

TB or not TB?

An evaluation of children with an incorrect initial diagnosis of pulmonary tuberculosis

R. P. Gie, N. Beyers, H. S. Schaaf, E. D. Nel,
N. A. Smuts, S. van Zyl, P. R. Donald

Object. The aim of the study was to identify diagnoses that are confused with pulmonary tuberculosis in children.

Design. Prospective, investigative clinical study.

Setting. Tertiary care teaching hospital and an urban tuberculosis clinic in an area with a very high incidence of pulmonary tuberculosis (> 800 new cases/100 000/year).

Patients. Children suspected of having tuberculosis, children followed up for pulmonary infiltrates with eosinophilia and children with congenital pulmonary anomalies were investigated.

Intervention(s). None.

Outcome measure. Pulmonary tuberculosis was diagnosed using modified World Health Organisation criteria and the diagnoses of those children not suffering from pulmonary tuberculosis were analysed.

Results. Of the 354 children initially suspected of suffering from tuberculosis 71 (20%) were found to be suffering from other pulmonary disease, viz. pneumonia or bronchopneumonia (29%), bronchopneumonia with wheezing (18%), and asthma with lobar or segmental collapse (12%). Of 14 children suffering from pulmonary infiltrates with peripheral eosinophilia 6 (43%) were initially incorrectly diagnosed and treated for tuberculosis. Of 54 children with congenital pulmonary anomalies, 8 (15%) were treated for tuberculosis before the correct diagnosis was made. Congenital anomalies most often confused with tuberculosis were unilateral lung hypoplasia, bronchogenic cyst and tracheal bronchus with an anomalous lobe.

Conclusions. The criteria for diagnosing tuberculosis in children is complicated in areas with a high incidence of tuberculosis and poor socio-economic circumstances where many children presenting with conditions other than tuberculosis will be in contact with an adult case of pulmonary tuberculosis. The commonest conditions confused with tuberculosis are pneumonia, bronchopneumonia and asthma. Pulmonary infiltrates with

Departments of Paediatrics and Child Health and Radiology,
University of Stellenbosch, Tygerberg, W. Cape

R. P. Gie, M.MED. (PED.), F.C.P.

N. Beyers, F.C.P. (PAED.), M.SC., PH.D.

H. S. Schaaf, M.MED. (PED.)

E. D. Nel, M.MED. (PED.)

N. A. Smuts, F.F.RAD.(D.) (S.A.), B.SC, HONS

S. van Zyl, B.NURS.

P. R. Donald, D.C.H., F.C.P. (S.A.), M.R.C.P., D.T.M.&H., M.D.

peripheral eosinophilia and congenital lung abnormalities should be considered especially if the children have an atypical clinical picture or do not respond to tuberculosis treatment.

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The diagnosis of pulmonary tuberculosis (PTB) in childhood is fraught with imprecision and is usually made by drawing upon a constellation of physical signs, a history of contact with an adult case of PTB, the result of a Mantoux test and a chest radiograph.¹ The symptoms and signs of PTB in childhood are often nonspecific and radiology is often not diagnostic.^{2,3} Tuberculin skin testing will frequently be negative in children with tuberculosis and the skin test reading is influenced by a variety of factors, including technique, BCG administration after birth, nutritional status, intercurrent viral infection and age of the child.^{2,3} Gastric aspirate for culture of *Mycobacterium tuberculosis* will seldom be undertaken outside of referral hospitals and when done usually yields positive results in less than 30% of cases.^{4,5} In areas with a high tuberculosis incidence children from disadvantaged socio-economic backgrounds are often exposed to a variety of infections, parasitic diseases and allergens which, when causing disease, will often present with the same nonspecific symptoms and signs as tuberculosis. These children will also frequently be in contact with adults with PTB, so that the diagnosis of childhood tuberculosis will frequently be considered and this may lead to inappropriate anti-tuberculosis treatment.

In this report we describe firstly our experience with a group of children initially suspected but later shown not to have tuberculosis, and secondly the diagnostic confusion caused by cases of pulmonary infiltrates with eosinophilia and congenital pulmonary anomalies which were initially diagnosed as PTB and treated as such.

Patients and methods

The study was undertaken at Tygerberg Hospital, a tertiary care hospital situated in an area with a tuberculosis incidence of more than 800 new cases per 100 000 population per year.⁶

During the study period 354 children were initially suspected of having active PTB by the attending physicians on the basis of history, physical examination or chest radiography.

The children were drawn from three groups. The first group were part of a prospective study which over a period of 16 months evaluated 340 children in the overnight ward who were thought to have PTB.

The second group of 14 children were admitted to the paediatric pulmonology unit with a diagnosis of pulmonary infiltrates with eosinophilia. This diagnosis was made if the child had an absolute eosinophil count greater than $2.5 \times 10^9/l$ and a chest radiograph showed widespread alveolar opacification. All these children responded to anthelmintic drugs, bronchodilators and steroids. In addition, in the majority of cases the diagnosis was confirmed by broncho-alveolar lavage where more than 10% of the cells recovered were eosinophils. Of the 14 children seen over a 6-month period, 6 (43%) had previously been treated for PTB.

The third group of 54 children were referred for evaluation

of congenital pulmonary anomalies. All these children were extensively investigated and the anomalies diagnosed by bronchoscopy, bronchography and computed tomography (CT), and confirmed by excision biopsy. Of the 54 children, 8 (15%) had received treatment for PTB.

All 354 children suspected of having tuberculosis were evaluated for tuberculosis. Evaluation included taking a history of close contact with an adult suffering from active PTB, confirmed weight loss, a Mantoux skin test using 5 IU of PPD and a chest radiograph. Owing to the fact that more than 80% of South African children receive BCG in the neonatal period, a Mantoux test was regarded as significantly positive in the presence of ≥ 15 mm induration. Early morning gastric aspirate specimens from each child were submitted for *M. tuberculosis* culture using a radiometric assay (Bactec). Other investigations, done as clinically indicated, included a full blood count, C-reactive protein concentrations, blood culture, pleural fluid aspiration for microscopy and culture and serology for detection of causative organisms.

Subsequently, these results, as well as the child's response to therapy, were taken into account and the children were reclassified using the criteria proposed by the World Health Organisation¹ and modified by other workers^{7,8} as having probable tuberculosis, confirmed tuberculosis (if *M. tuberculosis* was cultured from the gastric aspirate), or as not having tuberculosis.

In an attempt to ensure that the children classified as not having tuberculosis were correctly diagnosed their hospital folders were re-evaluated after 12 - 24 months to assess if the diagnosis was correct and whether the children subsequently developed tuberculosis.

Results

Of the 354 children suspected of having PTB, 86 (24%) (median age 24.5 months) had probable and 191 (54%) (median age 19 months) confirmed tuberculosis, while 71 (22%) (median age 19 months) were subsequently diagnosed as not having tuberculosis. The diagnoses of the children not having tuberculosis are shown in Table I.

Table I. Final diagnosis in 71 children initially suspected but subsequently found not to have tuberculosis

Pneumonia/bronchopneumonia	22
Bronchopneumonia with bronchospasm	15
Asthma	9
Pneumonia with cavity formation	3
Paraffin inhalation	3
Persistent collapse of a lobe	2
Foreign body	1
Bronchiectasis	1
<i>Moraxella vincenti</i> effusion	1
AV canal defect with azygos vein	1
Liver abscess	1
Pulmonary hypertension due to upper airway obstruction	1
Aspiration pneumonia due to cleft palate	1
Retropharyngeal abscess	1
Chronic cough of unknown origin	1
Congenital pulmonary anomalies	8
Pulmonary infiltrates with eosinophilia	6

Not surprisingly, pneumonia/bronchopneumonia (29%), bronchopneumonia with bronchospasm (18%) and asthma (12%), especially if associated with gastro-enteritis and malnutrition, were the commonest cause of confusion. The most common clinical findings of the children suspected of having tuberculosis were wheezing (37%), crepitations (17%) and weight below the third percentile for age (37%). The children had been in contact with an adult with active PTB in 15 (21%) of the 71 cases where the information was available.

Twenty children (26%) with repeated respiratory symptoms and signs were, without further evidence, erroneously treated for tuberculosis. This was particularly common in the children with asthma (4) and pneumonia with eosinophilia (6) and pulmonary congenital anomalies (8). Poorly controlled asthma can lead to mucus plugging of the bronchi, causing segmental or lobar collapse which on chest radiography is confused with PTB (Fig. 1).



Fig. 1. Chest radiograph of a child after an acute asthma attack which resulted in mucus plugging of the right middle lobe bronchus and lobar collapse.

Six (43%) of the children with pulmonary infiltrates with eosinophilia (mean age 39 months, range 15 - 94 months) were initially diagnosed as having and treated for tuberculosis. These children had a mean duration of symptoms of 450 days (range 90 - 840 days), only 1 had a significantly positive Mantoux test, none had positive cultures of *M. tuberculosis* and none responded to anti-tuberculosis therapy. The chest radiographs of these children revealed perihilar opacifications (interpreted as hilar adenopathy) in 4 and lobar or segmental collapse (interpreted as endobronchial tuberculosis) in 2 (Fig. 2). In addition, 1 child also had a pleural effusion. The single most important diagnostic finding in these children was a mean absolute peripheral eosinophilia count of $9,1 \times 10^9/l$ (range $2,6 - 28,9 \times 10^9/l$). The cause of this severe peripheral eosinophilia was most probably *Ascaris lumbricoides* infestation as all the children had *Ascaris* eggs in their stools. All the children responded to anthelmintics, bronchodilators and a short course of steroids. None of the children followed up developed tuberculosis.

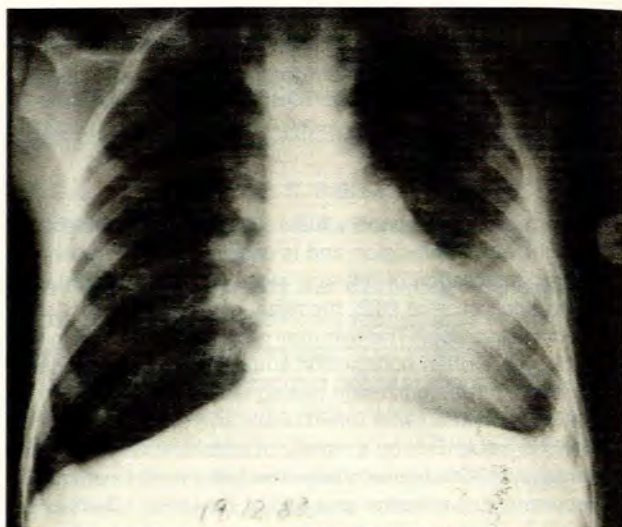


Fig. 2. Chest radiograph of a 7-year-old boy with pulmonary infiltrates with eosinophilia. Dense opacification of the lingula is present, which cleared on steroid therapy.

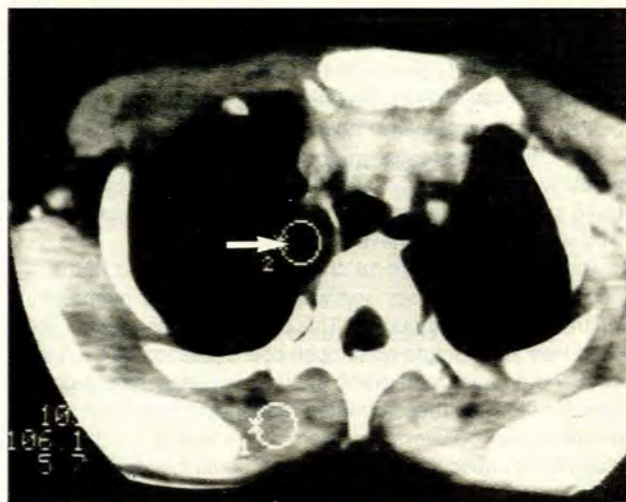
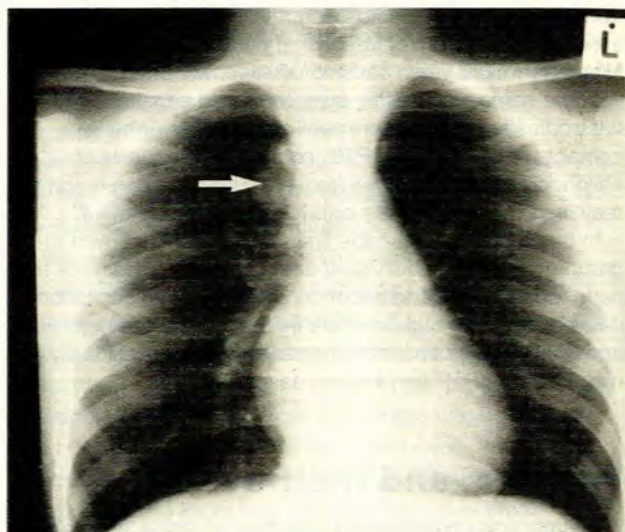


Fig. 3. Chest radiograph (above) and CT scan (below) of an 8-year-old girl with a bronchogenic cyst (arrow) initially mistaken for paratracheal adenopathy.

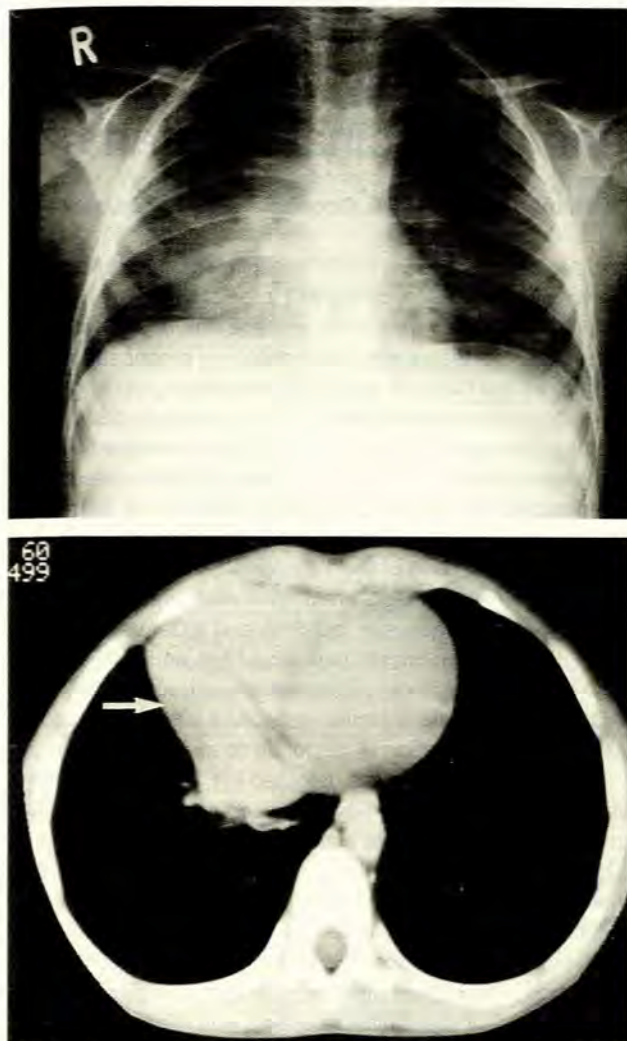


Fig. 4. Chest radiograph (above) and CT scan (below) of a boy with unilateral pulmonary hypoplasia (arrow).

In the 8 children (mean age 34 months) with congenital pulmonary anomalies the most significant finding was that they had experienced symptoms for a mean of 481 days and all 8 children had been fully treated (some more than once) for tuberculosis even though none had a positive skin test or gastric aspirate culture for *M. tuberculosis*. None of the children had responded to anti-tuberculosis therapy.

The chest radiographs of these 8 children showed large masses originally considered as hilar or mediastinal glands in 6 children and dense opacifications regarded as endobronchial tuberculosis in 2. The final diagnoses confirmed on surgery and histology were that of bronchogenic cyst in 4 children (Fig. 3), unilateral lung hypoplasia in 2 (Fig. 4) and a tracheal bronchus supplying a portion of the right upper lobe in 2.

Only 1 of the 71 children initially diagnosed as not having tuberculosis subsequently developed tuberculosis. The child who initially presented with vague symptoms and an interstitial pneumonitis on chest radiography and whom we initially thought did not have tuberculosis, developed hilar adenopathy on subsequent radiography and justifiably was started on anti-tuberculosis therapy.

Discussion

The decision to institute anti-tuberculosis therapy in a child is influenced on the one hand by the degree of diagnostic certainty and on the other hand by the possible consequences of failure to start treatment timeously. One of the factors which influences mortality and morbidity is the age of the child; in particular, those less than 1 year of age are known to be at greatly increased risk of morbidity and mortality as a result of progressive and disseminated forms of tuberculosis.⁹ It is therefore not unexpected that children suspected of having tuberculosis but subsequently thought not to have tuberculosis should be younger (median age 19 months) although not significantly younger than those with probable (median age 24,5 months) or confirmed tuberculosis (median age 19 months).

Wheezing as a result of airway narrowing caused by tuberculous adenopathy is known to be a relatively common presenting symptom in young children with tuberculosis and in a series of bacteriologically proven cases of childhood tuberculosis presenting to our hospital wheezing was the presenting symptom in 17%.¹⁰ When asthma is associated with pulmonary opacification or collapse of a lobe or segment due to mucus plugging, especially if the child is in contact with an adult tuberculosis patient, it is not surprising that some confusion should ensue. During the follow-up of the group of 71 children initially suspected of having tuberculosis, 20 were subsequently erroneously treated for tuberculosis. Of these 20 children, 4 had asthma and were repeatedly admitted, sometimes with mucus plugging and lobar or segmental collapse. The same mechanisms are probably the cause of lobar and segmental collapse in children with pneumonia and eosinophilia.

In developing communities failure to thrive or loss of weight are all too common and a significant proportion of young children in the Western Cape experience a fall in growth velocity during the 2nd year of life.¹¹ While malnutrition frequently accompanies tuberculosis the fact that more than half of the children subsequently thought not to have tuberculosis had a history of recent weight loss suggests some reservations as to the use of weight loss, failure to gain weight or low body mass as important criteria for the diagnosis of tuberculosis in childhood in developing countries. This should, however, not be taken to imply that children with malnutrition should not be evaluated for tuberculosis as a significant proportion of such children will be suffering from tuberculosis.^{7,12,13}

A significant proportion (21%) of the children gave a history of contact with an adult case of tuberculosis. Children presenting to us with confirmed and probable tuberculosis, however, have a far higher reported incidence of contact with an adult case of PTB, i.e. 41% and 56% respectively.¹⁴ While children in contact with an adult case of tuberculosis are exposed to a considerable risk of infection and disease, particularly if the sputum of the adult is positive for acid-fast bacilli on microscopy,¹⁵ the mere finding of such a history does not necessarily mean that the child in question is suffering from tuberculosis.

Given the uncertainties associated with the diagnosis of tuberculosis in childhood it is not surprising that children living in an area with a high incidence of tuberculosis have been unnecessarily treated for tuberculosis especially if they

have a chronic lung problem associated with malnutrition. Careful consideration of the child's previous history, review of previous chest radiographs, a full blood count to exclude peripheral eosinophilia and a Mantoux skin test will minimise the errors. Critical evaluation of all available chest radiographs for perihilar opacification, segmental or lobar collapse and congenital pulmonary anomalies will further decrease incorrect diagnoses.

In conclusion, our experience draws attention to some of the diagnostic pitfalls in the diagnosis of tuberculosis in childhood. HIV infection and AIDS in children is not yet a serious factor in our community, but seems likely in due course to complicate the already difficult task of diagnosing primary tuberculosis and its complications in childhood even further.

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