of age, odds ratio 21.69 (95% confidence interval 2.73-172.67); p <0.01. Among 6 HIV-infected children, 3 (50%) had intrathoracic lymphadenopathy.

CONCLUSION: The majority of children with TBM, including the very young, did not have signs suggestive of TB on chest radiograph.

INTRODUCTION

Globally there were an estimated 8.6 million new cases and 1.3 million deaths from tuberculosis (TB) in 2012[1]. TB is predominantly a pulmonary disease, but extrapulmonary involvement is particularly common in young children and in immunocompromised individuals[2]. Central nervous system (CNS) involvement, mostly tuberculous meningitis (TBM), accounts for approximately 1% of all TB cases[3]. TBM is the most devastating manifestation of TB and early treatment initiation is critical to achieve optimal outcomes[4]. In clinical practice, diagnosis is hampered by non-specific clinical features and sub-optimal accuracy of existing diagnostic methods[5-9], therefore TBM is mainly diagnosed based on a combination of clinical, laboratory, and radiological findings.

A uniform research case definition was proposed by an international panel of experts, categorizing patients as definite, probable, or possible TBM (Table 1)[10]. Chest radiograph findings are included within the scoring criteria. Previous observations suggest that chest radiograph findings consistent with active pulmonary TB are observed in 30% to 65% of adults with central nervous system TB[11-13]. Chest radiograph evidence of TB in children with TBM is usually considered to be more frequent, ranging from 70% of HIV-uninfected to 84% of HIV-infected children diagnosed with TBM[14]. In the group of children with TBM and HIV co-infection, hilar lymphadenopathy, pleural effusion and cavity formation was significantly increased compared to HIV uninfected children[14].

We aimed to describe the radiological features and frequency of chest radiograph signs suggestive of TB in children with TBM.

METHODOLOGY

This prospective descriptive cross-sectional study was conducted at Tygerberg Children's Hospital, South Africa, a major referral centre for Cape Town and surrounding areas. Children were enrolled between January 2010 and January 2014. Inclusion criteria were 1) age 3 months to 13 years 2) clinical suspicion of TBM 3) CSF evaluation 4) chest radiograph performed at admission 5) written consent from the caregiver and assent if the child was older than 7 years and competent to do so. The study was approved by the Human Research Ethics Committee of Stellenbosch University, South Africa (study nr. N11/01/006).

Clinical procedures

All patients underwent a comprehensive clinical evaluation. Routine investigations included full blood count, basic biochemistry, human immunodeficiency virus (HIV) screening, tuberculin skin test (TST), microbiological analysis of sputum or gastric washings, bacterial blood culture, chest radiography and neuroimaging (if clinically indicated). Chest radiographs were independently interpreted by a pediatrician and an experienced pediatric pulmonologist, using a standard reporting form. Findings were categorized as certain TB, uncertain TB or not TB. Intra-thoracic lymph node disease was classified as either uncomplicated or complicated, accordingly to a radiological classification of childhood intrathoracic tuberculosis, using a structured approach to interpretation and recording chest radiograph findings[15]. Airway compression was defined as either compression of the trachea, left main bronchus or bronchus intermedius. Parenchymal changes were defined as either consolidation (including expansile pneumonia) or miliary.

Case definition of tuberculous meningitis

A diagnosis of TBM was based on the proposed uniform research case definition (Table 1)[10]. TBM was classified as 'definite' when CSF demonstrated acid-fast bacilli, positive *M. tuberculosis* culture and/or positive *M. tuberculosis* commercial nucleic acid amplification test (NAAT). TBM was classified as 'probable' when patients scored ≥ 12 when neuroimaging was available and ≥10 when neuroimaging was unavailable. TBM was classified as 'possible' when a patient had a diagnostic score of 6–11 when neuroimaging was available and 6–9 when neuroimaging was unavailable[10]. TBM was staged according to revised British MRC criteria as: Stage I) Glasgow Coma Scale (GCS) of 15 and no focal neurology, Stage IIa) GCS of 15 plus focal neurology, Stage IIb) GCS of 11-14 with focal neurology and Stage III) GCS <11[16,17]. All patients diagnosed with TBM were treated with a standard short-course regimen[18].

Statistical analysis

Data analysis was performed using SAS (Statistical analysis system) version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Frequencies were obtained for chest radiograph findings, stratified for TBM stage. An unweighted kappa statistic was used to assess inter-observer agreement. Comparison was made, using the X^2 test with a p-value <0.05 considered statistically significant. Chest radiograph criteria were further compared between children ≤3 years and age >3 years and odds ratios determined. A need to treat calculation was used to reflect the number of TBM patients ≤3 years of age with "certain TB" on chest radiograph evaluation.

Table 1. Diagnostic criteria in the uniform TBM research case definition[10]

	Diagnostic score
Clinical criteria (Maximum category score=6)	
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of TB (1 or more of): weight loss/(poor weight gain in children), night sweats or persistent cough > 2 weeks	2
History of recent close contact with an individual with pulmonary TB or a positive TST/IGRA in a child <10 years	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
CSF criteria (Maximum category score=4)	
Clear appearance	1
Cells: 10–500 per µl	1
Lymphocytic predominance (>50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2·2mmol/L	1
Cerebral imaging criteria (Maximum category score=6)	
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Pre-contrast basal hyperdensity	2
Evidence of tuberculosis elsewhere (Maximum category score=4)	
Chest X-ray suggestive of active TB (excluding miliary TB)	2
Chest X-ray suggestive of miliary TB	4
CT/ MRI/ US evidence for TB outside the CNS	2
AFB identified or *M.tuberculosis* cultured from another source i.e. lymph node, gastric washing, urine, blood culture	4
Exclusion of alternative diagnoses- An alternative diagnosis must be confirmed microbiologically, serologically or histopathologically	
Definite TBM = AFB seen on CSF microscopy, positive CSF *M.tuberculosis* culture, or positive CSF *M.tuberculosis* commercial NAAT in the setting of symptoms/signs suggestive of meningitis; or AFB seen in the context of histological changes consistent with TB brain or spinal cord together with suggestive symptoms/signs and CSF changes, or visible meningitis (on autopsy).	
Probable TBM = total score of ≥12 when neuroimaging available = total score of ≥10 when neuroimaging unavailable	
Possible TBM = total score of 6-11 when neuroimaging available = total score of 6-9 when neuroimaging unavailable	

TBM- tuberculous meningitis, TB- tuberculosis, TST- tuberculin skin test, IGRA- interferon gamma-release assay, CSF- cerebrospinal fluid, CT- computed tomography, MRI- magnetic resonance imaging, US- ultrasound, AFB- acid-fast bacilli, NAAT- nucleic acid amplification test

RESULTS

In total 84 children met the inclusion criteria; 31 (37%) had 'definite/microbiologically-confirmed' TBM, 45 (55%) had 'probable' TBM and 8 (9%) had 'possible' TBM[10]. According to revised British MRC TBM staging criteria, 12 (14.3%) had stage I, 13 (15.5%) stage IIa, 30 (35.7%) stage IIb and 29 (34.5%) stage III disease. Tuberculin skin testing was positive in 24 (28.6%) TBM patients, of whom 11/37 (29.7%) had certain pulmonary TB on chest radiograph, 10/39 (25.6%) had no visible abnormality, and 3 had inconclusive signs. HIV co-infection was identified in 6 patients. Of these, 3 had no radiographic evidence of pulmonary TB. Of the three HIV-infected patients with abnormal chest radiograph, one had isolated lymph node involvement, one lymph node involvement plus lobar pneumonia and the third lymph node involvement plus a miliary picture.

A summary of chest radiograph findings is reflected in table 2. Inter-reviewer variability between the pediatrician and pediatric pulmonologist was minimal (unweighted kappa statistic 0.62 95% confidence interval (CI) 0.46-0.79); differences were resolved by consensus. The proportion of 'certain TB' and miliary TB on chest

Table 2. Demographics and chest radiograph findings in 84 children with childhood TBM

Demographics	**n/N (%)**
Male	43/84 (51)
Age group	
≤3 years	46/84 (55)
>3 years	38/84 (45)
Chest radiograph findings	
Normal CXR	39/84 (46)
Abnormal CXR (not TB)	5/84 (6)
Abnormal CXR (Uncertain TB)	3/84 (4)
Abnormal CXR (certain TB)	37/84 (44)
Miliary TB	9/84 (11)
Parenchymal consolidation	15/84 (18)
Intrathoracic lymphadenopathy	32/84 (38)
Paratracheal	16/84 (19)
Hilar	24/84 (29)
Complicated lymph node disease	18/84 (21)
Airway compression	16/84 (19)
Bronchus intermedius	8/84 (10)
Left main bronchus	8/84 (10)

TBM= tuberculous meningitis, CXR= chest radiograph, TB= tuberculosis

radiograph was 44% (37/84) and 11% (9/84) when including all TBM categories; 39% (12/31) and 13% (4/31) respectively in those with microbiologically-confirmed TBM. Among those with microbiological TBM confirmation, 1/31 (3%) had acid-fast bacilli on microscopy, 13/31 (42%) were *M. tuberculosis* culture positive, and 27/31 (87%) confirmed by commercial NAAT (Either GenoType MTBDR*plus*® assay and/or GeneXpert MTB/RIF® assay). *M. tuberculosis* was cultured in gastric washings from 27 patients; 10 with microbiologically-confirmed and 17 with 'probable' TBM. No significant differences were observed when comparing chest radiograph findings in children with different stages of TBM.

Chest radiographs were more frequently indicative of TB in very young children (≤3 years of age) compared to older children (>3 yrs); 25/46 (54%) versus 12/38 (32%) (odds ratio (OR) 2.58 (95 % CI 1.05-6.33; p=0.04 (Table 3). Chest radiograph findings in children ≤3 years of age were more likely to include complicated intra-thoracic lymph node disease (OR 21.69; 95% CI 2.73-172.67), and the presence of airway compression (OR 17.90; 95% CI 2.24-143.27) than in older children Despite the fact that chest radiographs were most informative in young children, only 1 in 4.39 children ≤3 years of age had "certain TB" on chest radiograph evaluation.

Table 3. Chest radiograph findings in children investigated for TBM, comparing very young (≤3 years) to older children

	≤3 years (n=46)	>3 years (n=38)	Odds ratio (95% CI)	p-value
Normal CXR	17	22	0.43 (0.18-1.03)	0.06
Abnormal CXR (not TB)	3	2		
Abnormal CXR (Uncertain TB)	1	2		
Abnormal CXR (certain TB)	25	12	2.58 (1.05-6.33)	0.04
Miliary TB	5	4	1.04 (0.26-4.17)	0.96
Parenchymal consolidation	12	4	3.00 (0.88-10.24)	0.07
Intra-thoracic lymphadenopathy	23	9	3.22 (1.25-8.29)	0.02
Complicated lymph node disease	17	1	21.69 (2.73-172.67)	<0.01
Airway compression (any)	15	1	17.90 (2.24-143.27)	<0.01

TBM= tuberculous meningitis, CI= confidence interval, CXR= chest radiograph, TB= tuberculosis, LAD= lymphadenopathy

DISCUSSION

The main finding in this study is the lower percentage of chest radiograph findings suggestive of certain pulmonary TB in children with TBM, compared to the study by van Weert et al (44% vs 70%)[14], with a need to treat calculation showing that only

1 in 4.39 of children ≤3 years of age with TBM are likely to have certain TB on chest radiograph. The lower proportion of certain pulmonary TB in our study compared to van Weert et al could potentially be explained by our 2 reviewers reaching consensus on chest radiograph findings thereby minimizing the possibility of over-reporting of chest radiograph findings.[14] Another possible reason could be the difference in the study cohort, with 28% of our TBM group having positive tuberculin skin testing compared to 62% in the HIV-uninfected TBM group of the study by van Weert et al.[14] A normal chest radiograph was found in almost half (46%) of children clinically diagnosed with TBM, and in 52% of cases with microbiologically-confirmed TBM. This less than expected diagnostic sensitivity of the chest radiograph in TBM may impact the scoring of future diagnostic algorithms for the disease.

The most common radiological findings in young children (<5 years) with pulmonary TB is hilar or paratracheal lymph nodes[19]. This age group also has a higher risk for developing lympho-bronchial TB due to small airway size[15]. Our findings on chest radiograph of visible lymph nodes, complicated lymph node disease and airway compression were significant in children ≤3 years, confirming that this is the predominant radiological finding in young children. TBM stage did not affect the radiographic picture.

Sixteen of eight-four (19%) patients had radiological evidence of airway compression highlighting the need for pulmonary assessment, including flexible bronchoscopy[20]. The smaller percentage of patients with airway compression, compared to a reported figure of 41-63%[20], could possibly be explained by differences in the immune response between pulmonary TB in isolation versus pulmonary TB in the setting of CNS involvement. A better understanding of immunology in CNS TB is warranted[3].

Inter-observer variability is a well-recognized problem in the interpretation of chest radiographs in children with pulmonary TB. Swingler et al have reported difficulty in distinguishing lymphadenopathy from a normal thymus and were not able to distinguish normal from pathological nodes[21]. The areas most reliable for lymphadenopathy were the right hilum and the sites around the carina[22].

The uniform research case definition for TBM by Marais et al. uses chest radiograph findings as part of the scoring criteria[10]. The score weighting of a miliary pattern is higher than that of active TB on chest radiograph (excluding miliary TB). Our finding that hilar lympadenopathy is the more common finding of certain TB on chest radiograph, in both suspected and definite TBM, suggests that its weighting may have to be reconsidered.

A limitation of our study was the small number of HIV co-infected patients (7%), which did not allow separate statistical analysis of this group. This low percentage is consistent with a previous study that found that only 7% of 123 children with clinically diagnosed TBM had HIV co-infection[23]. The low number of microbiologically-confirmed TBM cases, (31/84), is another limitation but not unexpected in a cohort of this age group[5-9]. CSF NAATs offer improved sensitivity (27/84; 32.1%), compared to CSF culture (13/84; 15.5%), and a potential for same day diagnosis. A further limitation is that all the chest radiographs were from patients with TBM. A sample that includes other forms of meningitis could allow improved analysis of disseminated TB (miliary pattern on chest radiograph).

The main finding of this study is that about half of children with suspected and proven TBM have a normal chest radiograph. Significant chest radiograph findings in children ≤3 years of age were the presence of certain TB, complicated lymph node disease and the presence of airway compression. However, only 1 in 4.39 of children ≤3 years of age with TBM were likely to have certain TB on chest radiograph. Apart from a lower proportion of airway compression, the radiological findings of pulmonary TB in the setting of TBM, irrespective of stage of disease, did not differ from those reported for pulmonary TB in isolation. Definite evidence of TB on a chest radiograph remains valuable supportive evidence for TBM in a patient suspected of having the disease. However, in cases with a normal chest radiograph, diagnosis of TBM depends even more on microbiological confirmation of the disease.

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CONFLICT OF INTEREST

None of the authors declared a conflict of interest.

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