ORIGINAL ARTICLE

Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis

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Objective: To estimate the diagnostic accuracy of chest radiography in the detection of chest lymphadenopathy in children with clinically suspected pulmonary tuberculosis.
Methods: Design: Prospective cross sectional study. Setting: A short stay ward in a children's hospital in South Africa. Patients: Consecutive children under 14 years of age admitted with suspected pulmonary tuberculosis. Diagnostic test: Antero-posterior and/or lateral chest *x* rays interpreted independently and blind to the reference standard by three primary care clinicians and three paediatricians, all with a special interest in tuberculosis. Reference standard: Spiral chest computed tomography (CT) with contrast injection.
Results: One hundred children (median age 21.5 months) were enrolled. Lymphadenopathy was present in 46 of 100 reference CT scans and judged to be present in 47.1% of *x* ray assessments. Overall sensitivity was 67% and specificity 59%. Primary care clinicians were more sensitive (71.5% *v* 63.3%, p = 0.047) and less specific (49.8% *v* 68.9%, p<0.001) than paediatricians. Overall accuracy was higher for the paediatricians (diagnostic odds ratio 3.83 *v* 2.49, p = 0.008). The addition of a lateral to an antero-posterior view did not significantly increase accuracy (diagnostic odds ratio 3.09 *v* 3.73, p = 0.16). Chance adjusted inter-observer agreement (κ) varied widely between viewer pairs, but was around 30%.
Conclusions: Detection of mediastinal lymphadenopathy on chest *x* ray to diagnose pulmonary tuberculosis in children must be interpreted with caution. Diagnostic accuracy might be improved by refining radiological criteria for lymphadenopathy.

Tuberculosis is difficult to diagnose in children because of the non-specific symptoms and infrequent isolation of organisms. Strong reliance is thus often placed on chest radiography, with mediastinal lymphadenopathy regarded as a radiological hallmark of primary tuberculosis.[1] The World Health Organization's proposed diagnostic criteria for pulmonary tuberculosis include a "suggestive appearance on chest radiograph" as one of the criteria for probable tuberculosis.[2] Other diagnostic scoring systems for childhood tuberculosis also include radiographic changes.[3–5] Knowledge of the validity and reliability of the detection of radiographic lymphadenopathy is thus important for the diagnosis of childhood tuberculosis. In a MEDLINE literature search (to May 2004) we were unable to identify any studies of the validity of the radiographic detection of lymphadenopathy in any condition in children. The only identified study of observer variation found an average inter-observer agreement (weighted κ) of 33% (range for six observer pairs: 14%–52%) and intra-observer agreement of 55% (range for four observers: 44%–71%).[6] The poor observer agreement suggests low validity on average but, as no reference standard was used, it was not possible to determine whether some observers were correct in their assessment or whether all were incorrect. There is thus a need to assess the accuracy of lymph node detection against a reference standard, and to identify and validate specific diagnostic criteria for lymphadenopathy.

The use of lateral *x* ray views in routine practice adds to the resource implications of chest radiography as well as exposure to radiation. An assessment (using a reference standard) of the extent to which accuracy is improved by lateral views would inform policies regarding the use of lateral views.

This study was performed to estimate the validity and reliability of the detection of chest lymphadenopathy by conventional radiography in children with clinically suspected tuberculosis.

METHODS

Study population

Consecutive eligible children under 14 years of age admitted with suspected tuberculosis to the Red Cross Children's Hospital, Cape Town, were prospectively enrolled. Suspected tuberculosis was defined as pulmonary infiltrates on chest radiography plus at least one of: a positive tuberculin skin test; a family or other significant tuberculosis contact; failure to gain weight over the previous 2 month period; and chronic cough for longer than 1 month. Computed tomography (CT) was usually performed under sedation, and children with arterial oxygen saturation below 93% or the presence of upper airways obstruction were thus excluded. Red Cross Children's Hospital is situated in the Western Cape Province of South Africa, which has one of the highest incidences of tuberculosis in the world (468/100 000 in 1998).[7]

Chest *x* rays and reference standard

The chest *x* rays were antero-posterior (AP) and lateral views obtained during routine care. All chest radiographs were performed erect with 200 speed screens out of bucky at a film focal spot distance of 150 cm.

The reference standard was CT chest scan with contrast injection, obtained as soon as feasible after chest *x* ray, and always within 3 days. Spiral CT scans were performed with

Abbreviations: AP, antero-posterior; CT, computed tomography

5 mm collimation after an intravenous bolus hand-injection of low osmolar non-ionic contrast medium (dose: 2 ml/kg) on a General Electric Prospeed Fast scanner (Yokogawa Medical Systems, Toyko, Japan). Scans were performed from the thoracic inlet to an arbitrary level just below the hilar region determined on the scanogram, to reduce the radiation dose to the patient. The reference standard for the primary analysis was the presence of enlarged lymph nodes, taken as any node measuring 1 cm or more in any dimension at any site, as measured by a paediatric radiologist blind to the chest *x* ray findings. One previous small study has reported CT transverse axis measurements ranging from 4 to 7 mm (depending on site) as the cut off for normality in children with tuberculosis and a normal chest *x* ray.[8] In our study, identification of the transverse axis was not always possible because of matted and irregularly shaped tuberculous node masses. A cut off of 1 cm or more in any dimension or site was thus taken as representing definitely enlarged masses. The initially intended reference standard was the presence of any lymph nodes detectable on CT scan determined by consensus by a national panel of four radiologists experienced in tuberculosis radiology and using a composite assessment including radiographic features such as shape, position, and changes in density and contrast enhancement. This composite assessment showed only moderate inter-observer agreement and was thus used in a secondary analysis only.[9] All assessments of reference standards were performed blind to chest radiographic findings.

Observers

Three observers from two groups working in metropolitan Cape Town were studied: (i) paediatricians with a special interest in the diagnosis and management of tuberculosis; and (ii) doctors working in local primary care tuberculosis clinics.

Viewing of films

Each observer viewed chest *x* rays individually and blind to the reference standard. The clinical information provided was that the children had failure to gain weight over the previous 2 months, or cough for more than 2 months, or a close tuberculosis contact. For each film viewers were asked to answer the question ''Is lymphadenopathy present?''. Lymphadenopathy was recorded as ''Present, confident'', ''Present, equivocal'', ''Absent, equivocal'', or ''Absent, confident''. No criteria for lymphadenopathy were prescribed.

Each viewer independently examined three different combinations of the AP and lateral *x* rays for each child. Firstly AP films alone were examined in random order in sittings of a length and frequency convenient to the reader, usually two sittings of 50 films each. The second viewing was of the same AP films, this time also with lateral views, viewed in a different random order, using the same procedure as before. Finally, the lateral views alone were viewed in the initial random order.

Analysis

Sample size

Assuming a prevalence of lymphadenopathy of 30%, sensitivity of 67%, and specificity of 67% for the detection of lymphadenopathy, and a single viewing of each *x* ray, 100 *x* rays would have produced 95% confidence intervals (95% CI) for likelihood ratios for positive and negative findings of 1.3 to 3.0, and 0.29 to 0.85, respectively. The repeated measurements (using different views) and multiple viewers in each group would have increased the power of our estimates, narrowing the confidence intervals. Therefore we aimed for a sample of 100 patients.

The κ coefficients were calculated for a binary present/absent assessment. Diagnostic accuracy was expressed as sensitivity and specificity for binary present/absent assessments and as likelihood ratios for more than two categories of assessment.[10] As a measure of overall accuracy, we calculated the diagnostic odds ratios for a binary present/absent assessment.[11] The data were represented by a multiway contingency table and the diagnostic statistics defined as appropriate functions of the response frequencies. Categorical modelling was used to calculate the confidence intervals and also assess statistical significance of the diagnostic statistics. This method was used to ensure that the statistical dependence of the assessments on all the other variables was correctly incorporated.

Written informed consent for chest radiography and CT scan was obtained from the parent or legal guardian of eligible children. Confidentiality of viewers' identities was ensured by means of a code known only to the study nurse.

RESULTS

One hundred children were enrolled between 5 March and 14 August 2001. The median age (interquartile range) was 21.5 (16–31) months, 54% were male, 72 of 94 (76.6%) had failed to gain weight in the previous 2 months, 43 of 92 (46.7%) had a close contact with tuberculosis, and 39 of 87 (44.8%) had been coughing for longer than 1 month. Lymphadenopathy of more than 1 cm was present in 46 of the 100 reference CT scans, and lymph nodes of any size in 92 scans.

Table 1 shows, for each viewer, the number of chest *x* rays assigned to each of the four assessment categories. Lymphadenopathy was judged to be present in 47.1% of cases and 57% of assessments (positive or negative) were equivocal, ranging for individual viewers from 21% to 99%.

Overall sensitivity was 67% and specificity 59%. The sensitivity and specificity of groups of viewers and of the three views are shown in table 2. Primary care clinicians were generally more sensitive (71.5% *v* 63.3%, p = 0.047) and less specific than paediatricians (49.8% *v* 68.9%, p<0.001). Overall accuracy, as expressed by the diagnostic odds ratio, was higher for the paediatricians (3.83% *v* 2.49, p = 0.008). Use of AP together with lateral views showed a

Table 1 Number (%) of chest *x* ray views assigned by each viewer to each assessment category

	Observers						
	Paediatricians			Primary care doctors			
	Viewer 1	Viewer 2	Viewer 3	Viewer 1	Viewer 2	Viewer 3	Total
Assessment							
Absent, confident	41 (13.7)	141 (47.0)	139 (46.3)	43 (14.3)	29 (9.7)	0 (0)	393 (21.8)
Absent, equivocal	76 (25.3)	60 (20.0)	30 (10.0)	52 (17.3)	78 (26.0)	158 (52.7)	454 (25.2)
Present, equivocal	95 (31.7)	56 (18.6)	32 (10.7)	121 (40.3)	124 (41.3)	139 (46.3)	567 (31.5)
Present, confident	88 (29.3)	43 (14.3)	99 (33.0)	84 (28.0)	69 (23.0)	3 (1.0)	386 (21.4)
All *x* rays and views	300	300	300	300	300	300	1800

Three views per viewer per child.

Table 2 Accuracy of detection of lymph nodes

	Sensitivity (%)	95% CI	Specificity (%)	95% CI	% Correct	Diagnostic OR
AP and lateral views (all viewers)	68.1	60.6 to 75.6	63.6	55.8 to 71.4	65.7%	3.7
AP view alone (all viewers)	66.3	57.8 to 74.8	61.1	53.3 to 69.0	63.5%	3.1
Lateral view alone (all viewers)	67.8	60.4 to 75.1	53.4	46.3 to 60.5	60.0%	2.4

OR, odds ratio.

non-significant trend towards a higher diagnostic odds ratio than the use of the AP view alone (3.73 *v* 3.09, p = 0.16) or use of the lateral view alone. The addition of a lateral to an AP view increased sensitivity by 1.8% (95% CI –4.1 to 7.7%) and specificity by 2.5% (95% CI –6.0% to 10.9%). In the secondary analysis using the presence of any node on CT as the reference standard, sensitivity was lower, specificity higher, and overall diagnostic accuracy (diagnostic odds ratios) similar (data not shown).

Likelihood ratios and post-test probabilities for different levels of confidence of detection are shown in table 3. The post-test probability describes the prevalence of lymphadenopathy (CT) among the subgroups of children with radiologically probable (present, confident), possible (present, equivocal), unlikely (absent, equivocal), and absent (absent, confident) lymphadenopathy, respectively. It is equivalent to the positive predictive value for a ''present'' assessment or (100%−negative predictive value) for an ''absent'' assessment. The calculated probabilities are valid only for the prevalence in the sample (46%).

κ was around 30% with wide ranges for different pairs of viewers, from 5 to 55%. Agreement was similar for AP views alone and AP and lateral together, but less good for lateral views alone.

DISCUSSION

This study addresses the accuracy of the detection of lymph nodes using chest *x* rays, not the accuracy of radiographic diagnosis of tuberculosis. However, detection of lymphadenopathy on chest *x* rays is frequently used for diagnosing pulmonary tuberculosis in children in the setting of a clinical suspicion of tuberculosis. The detection of adenopathy has important implications for treatment as those diagnosed with pulmonary tuberculosis are generally treated with a full course of anti-tuberculous therapy, while children with normal *x* rays but a positive skin test would receive treatment for latent infection only.

The accuracy of lymphadenopathy detection was disappointing, both among paediatricians with a special interest in tuberculosis and primary level doctors with extensive experience of tuberculosis. There was ''fair'' agreement between individuals,[10] which was worse for lateral views. The low accuracy among expert observers suggests shortcomings inherent in chest radiography. The diagnostic usefulness of the assessment of lymphadenopathy varied with the confidence with which the finding was made, as illustrated by the post-test probabilities for different findings, given the 46% prevalence of nodes in this study. A confident assessment of the presence of lymphadenopathy on AP plus lateral view would increase the probability of enlarged lymph nodes from the baseline of 46% before chest radiography to 71% afterwards, but an equivocal ''call'' would increase the probability only to 53%. The pre-test probability (prevalence) of 46% is in the range of 40–60% at which diagnostic tests are most useful.[10] If the probability of lymphadenopathy were lower before performing the *x* ray, for example 10%, the post-test probability following a confident assessment of lymphadenopathy would be only 24.5%.

Table 3 Likelihood ratios for different levels of confidence of diagnosis

Lymph nodes of 1 cm or more	Likelihood ratio	95% CI	Post-test probability (%)
Present, confident	2.92	1.97 to 3.87	71.3
Present, equivocal	1.31	0.97 to 1.66	52.7
Absent, equivocal	0.72	0.53 to 0.92	38.0
Absent, confident	0.28	0.16 to 0.39	19.3

All viewers, AP plus lateral views, prevalence of lymphadenopathy of 46%.

There was no statistically significant difference in the use of AP view alone or together with the lateral view, but the confidence intervals for the differences in sensitivity and specificity are wide. Assuming the 46% probability of lymphadenopathy in this study, the point estimate for the improvement in accuracy suggests that 121 lateral views would be needed to detect one additional case of lymphadenopathy and 74 to avoid one false positive. The most favourable 95% confidence intervals for an increase in sensitivity and specificity suggest that, given the imprecision of the estimate, the most optimistic reasonable expectation of benefit would require 28 lateral views to detect one additional case and 17 to avoid one false positive.

The primary care practitioners were more sensitive and less specific as a group than the paediatricians, suggesting that they had a lower threshold for diagnosing lymphadenopathy. The significantly higher diagnostic odds ratio for the paediatricians suggests greater overall accuracy, but it is not possible from this study to conclude whether this difference is due to the difference in background or experience of the groups, or to other confounding factors.

A strength of this study is the defined, prospectively collected sample of a range of young children likely to need radiological assessment for the presence of tuberculosis. This clinically meaningful range of *x* rays is likely to result in more valid estimates of accuracy than comparisons of known cases and normal controls, or of highly selected groups of patients who happened to have a CT chest scan as part of their care.[12]

An important limitation of the study is the difficulty in establishing a credible reference standard. The presence of any lymph node on CT scan was regarded in 1993 as abnormal in children,[13] but the detection of nodes has presumably improved with progressively better scanner quality. This criterion may thus no longer be valid, especially for spiral CT used in this study. This is illustrated by the detection of any lymph node in 92% of scans studied, which is far more than the proportion of children expected to have tuberculosis in this clinical sample. This very high proportion of ''positive'' CT scans made meaningful analysis with this reference standard very difficult and suggests that the CT criterion of any thoracic lymph node has little discriminatory value in the diagnosis of tuberculosis in children. There was also only moderate inter-observer agreement on this assessment.[9] The use of stricter criteria for the reference standard was also problematic. Size cut offs for abnormal nodes in children with tuberculosis have been described only from a small sample of 15 children with tuberculosis and a normal *x* ray, as compared with children without tuberculosis.[8] These

cut offs were not useful in our sample of children with more advanced disease because of the matted and irregular appearance of the nodes that made identification of a transverse axis difficult in some scans. A somewhat arbitrary cut off of 1 cm or more in any dimension was thus taken as the primary reference standard for this study, representing definitely enlarged or abnormal lymph nodes or masses. Such a reference cut off for relatively obvious or advanced lymphadenopathy is expected to produce falsely high sensitivity of conventional chest radiography. Similarly, the more inclusive cut off of any small node in the secondary reference standard is expected to produce falsely high specificity. However, even taking together the unrealistically favourable estimates of sensitivity for the reference standard (68% for AP plus lateral view) and specificity for the secondary reference standard (79%), accuracy remains unimpressive.

The inter-observer agreement for paediatricians in this study (κ 0.36) is similar to the weighted κ of 0.33 in a previous study of paediatric pulmonologists reading similar *x* rays,[6] and is lower among the primary care doctors.

Although the study sample included children under 14 years of age, the median age was 21.5 months, and the findings do not necessarily apply to older individuals. However, the diagnosis of primary pulmonary tuberculosis is particularly difficult in these young children who do not produce sputum, and in whom the diagnosis is more frequently based on detection of lymphadenopathy on chest *x* ray. The assessment of diagnostic accuracy in this study was of current practice. No criteria for the detection of nodes were prescribed. The diagnostic accuracy of specific criteria, and combinations of criteria, will be examined in the next phase of this study.

In conclusion, the low accuracy of both specialist paediatricians and primary level practitioners, all experienced in assessing lymphadenopathy, suggests that caution should be exercised in using the presence of radiographic lymphadenopathy to diagnose tuberculosis in children, especially in the many cases where the findings are equivocal. It is possible that diagnostic accuracy will be improved by refining radiological criteria for lymphadenopathy.

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Competing interests: none declared

What is already known on this topic

- The presence of lymphadenopathy on chest *x* ray is frequently used for diagnosing pulmonary tuberculosis in children
- Inter-observer agreement in the detection of lymphadenopathy has been found to be low in a single study
- The diagnostic accuracy of lymph node detection compared with a reference standard is not known

What this study adds

- The diagnostic accuracy of experienced specialist paediatricians and primary level practitioners in detecting radiographic lymphadenopathy was low
- The addition of a lateral to an antero-posterior view did not significantly increase accuracy

Ethical approval: written informed consent for chest radiography and CT was obtained from the parent or legal guardian. The study was approved by the Research Ethics Committee of the University of Cape Town (Ref No: 258/2000)

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