Well-defined symptoms are of value in the diagnosis of
childhood pulmonary tuberculosis

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Key words: well-defined, persistent, symptoms, tuberculosis
Abstract

Background: The diagnosis of childhood pulmonary tuberculosis presents a major challenge, as the symptoms traditionally associated with tuberculosis are exceedingly common in children from endemic areas. The natural history of tuberculosis in children illustrate that progressive disease is associated with symptoms that have a persistent, non-remitting character. The aims of the study were to investigate whether improved symptom definition is possible in a clinical setting, and whether the use of these well-defined symptoms have improved value in the diagnosis of childhood pulmonary tuberculosis.

Methods: A prospective, community-based study was conducted in two suburbs of Cape Town, South Africa. All children (<13 years), presenting to the local community clinic with a cough of more than 2 weeks duration, were referred to the investigator. Parents completed a symptom-based questionnaire, where-after reported symptoms were characterised in a standard fashion.

Results: Of the 151 children enrolled, 21 (15.6%) reported symptoms with a persistent, non-remitting character. Tuberculosis was diagnosed in 16 (10.5%) children, all of whom reported these symptom characteristics. A persistent, non-remitting cough was reported in (15/16, 93.8%) children with tuberculosis and (2/135, 1.5%) children without tuberculosis, indicating a specificity of 98.5% (135/137). Persistent fatigue of recent onset was also sensitive (13/16, 81.3%) and specific (134/135, 99.3%). Persistent fever and/or chest pain were exclusively reported in children with tuberculosis, but were present in only 4/16 (25.0%) children with tuberculosis.

Conclusion: The use of well-defined symptoms is feasible, even in resource-limited settings, and may offer significantly improved value in the diagnosis of childhood pulmonary tuberculosis.
Background

The diagnosis of childhood pulmonary tuberculosis presents a major challenge, because bacteriological confirmation is rarely achieved and radiological signs are often difficult to interpret. Various symptom-based diagnostic approaches have been developed, but these were mostly based on clinical experience and lack proper validation.

Hospital-based studies have reported widely variable results regarding the utility of a symptom-based approach to the diagnosis of childhood pulmonary tuberculosis. However, the selection bias inherent to these hospital-based studies limit extrapolation to the community level. To our knowledge, only one study has documented the prevalence of symptoms traditionally associated with tuberculosis, such as a prolonged cough, night sweats, subjective weight loss etc., in a random selection of children from an endemic area. This community-based survey found that these poorly defined symptoms were exceedingly common, even in children without tuberculosis.

The finding prompted a careful re-evaluation of the symptoms associated with tuberculosis in children, which is best documented in the pre-chemotherapy literature that described the natural history of tuberculosis in children. According to this literature, children can be categorized into two main risk groups; high-risk (children <3 years of age and/or immune compromised children) and low-risk (immune competent children ≥3 years of age). In low-risk children, progressive disease following primary infection with M.tuberculosis was rare, and it was associated with persistent, non-remitting symptoms. In high-risk children, progressive disease occurred more frequently; symptoms were also persistent and non-remitting, but sometimes had a more acute onset. In the vast majority of children (>95%), disease progression occurred within 12 months of primary infection. These disease descriptions from the pre-chemotherapy literature identified two previously unexplored symptom characteristics that may improve specificity, namely to focus on persistent, non-remitting symptoms of recent onset.

The aims of this study were to investigate whether improved symptom definition is possible in a clinical setting, and whether the use of these well-defined symptoms have improved value in the diagnosis of childhood pulmonary tuberculosis.

Methods

A prospective, community-based study conducted from September through December 2003 in Cape Town, South Africa.

Setting

The study community is adjacent to the community where the previous symptom survey was done. These communities are similar with regards to ethnic and socio-economic parameters, high tuberculosis incidence (>300/100 000 new smear
positive cases per year) and relatively low prevalence of human immunodeficiency virus (HIV) infection (<8%).12

**Study population**
All children under the age of 13 years, who presented to the local clinic with a cough of more than 2 weeks duration, not responding to first-line antibiotic therapy (5 days of oral amoxicillin), were referred to the investigator. A standard symptom-based questionnaire was completed and reported symptoms were individually characterised. A tuberculin skin test (TST) and chest radiograph were performed in all children.

**Questionnaire**
The questionnaire was identical to the one used in the previous community-based symptom survey.8 Parents were asked about the presence and duration of symptoms during the previous 3 months, including cough, shortness of breath, chest pain, haemoptysis, fever, fatigue, night sweats, anorexia and weight loss. Reported symptoms were then characterised in a standard fashion to identify those with a persistent, non-remitting character.

**Symptom characterization**
Parents were asked the following standard questions to characterize reported symptoms; 1) Is your child symptomatic at present? and 2) What is/was the uninterrupted symptom duration? This allowed differentiation between persistent, non-remitting symptoms and those that resolved spontaneously (without specific anti-tuberculous treatment). Children not diagnosed with tuberculosis after initial screening were treated according to the most likely alternative diagnosis and followed up after 2-4 weeks. If symptoms persisted beyond 4 weeks of follow-up, a repeat TST and chest radiograph were performed. The uninterrupted symptom duration, until spontaneous symptom resolution or the onset of anti-tuberculosis chemotherapy, was recorded in weeks.

In addition, three distinct cough patterns were differentiated; 1) acute cough with delayed recovery, 2) recurrent acute cough and 3) persistent, non-remitting cough. (Fig. 1) Parents were shown a graphic illustration of these three cough patterns and requested to identify the pattern that best described their child’s condition. Questions were piloted in the community prior to the onset of the study.

**Weight loss**
Both subjective (reported) and objective weight loss were recorded. Objective weight loss was defined as crossing at least one centile line in the preceding 3 months or having lost more than 10% of bodyweight (minimum 1kg) over any time interval.

**Tuberculin skin test (TST)**
A tuberculin skin test, using intra-dermal injection of 2 tuberculin units of *M. tuberculosis* PPD RT 23 (Statens Serum Institut, Copenhagen, Denmark), was performed on the volar aspect of the left forearm. The largest transverse diameter of induration was measured after 48-72 hours.
**Chest radiograph (CXR)**

Standard antero-posterior and lateral views were done. Two independent experts, blinded to all clinical information, evaluated the chest radiographs and documented their findings on a standard report form.

**M. tuberculosis culture**

Children with a CXR suggestive of tuberculosis had sputum or gastric aspirate samples taken for culture. Samples were inoculated into Bactec 12B liquid medium (Becton Dickinson, Sparks, MD, USA). Positive cultures were confirmed as *M. tuberculosis* by polymerase chain reaction (PCR).

**Definitions used for clinical diagnoses**

Probable tuberculosis was defined as a CXR indicative of tuberculosis, confirmed by two independent experts. Where the two objective experts disagreed, a third expert made the final decision. Confirmed tuberculosis was defined as isolation of *M. tuberculosis* on culture. Viral infection was defined as a transient runny nose and/or fever at symptom onset, no clinical response to antibiotics and no CXR signs suggestive of tuberculosis. Asthma was defined as recurrent cough episodes together with current and/or exercise-induced wheeze and bronchodilator response, without CXR signs suggestive of tuberculosis.

Children diagnosed with probable or confirmed tuberculosis received anti-tuberculosis treatment and were offered a rapid human immuno-deficiency virus (HIV) test (ABBOT Determine HIV1/2) after appropriate counselling. All children not treated for tuberculosis were monitored for a period of 6 months to exclude subsequent treatment for tuberculosis. The study was approved by the Ethics Review Board of Stellenbosch University, the City of Cape Town Health Department and local health committees.

**Statistical analysis**

Statistical analysis was done with SPSS for Windows version 11.0. Symptom frequencies and symptom characteristics were compared between age groups and between different clinical diagnoses. Comparisons were performed using the Mantel-Haenszel $\chi^2$ test and the Fisher’s Exact test to determine two-sided p-values.

**Results**

Of 156 children referred, 151 (96.8%) were enrolled in the study. Four children did not turn up for evaluation and study participation was refused in 1 child. A questionnaire and TST was completed in all 151 children and a chest radiograph in 129 (85.4%). The 22 children who did not receive a CXR, all reported spontaneous symptom resolution before evaluation by the investigator. Table 1 reflects the demographics and clinical diagnoses; 102 (67.6%) children were less than 5 years of age, while viral infection (100, 66.2%) and asthma (24, 15.9%) were the most frequent clinical diagnoses.

Viral infection was the most common diagnosis in all age groups, particularly in children less than 2 years of age (45/54, 83.3%). The frequency of asthma peaked in the 5 to 9 year age group (16/38, 42.1%), where it rivalled viral infection as the
most common clinical diagnosis. Tuberculosis was diagnosed in a total of 16/151 (10.6%) children, of whom 9 (56.2%) were less than 5 years of age. The two radiology experts disagreed in 2 cases, judged to have tuberculosis; 1 had culture confirmation, the other was less than 2 years, had a TST of 18mm and showed excellent clinical response to treatment. Bacteriological confirmation was achieved in 10/16 (62.5%) children with tuberculosis. The bacteriologic yield was highest in children with cavitating disease (4/4, 100%), and those with alveolar consolidation (4/6, 66.7%). None of the children had clinical signs indicative of acquired immune deficiency syndrome (AIDS). All 16 diagnosed with tuberculosis were tested for HIV; none were HIV-infected.

Figure 2 shows the association between specific cough patterns and clinical diagnoses. An acute cough with delayed recovery was most common in children under 2 years of age, and was associated with a viral infection diagnosis. Recurrent cough episodes were most common in children aged 2 to 10 years, and associated with either recurrent viral infections or asthma. A persistent, non-remitting cough was uncommon in all age groups and was almost exclusively (16/18, 88.9%) associated with tuberculosis. Only two children, without tuberculosis, reported a persistent cough beyond 4 weeks of follow-up. One was an ex-premature baby with bronchiectasis whose symptoms were not of recent (<12 months) onset, and the other a child with atypical pneumonia in whom the cough resolved over a period of two months. No child who reported spontaneous symptom resolution was diagnosed with tuberculosis in the 6 months subsequent to the study.

Table 2A reflects the frequency of the 5 most relevant symptoms (cough, chest pain, weight loss, fatigue and fever), in children with and without tuberculosis. In agreement with the inclusion criteria, all children reported a cough. Additional symptoms were common; chest pain (33, 21.9%), weight loss (40, 26.5%), fatigue (37, 24.5%), fever (50, 33.1%). Only weight loss and fatigue were significantly more frequent in children with tuberculosis. The results for difficult breathing, haemoptysis, poor appetite (anorexia) and night sweats are not reported, as parents showed variable symptom interpretation. Difficult breathing was interpreted as either dyspnoea at rest or exercise induced wheezing. Haemoptysis was uncommon, being reported in only two children, neither of whom had tuberculosis, but it was frequently confused with nose bleeds or haematemesis. Night sweats were frequently reported (37/151, 24.9%), especially in children less than 2 years of age (20/54, 37%) who shared a bed with their parents; it was generally not associated with a tuberculosis diagnosis.

Table 2B focuses on symptoms of recent onset with a persistent, non-remitting character. These well-defined symptoms were uncommon; cough (16, 10.6%), chest pain (4, 2.6%), objective weight loss (9, 6.0%), fatigue (14, 9.3%) and fever (4, 2.6%), and were all significantly associated with tuberculosis. A persistent, non-remitting cough was reported in (15/16, 93.8%) children with tuberculosis and (2/135, 1.5%) children without tuberculosis, indicating a specificity of 98.5% (135/137). Persistent fatigue of recent onset was also sensitive (13/16, 81.3%) and specific (134/135, 99.3%). Persistent fever and/or chest pain were exclusively reported in children with tuberculosis, but were present in only 4/16 (25.0%) children with tuberculosis, two of whom had a pleural effusion.
Discussion

The results of this study demonstrate that it is possible to identify symptoms with a persistent, non-remitting character at primary health care level, even in resource-limited settings. It may be difficult to distinguish between the different cough patterns at the initial evaluation, but clinical follow-up after 2-4 weeks proved to be a valuable diagnostic tool. Only 2 children without tuberculosis reported a non-remitting cough that persisted beyond 2-4 weeks of follow-up.

In this study, well-defined symptoms had excellent diagnostic value. Both a persistent cough and/or persistent fatigue of recent onset were highly sensitive and specific. Persistent chest pain, confirmed by the child, was the presenting symptom in both children with tuberculous pleural effusion, which correlates with the typical clinical picture described in children with this disease manifestation, although it was present in only 25% of all children diagnosed with tuberculosis. Subjective and objective weight loss showed poor correlation with each other, but both were significantly associated with tuberculosis. In tuberculosis endemic settings, the diagnostic value of weight loss may be enhanced by first eliminating other common causes of poor weight gain, such as worm infestation and food insecurity.

The study had several limitations. It was questionnaire driven and thus subject to recall bias and reporter subjectivity. Recall bias was limited by focusing on current symptoms. Reporter subjectivity was reduced by standard symptom characterisation. Investigator bias was limited, as symptoms characterisation was done before the TST or CXR results were known. The study population was a very select group; only those presenting with a cough of more than 2 weeks duration, not responding to first-line anti-biotics, were recruited. The use of a therapeutic trial of broad spectrum antibiotics is widely advocated, but is controversial, as patients with tuberculosis may show some symptomatic response, and anti-tuberculosis treatment of infectious patients may be delayed. However, first-line antibiotics should not lead to complete symptom resolution in children with tuberculosis. In this study the trial of antibiotics was given before referral, not prolonging diagnostic delay, and none of the children with complete symptom resolution required anti-tuberculosis treatment in the subsequent 6 months, indicating that they did not have tuberculosis.

In conclusion, the use of well-defined symptoms is feasible, even in resource-limited settings, and may offer significantly improved value in the diagnosis of childhood pulmonary tuberculosis. A large prospective, community-based study is required to validate the diagnostic value of this symptom-based approach.
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There are no competing interests to declare.

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What is already known about this topic?

- There is a need to reassess the value of symptom-based approaches for the diagnosis of childhood pulmonary tuberculosis, especially in high-burden settings with limited resources
- Current symptom-based diagnostic algorithms are poorly validated; symptoms traditionally associated with tuberculosis are too common in children from high-burden communities to be of real diagnostic value

What this study adds

- Well-defined symptoms, including only persistent, non-remitting symptoms of recent onset, are uncommon and offers potentially excellent diagnostic value in HIV-uninfected children in high-burden tuberculosis settings
- Prospective, community-based studies are required to validate the diagnostic value of these well-defined symptoms in communities with a high-burden of tuberculosis
References

11. Statistics South Africa (National census 2001)
Table 1
Demographics and clinical diagnoses of all children enrolled (n=151)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>79 (52.3)</td>
</tr>
<tr>
<td>Female</td>
<td>72 (47.7)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>54 (35.8)</td>
</tr>
<tr>
<td>2-4 years</td>
<td>48 (31.8)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>38 (25.2)</td>
</tr>
<tr>
<td>10-12 years</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td><strong>Clinical diagnoses</strong></td>
<td></td>
</tr>
<tr>
<td>Viral infection</td>
<td>100 (66.2)</td>
</tr>
<tr>
<td>Bacterial infection (good antibiotic response)</td>
<td>10 (6.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>24 (15.9)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>16 (10.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

A total of 156 children were referred of whom 151 (96.8%) were enrolled.
Table 2
A) Symptoms reported in children without TB compared to children with TB

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No TB (n=135)</th>
<th>TB (n=16)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>1335 (100%)</td>
<td>16 (100%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chest pain</td>
<td>29 (21.8%)</td>
<td>4 (25.0%)</td>
<td>1.2 (0.4 - 4.1)</td>
<td>0.752</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30 (22.6%)</td>
<td>10 (62.5%)</td>
<td>5.8 (2.0 - 17.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (17.3%)</td>
<td>14 (87.5%)</td>
<td>34.1 (7.3 – 160.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>45 (33.8%)</td>
<td>5 (31.3%)</td>
<td>0.9 (0.3 – 2.8)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

B) Persistent, non-remitting symptoms reported in children without TB compared to children with TB

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No TB (n=135)</th>
<th>TB (n=16)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>2 (1.6)</td>
<td>15 (93.8%)</td>
<td>2.010.0 (119.5-33812.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain (confirmed by child)</td>
<td>0 (0.0%)</td>
<td>4 (25.0%)</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight loss (objective)</td>
<td>3 (2.6%)</td>
<td>6 (37.5%)</td>
<td>25.0 (3.4–184.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.8%)</td>
<td>13 (81.3%)</td>
<td>580.7 (56.3 – 5990.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>0 (0.0%)</td>
<td>4 (25.0%)</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TB – tuberculosis
OR – Odds ratio, CI – Confidence interval
NA – not applicable (2A - all children coughed, 2B - no children without TB reported persistent chest pain or fever)
Fig. 1
Cough patterns that were differentiated

1) Acute cough with delayed recovery
2) Recurrent acute cough
3) Persistent, non-remitting cough

Intensity of Cough

Duration in weeks

1w  2w  3w  4w
Figure 2
The frequency of specific cough patterns associated with different clinical diagnoses (n=151)
Diagnosis of childhood pulmonary tuberculosis

Well defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis.

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