Clinical basics

Tuberculosis: 5. Pediatric disease

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Education

Éducation

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Between 1980 and 1995, the total number of active cases of tuberculosis (TB) in Canada declined steadily, from 2762 to 1930; the corresponding rates per 100 000 population were 11.2 and 6.5. During the same period, the number of cases of primary TB among children younger than 15 years remained disturbingly similar: 145 cases in 1980 and 156 in 1995.[1] The rates were higher for those under 4 years of age than for those 5–14 years of age (Table 1). In 1995, 99 of 176 cases of pediatric TB occurred in aboriginal children.[1] Over the 10-year period 1985 to 1994, the number of cases of pediatric TB reported in the United States increased by 33%.[2] The occurrence of TB in children implies recent transmission in the community and reflects the effectiveness of TB control programs. A history of the disease in the household, foreign birthplace and poor socioeconomic circumstances, such as in the inner city, are the main risk factors. Around the world, almost 500 children die of TB each day, and it has been estimated that 170 000 children die each year from the 2 most severe forms of disseminated disease, meningeal and miliary TB.[3]

Pathogenesis

The tubercle bacillus is usually inhaled. The initial infection consists of a peripheral lesion in any lobe of the lung, accompanied by acute alveolitis around the tubercle bacilli and intracellular replication. After a few weeks the infection is carried by alveolar macrophages through the lymphatic system to the regional lymph nodes. Enlargement of the regional lymph nodes is a hallmark of primary TB. From there, the organisms may reach the thoracic duct, which sets the stage for lymphohemotogenous dissemination to the lung (miliary or apical) and extrapulmonary sites such as the brain (where tuberculoma or TB meningitis may occur), the pleura, bone, the renal cortex and other lymph nodes. In a child with a normal immune system, tuberculin sensitivity develops within 3 to 12 weeks. The T-cell mediated response that occurs kills or contains the tubercle bacilli, and the infection heals. The initial infection in children is often asymptomatic. A few children experience a febrile illness (lasting 1 to 3 weeks), erythema nodosum or phlyctenular conjunctivitis. In 95% of cases the infection heals spontaneously and the site may calcify 6 to 12 months later, which produces a Ghon lesion visible on radiographic examination of the chest. Thus, infection with *Mycobacterium tuberculosis* does not necessarily cause disease.

Meningeal and miliary TB are early complications of disseminated disease, peaking 1 to 3 months after infection. These conditions now account for less than 4% of active disease in children under 15 years of age.[1] Pleural effusion due to rupture of a subpleural focus is uncommon in children under 5 years of age. Pleural effusion occurs within 3 months of infection in 25% of cases and within 6 months of infection in 75% of cases.[4] Complications arising from progression of an intense reaction in the regional lymph nodes include direct extension to lung tissue, erosion into a bronchus accompanied by seeding of distal lung tissue (endobronchial disease), atelectasis and pooling of secretions distal to obstruction. Most bone lesions occur within 3 years of infection. Renal TB is a late complication that usually occurs 5 or more years after initial infection; it may therefore be seen in adolescence (Table 2).

Case presentation

This case presentation will illustrate the management issues related to TB exposure, infection and disease in children.

A 7-year-old aboriginal boy from an isolated reserve was said to be in close but not household contact with an adult with sputum-positive TB, but the result of a tuberculin skin test for the child was negative on initial contact follow-up. The boy had no history of BCG (bacille Calmette-Guérin) vaccination and was not offered isoniazid prophylaxis. Over the next few weeks, he became listless, slept for long periods, and experienced headaches, and his gait became broad based. His mother took him to the doctor twice because he "didn't play anymore." On repeat tuberculin testing, a positive result was obtained. He had left nystagmus and palsies of the left sixth and seventh cranial nerves. Radiography of the chest showed an enlarged right paratracheal lymph node with adjacent consolidation in the right upper lobe (Fig. 1). CT of the head revealed a brain stem (pontine) lesion (Figs. 2 and 3). Examination of cerebrospinal fluid, sputum and urine smears for acid-fast bacilli yielded negative results. However, *M. tuberculosis* was subsequently cultured from sputum. The patient was given a triple regimen of antituberculous drugs, along with a course of systemic steroids. Minimal residual paresis of the sixth cranial nerve persisted for a few months, but he eventually recovered. The treatment continued for 9 months and was fully supervised.

Table 1: Rate of tuberculosis (TB) by age group in Canada, 1975 to 1995*

	Age group; rate, no. of cases per 100 000 population		
Year	≤ 4 yr	5–14 yr	All ages
1975	5.5	4.0	15.6
1980	4.5	3.1	11.2
1985	4.0	1.0	8.3
1990	7.0	1.7	7.2
1991	6.1	1.6	7.2
1992	5.5	2.2	7.4
1993	4.7	2.8	7.0
1994	4.6	2.5	7.1
1995	4.6	2.1	6.5

*Source: Statistics Canada and Health Canada data.[1]

Table 2: Number of cases of extrapulmonary TB in Canadian children, 1990–1995

	Age group; no. of cases (and rate per 100 000 in age group)	
Year of diagnosis	≤ 4 yr	5–14 yr
1990	14 (0.7)	6 (0.1)
1991	6 (0.3)	8 (0.2)
1992	9 (0.4)	16 (0.4)
1993	10 (0.5)	17 (0.4)
1994	7 (0.3)	16 (0.4)
1995	4 (0.2)	9 (0.2)
Total	50	72

Source: Health Canada data.[1]

Diagnosis of TB in children

The diagnosis of TB infection or disease in children depends primarily on a high index of suspicion. Routine annual skin testing of children is not recommended because it is not cost-effective in low-risk populations, such as the vast majority of children. In addition, false-positive reactions are not uncommon. Most cases of TB infection without disease are now found by Mantoux testing of targeted high-risk populations (e.g., aboriginal Canadians and recent immigrants), through an active program of contact investigation in Canada. Nevertheless, TB should be considered as a potential cause of disease in any child with poorly resolving pneumonia, pleural effusion or radiologic evidence of enlargement of the hilar or paratracheal lymph nodes.

TB should be suspected in children who have clinical or radiographic findings suggestive of TB, those who have been in recent close contact with an adult with smear-positive TB and those with cellular immunodeficiency such as HIV infection. Children receiving high doses of steroids or other immunosuppressive drugs are also at risk. Children at moderate risk include those younger than 4 years of age, those born or living in an area with a high prevalence of TB and those with a parent who comes from such an area.

In children, the Mantoux test may produce a severe local reaction, including erythema, vesiculation or ulceration. Rarely seen are lymphangitis, regional lymphadenopathy, phlyctenular conjunctivitis and fever. False-positive reactions may occur in children with nontuberculous mycobacterial infection.

Previous vaccination with BCG may also make the interpretation of the Mantoux test difficult. Induration of at least 15 mm diameter in a child of any age who has received BCG vaccination clearly suggests recent TB infection and necessitates evaluation. Independent of a history of BCG vaccination, a Mantoux test with induration of at

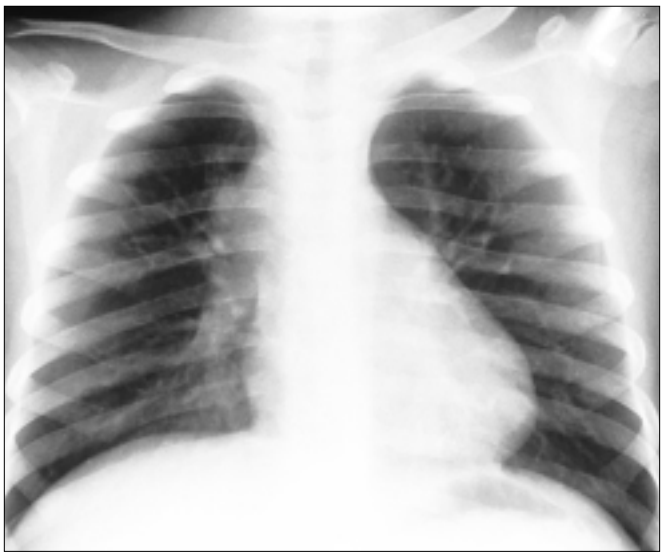

Fig. 1. Posteroanterior chest radiograph shows right paratracheal adenopathy and a small round density in the right upper lobe.

least 5 mm diameter should be considered a positive test result in high-risk groups such as aboriginal children and recent immigrants from developing countries (Table 3).

False-negative reactions may occur during the incubation period, so the test should be repeated at least 10–12 weeks after initial contact with an adult with TB. A false-negative Mantoux test may also occur with severe systemic TB such as meningeal or miliary disease. The reaction may be depressed by malnutrition, corticosteroids and a wide variety of viral infections, as well as by infection with *Mycoplasma pneumoniae*.

History and physical examination

In contrast to the disease in adults, pulmonary TB in children occurs with minimal if any clinical manifestation except when the child has severe progressive disease. Nonspecific signs and symptoms may be present, including fever, malaise, anorexia, weight loss, nonproductive cough, stridor, crackles, erythema nodosum and phlyctenular conjunctivitis. If there is pleural effusion, dullness to percussion and reduced air entry may be present.

Table 3: Criteria for positive result for a Mantoux test*

Risk category†	Diameter of induration, mm
High	≥ 5
Moderate	≥ 10
Low	≥ 15

*The criteria apply regardless of age.
†Children at high risk for TB include aboriginal children, recent immigrants, those with HIV infection and those in recent close contact with an adult with active disease. Children at moderate risk include those younger than 4 years of age, those born or living in an area with a high prevalence of TB and those with a parent from such an area.

Radiographic examination of the chest

If the Mantoux test result is positive, then posteroanterior and lateral chest radiography must be done, because more than 95% of primary TB infections occur in the lung. The primary complex is most likely to be seen in infants and small children and may be located in any lobe. Hilar and paratracheal lymphadenopathy is the hallmark of primary TB in children and is evident on either posteroanterior or lateral chest radiography. Other pulmonary manifestations may include linear, interstitial or nodular densities, pleural effusion, lobar atelectasis or miliary TB.

Other diagnostic tests

In most cases of childhood TB the diagnosis is based on contact history, skin testing and chest radiography. Because children under 12 years of age rarely produce sputum, recovery of the causative organism depends on early-morning gastric lavage, which is done on 3 consecutive mornings with 30 to 50 mL of sterile water. The sample must be buffered for transport. In the hospital setting, gastric aspirates reportedly yield positive results in 70% of infants (those 2 years of age or younger) and 30% to 40% of children (2–12 years of age).[2] A public health nurse could probably obtain the necessary sample in the home setting if arrangements were made for the early-morning hours (6 to 7 am). For example, such testing has been performed in Winnipeg since July 1997, and admission to hospital has been avoided in approximately 10 children.

Bronchoscopy, culture of pleural fluid or pleural biopsy may be indicated, but rarely, in childhood TB.

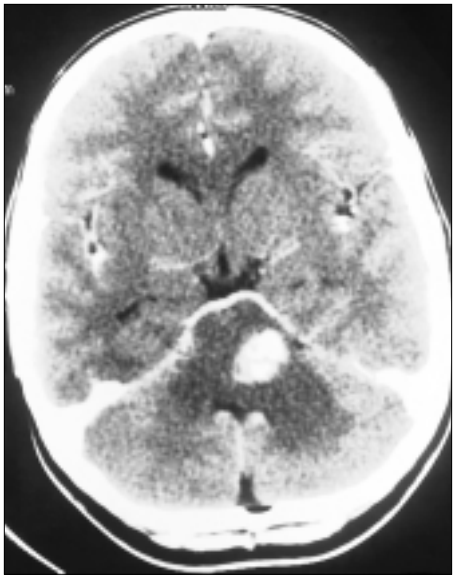

Fig. 2. Contrast-enhanced CT of the head shows a densely enhancing pontine lesion extending into the midbrain.

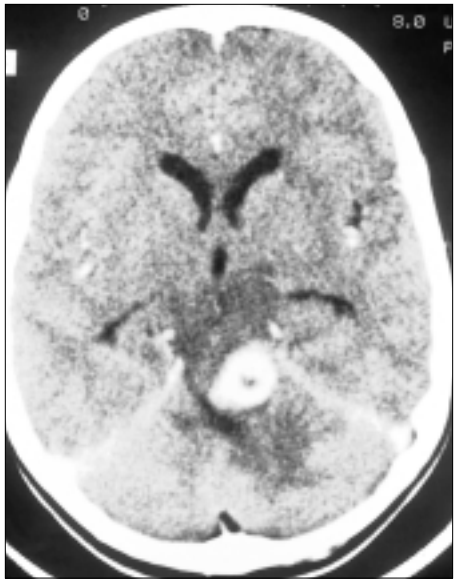

Fig. 3. Progression of brain lesion with development of central necrosis, edema and early hydrocephalus.

Management of TB in children

Management of TB in children differs in several respects from management of the disease in adults. First, children with TB are never contagious, except for rare cases in adolescents with open cavitary lesions. Second, children with TB require no limitation of physical activity.

Therapy for exposed children

Newborns

Congenital TB is extremely rare. In such instances, the Man-

toux test result is usually negative and the diagnosis is based on examination of the placenta, radiographic examination of the chest, lumbar puncture and cultures. Four-drug therapy should be initiated, as for meningeal TB.[5] If the mother or a household contact has evidence of TB infection or disease, but there is no congenital TB, the approach differs depending on the degree of suspicion of transmission to the infant.

- If the mother has no abnormal findings on chest radiography, the infant need not be separated from the mother. Household contacts must be carefully evaluated for evidence of TB.
- If the mother has abnormal findings on chest radiography, then the infant and the mother should be separated until the mother is evaluated for TB and, if she has disease, begins therapy.
- If the mother has abnormal findings on chest radiography that suggest quiescent TB, but there is no evidence of active disease and she has not previously been treated, she should be actively treated, and the infant should be followed with repeat Mantoux testing at 3 and 6 months of age.
- If the mother (or household contact) has active, probably contagious disease, then all household contacts should undergo investigation. The infant should be evaluated for congenital TB and tested for HIV infection. The mother and the infant should be separated until both are receiving appropriate therapy.

Older infants and children

Tuberculin-negative children 5 years of age or younger who are exposed to an active case of TB in an adult should be treated with prophylactic isoniazid for 3 months; the test should then be repeated (Table 4). If the result is still negative, the drug may be discontinued. If the index case has isoniazid-resistant organisms, rifampin prophylaxis should be used.

Treatment of TB infection (preventive therapy)

Children with infection diagnosed by a positive tuberculin test result with or without granuloma (as shown by chest radiography) or a calcified regional lymph node are considered to have TB infection. In these patients, isoniazid therapy for 9 months is extremely effective in preventing progression to tuberculous disease. This treatment reduces the incidence of TB disease by 90% during the first year after treatment, and the protective effect can last at least 30 years.[6] In a child with HIV and TB infection, treatment is continued for one year. Pyridoxine (vitamin B_6) is recommended only for breast-fed infants or malnourished children.

Table 4: Pediatric dosages of commonly used antituberculous drugs

	Frequency of administration; recommended dose, mg/kg (and maximum dose)	
Drug	Daily	Twice per week
Isoniazid*	10–20 (300 mg/d)	20–40 (900 mg/dose)
Rifampin*	10–20 (600 mg/d)	10–20 (600 mg/dose)
Pyrazinamide	20–40 (2 g/d)	50–70 (4 g/dose)
Ethambutol	15–25 (2.5 g/d)	50 (2.5 g/dose)

*If isoniazid plus rifampin are to be given together on a daily basis, the doses should be 10 mg isoniazid per kilogram and 15 mg rifampin per kilogram.

Treatment of TB disease (active therapy)

As in adults, treatment of tuberculous disease in children by short-course chemotherapy (over 6 months) is curative in 99% of cases.[5–7] The most frequently occurring form of primary pulmonary TB in children is enlargement of the mediastinal lymph nodes without parenchymal focus on chest radiography. This form of disease may be treated for 9 months with daily doses of isoniazid and rifampin or with twice-weekly directly observed therapy (DOT). DOT has been shown to decrease rates of relapse, treatment failure and drug resistance.[5] If the chest radiograph shows a parenchymal lesion, pleural effusion or pneumonia, then treatment consists of isoniazid and rifampin for 6 months, supplemented by pyrazinamide for the first 2 months. The optimal treatment for TB in HIV-infected children has not been established; most experts suggest that the initial regimens should be the same as for children without HIV but that the duration of treatment be extended to 9 or 12 months with a 4-drug regimen because of the problem of resistant organisms (the 4th drug is either ethambutol or streptomycin).[8]

It is beyond the scope of this paper to review the treatment of all other forms of childhood TB (e.g., meningeal TB, miliary TB, endobronchial TB), but excellent recent reviews are available.[2,9,10]

Competing interests: None declared.

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