Clinical features and outcome in children admitted to a TB hospital in the Western Cape – the influence of HIV infection and drug resistance

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Background. The Western Cape has a high incidence of tuberculosis (TB) and a rising prevalence of HIV infection. Children form 15 - 20% of this TB burden.

Objective. To document the clinical features and outcome of TB among children admitted to a regional TB hospital.

Method. A retrospective, descriptive study was undertaken of children under 15 years of age admitted to Brooklyn Hospital for Chest Diseases from January 2000 to December 2001. Demographic and clinical details of children were recorded routinely in a register that formed the basis of this review.

Results. Two hundred and thirty-eight of the 250 children admitted had TB, of whom 120 (50.4%) were boys. The median age was 25 months. Reasons for admission were disease severity in 99 cases, social reasons in 36, and a combination in 103. Adult source cases were identified in 138 instances; 9 had drug-resistant TB, 31 drug-susceptible TB and in 98 cases susceptibility was unknown. TB was confirmed by culture in 119 children. Of 79 in whom susceptibility testing was done, 10 had isoniazid-resistant TB and 8 multidrug-resistant TB. HIV serology was positive in 43 of 138 children tested (31%). Previous antituberculosis treatment, severe malnutrition and weight under the 3rd percentile for age, a negative Mantoux test, and mortality were significantly more common in the HIV-infected children. Twenty-two of 41 previously negative Mantoux tests (< 5 mm induration) were positive on retesting.

Conclusions. HIV infection is common in children with TB and malnutrition, and mortality in this group is high. Repeat Mantoux tests may show an increased number of positive results.

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The Western Cape province of South Africa has a high incidence of tuberculosis (TB); in 2000 and 2001 the incidence within the Cape Town metropole region was 562 and 581/100 000 population, respectively.[1] Children under 15 years of age form between 15% and 20% of this TB burden. Further, during the 2001 anonymous national HIV survey of women attending public antenatal clinics 8.6% (95% confidence interval (CI): 5.6 - 11.6%) of pregnant women in the Western Cape were HIV-infected.[2] During 1998 and 1999 the antenatal HIV prevalence rates were 5.2% and 7.1%, respectively. This coincidence of high TB incidence rates and increasing HIV infection rates in mothers has meant that considerable numbers of young children with TB are co-infected with HIV.

Directly observed therapy, short-course (DOTS) is the preferred manner to manage TB treatment in the community.[3] Severely ill patients or those who have socio-economic problems may, however, still require hospitalisation. In children, problems may be compounded by the caregivers' inability to take them to a clinic or community DOTS supporter because of infirmity, old age or fear of losing their employment. Children are admitted to Brooklyn Hospital for Chest Diseases (BHCD) once they have been evaluated at a referral hospital. BHCD accommodates 60 children, 40 aged up to 5 years and 20 aged from 6 to 14 years. A previous descriptive study[4] documented the clinical features of children with TB admitted to BHCD during 1998 and 1999; 25% of 150 were found to be HIV-infected. An increased mortality rate and a higher incidence of multidrug resistance was found among the HIV-infected children. This study continues the documentation of the clinical features and outcome of TB among children admitted to BHCD during 2000 and 2001.

Materials and methods

This was a retrospective, descriptive study of all children under 15 years of age admitted to BHCD from 1 January 2000 to 31 December 2001. Demographic data and clinical details of all children were routinely recorded in a register that formed the basis of this review. Missing information was retrieved from clinical folders and chest radiographs. Information regarding age at TB diagnosis, sex, clinical and radiological findings, the results of testing for HIV infection, Mantoux tuberculin skin testing (TST) and results of cultures for *Mycobacterium tuberculosis* and drug susceptibility were

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collected on data capture forms. Details of the history included contact with an adult TB source case, the relationship between the source case and the child, drug susceptibility results of the source case's isolates, previous TB treatment and the child's presenting symptoms.

The children were divided into nutritional categories according to the Wellcome classification of weight for age. Nosocomial infections and drug adverse events were recorded. Mantoux TST with 2 units RT/23 tuberculin (Statens Seruminstitut, Copenhagen, Denmark) was noted as significantly positive in HIV-uninfected children if an induration of ≥ 15 mm was measured.[5] In HIV-infected children an induration of ≥ 5 mm was regarded as significant.[5]

HIV serology was evaluated when clinical findings indicated HIV disease or the mother was known to be HIV-infected. HIV infection was confirmed by 2 enzyme-linked immunosorbent assays (ELISAs) using kits from different manufacturers, and by polymerase chain reaction (PCR) in children < 15 months of age.

Cultures for *M. tuberculosis* and drug susceptibility test results were obtained where available. Drug susceptibility testing was initially only for isoniazid (INH) and rifampicin (RMP) as previously described.[4]

A diagnosis of confirmed TB was made in the presence of a culture of *M. tuberculosis* from any source, or if sputum smear microscopy or histological assessment was positive for acid-fast bacilli. A diagnosis of probable TB was made in the presence of 2 or more of the following: (*i*) a positive TST; (*ii*) a chest radiograph showing hilar or paratracheal adenopathy; (*iii*) recent (within 12 months) close household contact with a sputum smear-positive pulmonary TB (PTB) case; and (*iv*) in the case of suspected tuberculous meningitis (TBM), a computed tomography (CT) scan showing hydrocephalus and basal enhancement. Children with a positive TST, but without any clinical or radiological signs were regarded as having TB infection only.

Uncomplicated primary TB (mediastinal adenopathy with limited involvement of lung parenchyma) was managed with INH, RMP and pyrazinamide (PZA) for 2 months followed by INH and RMP for 4 months. In the presence of pulmonary cavitation or dissemination to multiple organs excluding the brain, ethambutol (EMB) was added during the initial 2 months of treatment. Children with TBM and miliary TB received 6 months' treatment with INH, RMP, PZA and ethionamide.[6] Children with known drug-resistant TB or in contact with adults with known drug-resistant TB were treated taking into account the drug susceptibility test of the child or adult source case. Treatment in HIV-infected children was often extended to 9 months in the presence of more extensive disease.

Categorical data were analysed using the chi-square test with Yates' correction and Fisher's exact test where appropriate. Statistical analysis was done using EpiInfo version 6.03.

The study was approved by the Institutional Review Board of the Faculty of Health Sciences of Stellenbosch University.

Results

From January 2000 to December 2001, 250 children were admitted to BHCD. Twelve children were excluded from analyses; 2 were older than 15 years and 10 were considered not to have TB. The median age of the remaining 238 children, of whom 120 (50.4%) were boys, was 25 months (range 1 - 171 months) at diagnosis.

HIV serology was done in 138 of 238 children (58%), and was positive in 43 (31%). The children were divided into an HIV-uninfected group A ($N = 95$), an HIV-infected group B ($N = 43$) and those not evaluated for HIV, group C ($N = 100$). The median age (range) in months was 21 (1 - 171 months), 29 (1 - 137 months) and 29 (1 - 168 months) for children in groups A - C, respectively.

The reasons for admission to BHCD were severity of disease in 99 children (42%), social reasons such as the caregiver's inability to care for the child, failure to comply with treatment or admission of the mother to BHCD in 36 children (15%), and both severity of disease and social reasons in 103 children (43%). Tertiary hospital referrals accounted for 114 admissions (48%), secondary hospitals for 91 admissions (38%) and primary care facilities for 33 admissions (14%). Of these, 69, 31 and 4 children from the respective referral levels presented with TBM.

Contact with adult PTB was documented in 56 (59%), 27 (63%) and 55 (55%) children in groups A, B and C, respectively. Of these 138 children, 104 (76%) had 1, 28 (20%) had 2, and 6 (4%) had 3 or more known adult source cases; the mother in 50 (36%), the father in 26 (19%), an uncle and/or aunt in 39 (28%), a grandparent(s) in 17 (12%), another household member in 29 (21%), and a neighbour in 5 (4%).

TB was confirmed by culture in 119 children (50%) and microscopy for acid-fast bacilli (AFB) was positive in a further 5 (2%). The culture source was gastric aspirate in 79 (33%), sputum in 32 (13%), cerebrospinal fluid in 17 (7%), lymph node biopsy in 5 (2%) and bronchial aspirate in 4 (2%). AFB only were found in 1 lymph node biopsy, 1 sputum and 3 gastric aspirates. TB was confirmed in 59 (62%), 23 (53%) and 42 (42%) children in groups A, B and C, respectively.

Nine of 138 children (7%) with known source cases were in contact with adults with drug-resistant TB, 8 of whom had multidrug-resistant (MDR) TB (i.e. resistance to INH and RMP, with or without resistance to other drugs). Cultures for *M. tuberculosis* were obtained from 4 of these children, of whom 3

had MDR and 1 had INH-resistant TB. The drug susceptibility patterns were identical to those of the adult source. Drug susceptibility test results of isolates from a further 31 (22%) children's adult source cases were known and were fully susceptible.

Drug susceptibility tests in 93 of 119 children (78%) with positive cultures confirmed resistance in 18 children (19%); 10 had INH resistance only and 8 had MDR TB. Only 1 HIV-infected child had drug-resistant (MDR) TB. In 8 children with confirmed resistance (3 MDR) the HIV status was unknown and in 9 (4 MDR) the children were HIV-uninfected.

A history of previous antituberculosis treatment was obtained from 52 children (22%); 18 (19%) in group A, 16 (37%) in group B (B and A odds ratio (OR) 2.53, 95% CI: 1.05 - 6.11) and 18 (18%) in group C (B and C OR 2.70, 95% CI: 1.12 - 6.50). Of these 52 cases, 8 (15%) had confirmed drug resistance (2 INH resistance and 6 MDR) and a further 2 had adult MDR source cases. Only 11 (21%) had been adherent to previous treatment, 28 (54%) were not adherent and in 13 (25%) adherence was not known.

Weight for age < 3rd percentile was significantly more frequent in group B children (33/43; 77%) than in groups A (53/95, 56%) (OR 2.62, 95% CI: 1.08 - 6.43) or C (40/100, 40%) (OR 4.95, 95% CI: 2.06 - 12.15). Group A also had significantly more underweight children than group C (OR 1.89, 95% CI: 1.03 - 3.49). Severe malnutrition (marasmus and/or kwashiorkor) was significantly more common in group B (14/43) than in groups A (15/95, OR 2.57, 95% CI: 1.02 - 6.50) and C (8/100, OR 5.55, 95% CI: 1.93 - 16.28). There was no significant difference between groups A and C. Nutritional status improved in all groups during hospitalisation, but the HIV-infected children's weight-for-age percentiles remained the lowest. At the time of discharge, 28 (29%), 20 (47%) and 20 (20%) of the children in groups A, B and C still had a weight for age < 3rd percentile.

Table I summarises the site of TB. Extrapulmonary tuberculosis (EPTB) was evenly distributed among the groups. Both PTB and EPTB were found in 58 (61%), 30 (69%) and 51 (51%) children in groups A, B and C respectively. The remaining 2, 3 and 2 children in the respective groups were diagnosed with TB infection only.

The intrathoracic manifestations of TB on chest radiograph are summarised in Table I. Only 3 group B children (7%) had a normal chest radiograph compared with 14 (15%) and 28 (28%)

Table I. Site of TB disease, Mantoux tuberculin test and chest radiograph results

	HIV infection status			Odds ratio (95% CI) group A compared with group B*
	Uninfected (group A) *N* = 95 (%)	Infected (group B) *N* = 43 (%)	Not determined (group C) *N* = 100 (%)	
Pulmonary TB	80 (84)	35 (81)	69 (69)	NS
Extrapulmonary TB (total)	71 (74)	35 (81)	80 (80)	NS
TB meningitis	31 (33)	11 (26)	62 (62)	NS
Miliary TB	22 (23)	13 (30)	13 (13)	NS
Pleural effusion	20 (21)	13 (30)	9 (9)	NS
Abdominal TB	13 (14)	7 (16)	3 (3)	NS
Pericardial effusion	2 (2)	0	4 (4)	NS
Peripheral lymph nodes	5 (5)	2 (5)	2 (2)	NS
Osteo-articular TB	5 (5)	0	1 (1)	NS
Mantoux test (done and read)	84 (88)	40 (93)	90 (90)	NS
Induration (in mm)				
≥ 15	55 (65)	16 (40)	61 (68)	2.32 (1.04 - 5.21)
≥ 5 - 14	10 (11)	6 (15)	18 (20)	
Chest radiograph features				
Mediastinal lympadenopathy	38 (40)	18 (42)	36 (36)	NS
Lobar/segmental opacification	39 (41)	25 (58)	35 (35)	NS
Bronchopneumonic opacification	6 (6)	4 (9)	4 (4)	NS
Miliary picture	22 (23)	13 (30)	13 (13)	NS
Pleural effusion	20 (21)	13 (30)	9 (9)	NS
Cavities or pneumatoceles	21 (22)	9 (21)	6 (6)	NS
Ghon focus	0	0	2 (2)	NS
Calcifications	2 (2)	0	4 (4)	NS
Normal chest radiograph	14 (15) †	3 (7) †	28 (28)†	NS

* Group C was not compared, as HIV status was not known.
† TB meningitis in 11, 0 and 22 children and infection only in 2, 2 and 3 children in groups A, B and C, respectively.
NS = not significant.

Table II. Outcome at the end of hospitalisation

HIV infection status	HIV-uninfected (group A) *N* = 95 (%)	HIV-infected (group B) *N* = 43 (%)	HIV not determined (group C) *N* = 100 (%)	Odds ratio (95% CI)* group A v. group B
Cured †	44 (46)	9 (21)	33 (33)	3.26 (1.32 - 8.24)
Cured with remaining pathology ‡	23 (24)	6 (14)	27 (27)	NS
Transferred to another hospital	8 (8)	4 (9)	6 (6)	NS
Discharged to complete treatment at a community clinic	16 (17)	16 (37)	29 (29)	0.34 (0.14 - 0.84)
Died	2 (2)	6 (14)	5 (5)	0.13 (0.02 - 0.78)
Absconded	2 (2)	2 (5)	0	NS

* No significant differences were found comparing groups A or B with group C.
† Cured – culture-negative, clinical findings normal with radiological resolution.
‡ Remaining pathology – culture-negative but clinical or radiological abnormalities persist.
NS = not significant.

in groups A and C (OR groups A and B not significant). Mediastinal lymphadenopathy was equally frequent among the 3 groups. The final Mantoux TST results are given in Table I. TST was repeated in 41 of 75 children after a month or more when the initial TST showed < 5 mm induration. Of these, 27 (66%) showed a greater response and 22 (54%) developed an induration of ≥ 15 mm. Eleven of 21 (52%), 4 of 6 (67%) and 11 of 14 (79%) children from groups A, B and C, respectively, had a follow-up Mantoux induration of ≥ 10 mm. If ≥ 15 mm induration is used as cut-off for a significantly positive Mantoux TST in the HIV-uninfected group and ≥ 5 mm induration for HIV-infected children, there was no significant difference in positive TSTs in the final results (OR = 1.55, 95% CI: 0.67 - 3.59).

While in hospital, jaundice as an adverse event developed in 7 children and drug rash occurred in 4. Drug adverse events did not differ significantly between groups. Nosocomial sepsis, bacterial meningitis or pneumonia were diagnosed in 2 (2%), 5 (12%) and 3 (3%) children in groups A, B and C, with a trend to more nosocomial infections in group B than A (OR 6.12, 95% CI: 0.99 - 47.8). During the review period a chickenpox outbreak occurred; 62 children were affected, with a similar percentage in each group.

The length of stay in BHCD was a median of 5 months in all groups, with a range from 1 to 12 months, 1 to 20 months and 1 to 15 months in groups A - C. The median treatment duration was 6 months (range 2 - 18 months in both) for groups A and C, but 9 months (range 1 - 24 months) for group B. The outcome at the end of hospitalisation is presented in Table II. A significantly higher percentage of group B children died than in either groups A or C. The cause of death was not always clear, but TBM stage III was present in 5 and miliary TB in 4. Of the 6 deaths among the HIV-infected children, only 1 was directly related to TB, 4 were HIV-related and 1 died of an unknown cause.

Discussion

This study documents the continued impact of HIV infection on the occurrence of childhood TB in our region. During a previous survey of paediatric admissions to BHCD[4] a very similar proportion of children were evaluated for HIV infection; 57% in the previous review and 58% during this survey. Despite measures to prevent mother-to-child HIV transmission in our region a higher proportion, although not significant, of children admitted to BHCD and evaluated for HIV infection during this survey (31%) were HIV-infected compared with the previous survey (25%) (OR 1.43 (0.83, 2.49)). In keeping with our previous survey,[4] and the experience of others in Africa,[7] HIV-infected children did not present with more EPTB than HIV-uninfected children. It is also noteworthy that all but 3 (7%) of the HIV-infected children had intrathoracic manifestations of disease in contrast to HIV-uninfected children (15%) and those not evaluated (28%).

A higher mortality rate was again experienced by the HIV-infected children and was the consequence of HIV infection and its complications rather than TB despite the children receiving cotrimoxazole prophylaxis. Cotrimoxazole prophylaxis has reduced the mortality rate in adults with TB.[8]

The adverse nutritional effects of both TB[9] and HIV infection[10] are well known; it is therefore not surprising that at TB diagnosis more children in group B than in groups A or C had a weight for age < 3rd percentile and suffered from both kwashiorkor and marasmus. In the absence of antiretroviral therapy and despite supervised antituberculosis treatment, adequate nutrition and supplements provided in hospital, many HIV-infected children also failed to gain weight satisfactorily.

It was distressing that 52 children (22%) had been treated previously for TB; this was particularly likely to be the case in the HIV-infected children, and treatment instructions were followed in only a minority of these cases. It has been forcibly

pointed out that such failures should be regarded as failures of the system and not necessarily ascribed to patient negligence, or in the case of children, to negligence of caregivers.[11]

Problems associated with compliance with treatment instructions with regard to childhood TB have been noted by several groups.[12,13] Distance from clinics, lack of help with the supervision of other children during clinic visits and fear of losing employment, have been identified as problems. Childhood TB is also not a priority for TB services in high-incidence communities, yet ironically it is in precisely these areas that large numbers of children needing treatment will be found.[14]

Drug resistance was confirmed in 18 of the 93 children (19%) for whom drug susceptibility test results were available. During the previous survey 20 isolates (25%) from 79 children were drug resistant.[4] The importance of a history of possible contact with a drug-resistant index case is again illustrated. It is distressing that a history of previous TB treatment and failure of compliance was associated with drug resistance in some patients. Drug resistance is usually considered to be new (primary) resistance in childhood, but several of our patients could be classified as having previously treated (acquired) drug resistance.

In developing countries with limited resources the TST is a mainstay of the diagnosis of childhood TB. A Mantoux TST gave an induration of ≥ 15 mm in approximately two-thirds of groups A and C children, but only 40% of the group B children. Nonetheless taking into account those HIV-infected children who reacted with ≥ 5 mm induration, more than 50% of the HIV-infected children did have a significantly positive result. We would also draw attention to the potential value of repeating the TST in those children in whom TB is strongly suspected. Improved nutrition and a booster response may contribute to improved results on retesting.

The high proportion of children with TBM admitted to BHCD is a reflection of the intensity of the TB epidemic in the Western Cape. In the period 1985 - 1987, before the advent of the HIV epidemic, an annual risk of TB infection for the Western Cape of 2 - 3% was calculated and the incidence of TBM in children 0 - 4 years of age was 24.3/100 000 population.[15] Our data indicate that the situation has not improved in the intervening 15 years. Our experience amply illustrates the pernicious interaction of the concurrent HIV and TB epidemics and their influence on children. It is hoped that the availability of antiretroviral agents will contribute to the better management of both these infections.

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