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REVIEW ARTICLE

Clinical perspectives of childhood tuberculosis in Taiwan

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Tuberculosis (TB) is an important public health issue in Taiwan and worldwide. Taiwan has made major progress in combating TB in the past 40 years. However, childhood TB still constitutes a significant challenge in disease control. From January to mid December 2011, 369 new cases of pediatric TB were confirmed. The relatively low case number and variable clinical presentations made it difficult for early detection. Latent TB infections in children also pose further complexity in clinical management. Knowledge of the clinical features of active and latent TB infection is crucial for efficient TB control.

Introduction

Tuberculosis (TB) is the disease caused by the *Mycobacterium tuberculosis* complex, which includes *M tuberculosis*, *M bovis*, and *M africanum*. Childhood TB comprises approximately 15–20% of all cases, increasing up to 40% in some high TB burden countries.[1,2] In Taiwan, there were 66.7 TB cases per 100,000 population in 2003, while in the U.S., according to the Centers for Disease Control and Prevention, there were 5.1 cases per 100,000 population. In the past 40 years, Taiwan has made tremendous progress in combating TB. In 1948, 18,000 Taiwanese people died from TB; in 1955, the number shrank to 7,000. After 1997, the death rate of TB per 10,000 people was 7–8. Overall, the death rate of TB has been decreasing while the incidence has not risen. Actually, due to the new medicines for TB, the cure rate is about 100%.[3] Analysis of data from Taiwan's

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National Tuberculosis Registry showed that incidence of TB in persons <20 years of age was 9.61/100,000 person-years, biphasic, and age-relevant, with a major peak in persons just above 12 years. Aboriginal children were 8.1—17.4 times more likely to have TB than non-aboriginal children.[4] TB transmission occurs mostly between close contacts, especially in the household. Approximately 30% of heavily exposed persons will become infected. Moreover, infection does not necessarily lead to disease. Childhood TB should be seen as a spectrum of *M tuberculosis* exposure, from infection to disease. Primary infection may stay latent or proceed immediately to primary active TB disease or disease years later (secondary active TB). Several factors influence latent TB infection progression to active disease, including age, nutritional, vaccination, and immune status.[5–8] In 5% of persons with latent infection, active disease will develop within 2 years.[9] Only 5—10% of immunocompetent children progress from TB infection to disease.[10] Primary infection before 2 years of age frequently progressed to serious disease within 1 year without significant prior symptoms. Primary infection between 2 years and 10 years of age rarely progressed to serious disease, and such progression was associated with significant clinical symptoms. Primary infection after 10 years of age frequently progressed to adult-type disease.[11] Early effective intervention in this group will reduce the burden of cavitating disease and associated disease transmission in the community. Vaccination with Bacillus Calmette-Guerin (BCG) is the most widely used preventive strategy, although studies have shown highly variable protection.[12] BCG vaccination seems to offer significant protection against disseminated (miliary) disease and TB meningitis in very young children but no protection against adult-type TB.[13]

Before microbiological confirmation, clinical diagnosis of childhood TB frequently rests on the triad of (1) close contact with an adult source case, (2) a positive tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA), and (3) signs suggestive of TB on chest radiograph.[14] The most helpful symptoms suggesting childhood TB include: (1) persistent, nonremittent cough or wheeze for more than 2 weeks, (2) documented failure to thrive or weight loss despite food supplementation, and (3) fatigue or reduced playfulness.[15] TB treatment aims to cure the individual patient with minimal adverse effects. From a public health perspective, it is important to rapidly terminate transmission and prevent the emergence of drug resistance. The success of three drugs (isoniazid, rifampin, and pyrazinamide) during the 2-month intensive phase and two drugs (isoniazid and rifampin) during the 4-month continuation phase for pediatric patients is well established.[16] However, higher drug dosages are now recommended for treatment of childhood TB, based on pharmacokinetic evidence.[17]

Is latent TB infection (LTBI) true LTBI?

Recent studies in Taiwan showed that the increase in childhood TB may be associated with the increase in the incidence of the disease in adults (Fig. 1).[4,18] Children with household exposure to a sputum smear-positive index case experienced the greatest risk of becoming infected and of developing subsequent disease.[5] By identifying and treating infectious sources, usually adults can reduce the risk of TB exposure in children. Children and adolescents are at higher risk for progression to TB disease than adults. Most cases of progression to TB disease occur within 2—12

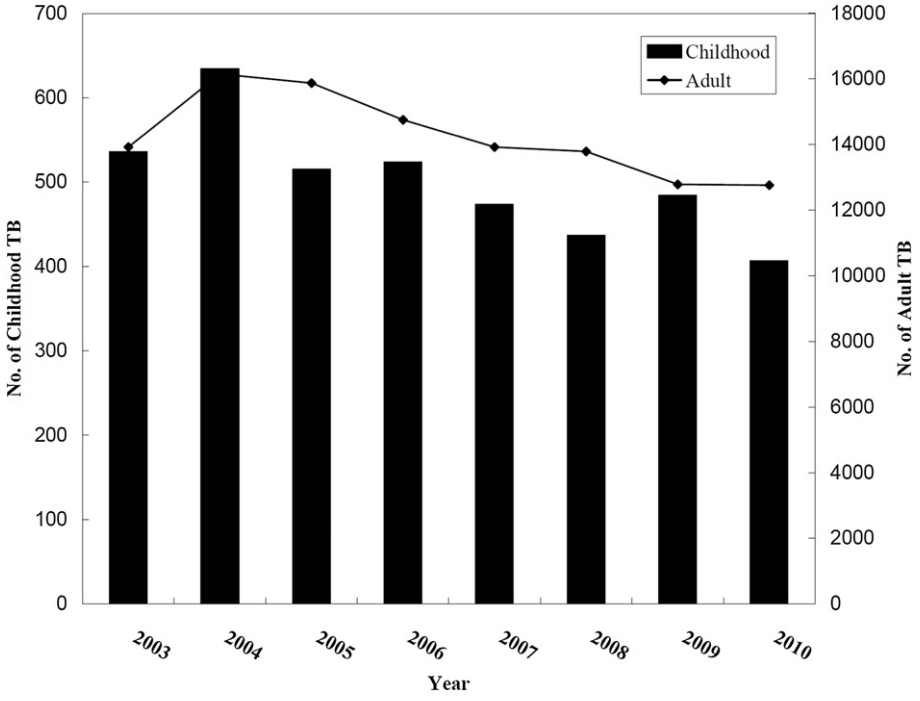

Figure 1 Numbers of confirmed childhood and adult tuberculosis (TB) cases per year in Taiwan, 2003—2010. Adapted from Notifiable Infectious Disease Statistics System (NIDSS), Centers for Diseases Control, Taiwan.

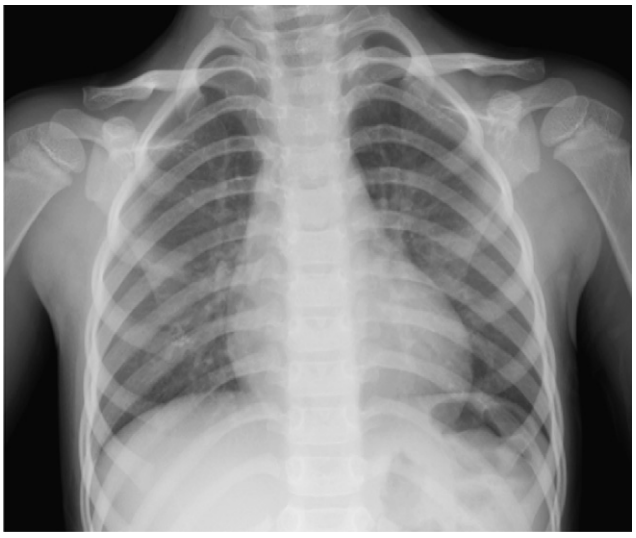

Figure 2 Is latent tuberculosis infection (LTBI) true LTBI? A 3-year-old girl with TB exposure history showed coarsening of bilateral peribronchovascular bundles and increased lung markings in the right lower lung. Two of three consecutive gastric aspirate cultures were positive for *Mycobacterium tuberculosis*.

months of initial infection.[10] Child contacts of a patient with TB must be evaluated for TB with a history, physical exam, chest radiograph, and TST.[19] LTBI is defined as *M tuberculosis* complex infection in a person who has a positive TST or IGRA result, no physical findings of disease, and chest radiograph findings that are normal or reveal evidence of healed infection (e.g., calcification in the lung, hilar lymph nodes, or both).[20] In 2009, as part of the "TB half" campaign, Taiwan started an LTBI treatment program for children younger than 13 years. Children who had TB contact history are advised to visit the LTBI clinic island-wide and have isoniazid (INH) prophylaxis treatment.[21] According to the guideline from the Centers for Disease Control of Taiwan, a child with positive TB contact history is considered to have latent TB infection if there was no abnormality in a chest radiograph. However, it is dangerous to exclude the possibility of active TB disease only by image studies. In the setting of LTBI, chest radiographs are usually normal or show coarsening of bilateral peribronchovascular bundles (Fig. 2) but may show dense nodules with calcifications, calcified nonenlarged regional lymph nodes, or pleural thickening. Obtaining expectorated sputum from children is difficult and its examination gives low yield (15% or less for smear and 30% or less for culture).[14,22] In our practice, children under 5 years of age with close contact history (i.e., index cases are parents, grandparents, or primary caregivers) are encouraged to have three gastric aspirates for *Mycobacterium* cultures in outpatient clinics before starting INH prophylaxis. If the culture results are positive for *M tuberculosis*, INH prophylaxis would be replaced by three-combination therapy with isoniazid, rifampin, and pyrazinamide. Increasing INH-resistant TB is an important issue in such a program, and recent studies also suggested that the recommended treatment for latent TB, 9 months of isoniazid, is both more expensive and less effective than rifampin. Rifampin should be considered for children with latent TB infection when the risk of isoniazid resistance exceeds 11%.[23] Because current LTBI policy in Taiwan covers only TB contacts younger than 13 years, adolescent contacts were not included in the isoniazid chemoprophylaxis. However, teenagers and children younger than 5 years constitute the majority of pediatric TB.[4] We recommend that the LTBI policy should include such age groups.

Primary pulmonary TB disease

Primary TB is seen in patients not previously exposed to *M tuberculosis*. It is most common in infants and children and has the highest prevalence in children less than 5 years of age.[24] Primary uncomplicated hilar adenopathy remains the most common disease manifestation in children and is usually regarded as the hallmark of primary TB (Fig. 3).[25,26] In children infected with *M tuberculosis*, a primary focus of infection will form (e.g., the Ghon focus on the lung). The subsequent recruitment of the cell-mediated immune response will result in regional or general adenopathies depending on the dissemination of infection. The upper lobes drain to ipsilateral—paratracheal nodes, whereas the rest of the lung drains to perihilar and subcarinal nodes,

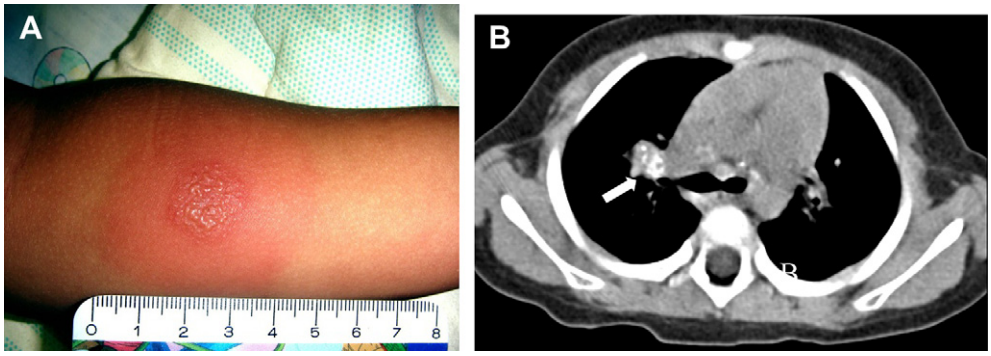

Figure 3 Primary tuberculosis (TB) infections with adenitis. A 22-month-old girl had not received Bacillus Calmette-Guérin (BCG) vaccination. Her grandmother was diagnosed with pulmonary TB. She had no fever, cough, or changes in bodyweight. (A) Tuberculin skin test showed induration larger than 40 mm with bulla formation. (B) The chest computerized tomography (CT) showed bulky calcifying lymph nodes (arrow) at right paratrachea, pretrachea, subcarina, and bilateral hilum.

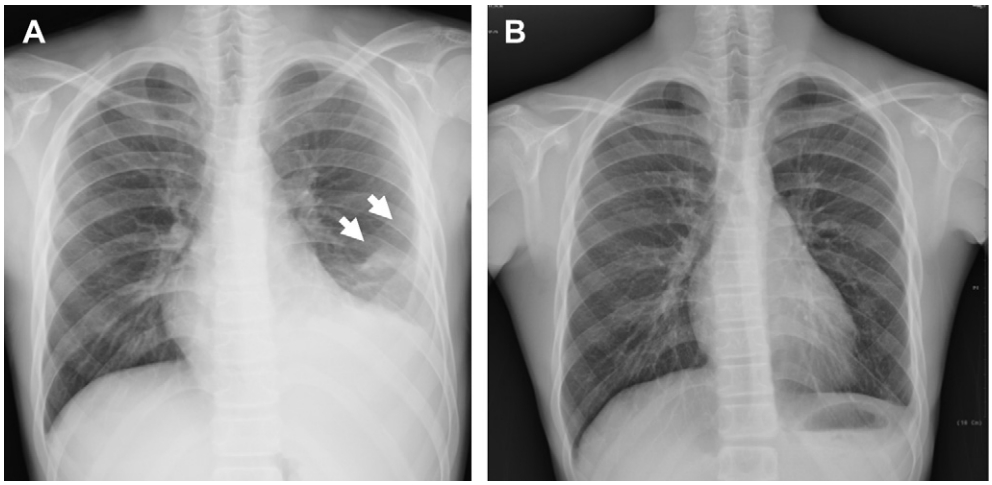

Figure 4 Primary tuberculosis (TB) infections: pleuritis with pleural effusion. (A) A 12-year-old boy was referred to our hospital because of massive pleural effusion without response to conventional antibiotics therapy. (B) There was no significant lung parenchyma involvement in the follow-up radiograph (after 6-month anti-TB treatment). Pleural effusion culture yielded *Mycobacterium tuberculosis* despite negative smear results. His grand-aunt was also diagnosed with pulmonary TB.

with dominant lymph flow from left to right. The Ghon complex is represented by both the Ghon focus, with or without some overlying pleural reaction, and the affected regional lymphnodes.[14,27,28] Development of a reaction to purified protein derivative (PPD) depends on an adequate cell-mediated immune response. A positive PPD only indicates that someone is infected. It does not give you any information on the time of acquisition, latency, or activity of TB disease. Abnormal radiographs have usually been the standard to differentiate infection and disease. However, it is challenging to diagnose subtle adenopathies in radiographs, even for experienced pediatricians.[29] Computed tomography (CT) of the chest would be useful to further define the anatomy in cases where findings in plain radiographs are equivocal. Findings in children with suspected primary pulmonary TB include multiple lymph nodes (Fig. 3), ''ghost-like'' ring enhancement, and bronchial compression; calcifications have been seen in 15—20% of cases.[30] Primary and secondary TB is also thought to have characteristic radiographic and clinical features: primary TB is said to be characterized by lower lobe disease, adenopathy, and pleural effusions, and termed atypical, whereas secondary or reactivation TB is associated with upper lobe disease and cavitations termed typical.[31]

Pleural effusions complicate 2—38% of cases of pulmonary TB in children, usually unilaterally (Fig. 4).[32] Primary pulmonary TB disease with pleural effusion is often found in the absence of pulmonary parenchyma disease. Secondary (post primary) pulmonary disease associated with pleural involvement is characteristically associated with focal parenchymal disease.[33] The most common symptoms are thoracic pain, cough, fatigue, shortness of breath, and anorexia. The findings on physical examination can mimic bacterial pneumonia, with dullness to percussion, diminished

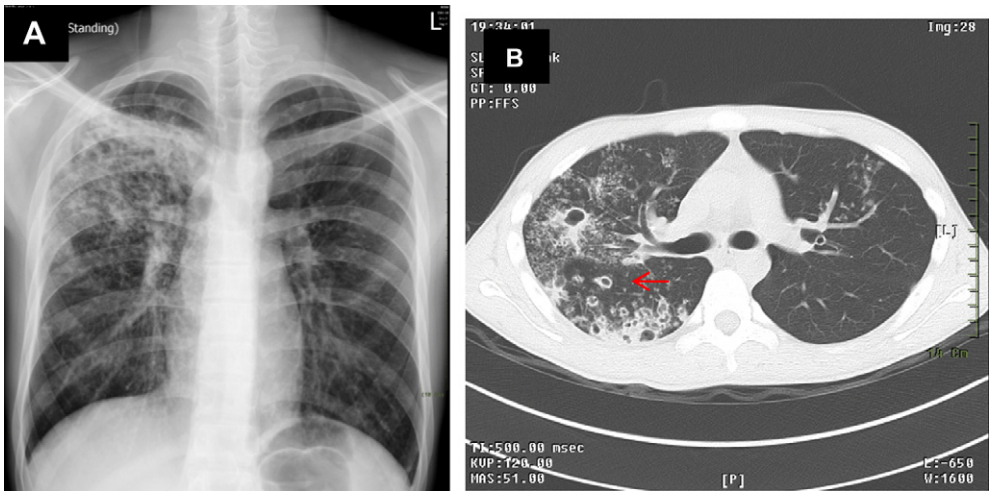

Figure 5 Secondary (post-primary) pulmonary tuberculosis. A 16-year-old male had a chronic cough and lost 10 kg bodyweight during the previous 6 months. (A) On admission, the chest X ray showed patchy, poorly defined consolidation with multiple cavitations over right upper lobe and upper segment of right lower lobe (posterior—anterior view). (B) Computed tomography (CT) showed bronchiectasis with bronchial wall thickening and a so-called ''signet ring sign'' (arrow).

breath sounds, and fever. Pleural fluid is rarely acid fast bacillus (AFB) smear-positive, and cultures are positive in only 20—40% of cases.[34]

Secondary (post-primary) pulmonary TB disease

Secondary pulmonary disease usually presents during adolescence and is most common in areas endemic for TB and in HIV-infected patients. Symptoms include weight loss, fever, productive cough, hemoptysis, and night sweats. Findings on physical examination may be minimal. Radiographic findings can overlap with those seen in primary disease (Fig. 5).[31] Radiographic features of secondary TB include patchy, poorly defined consolidation for the upper lobes and cavitations (about half of the patients) in the absence of lymphadenopathy.[35—37] Chest CT shows tree-in-bud opacities and traction bronchiectasis, particularly of the upper lobes, and bronchial stenosis is seen in 10—40% of patients with active TB.[24]

Localized pleurisy overlying a peripheral Ghon focus was common. Limited adhesions developed between the visceral and parietal pleura, but this did not cause symptoms or lung function abnormality.[11] Effusions were rare in children under 5 years of age and were most common in adolescent boys.[34] Pleural effusions occur most often in primary TB but are seen in approximately 18% of patients with secondary TB; they are usually small and associated with parenchymal disease. The pleura may become thickened, which can result in a tuberculous empyema (Fig. 6) and an associated risk of developing a bronchopleural fistula. Residual pleural thickening and calcification may also occur.[24]

Central nervous system (CNS) TB infection

Involvement of the CNS is seen in approximately 5% of patients with TB. CNS TB can manifest in a variety of forms, including tuberculous meningitis, tuberculomas, tuberculous brain abscesses, tuberculous cerebritis, and miliary TB.[38—42] The most common complication of TB meningitis is communicating hydrocephalus, followed by ischemic infarcts (20—40%) and cranial nerve involvement (17—70%).[43—45] CNS TB most commonly presents 2—6 months after primary infection, and almost half of patients are under 2 years of age.[46] Chest radiographs are abnormal in

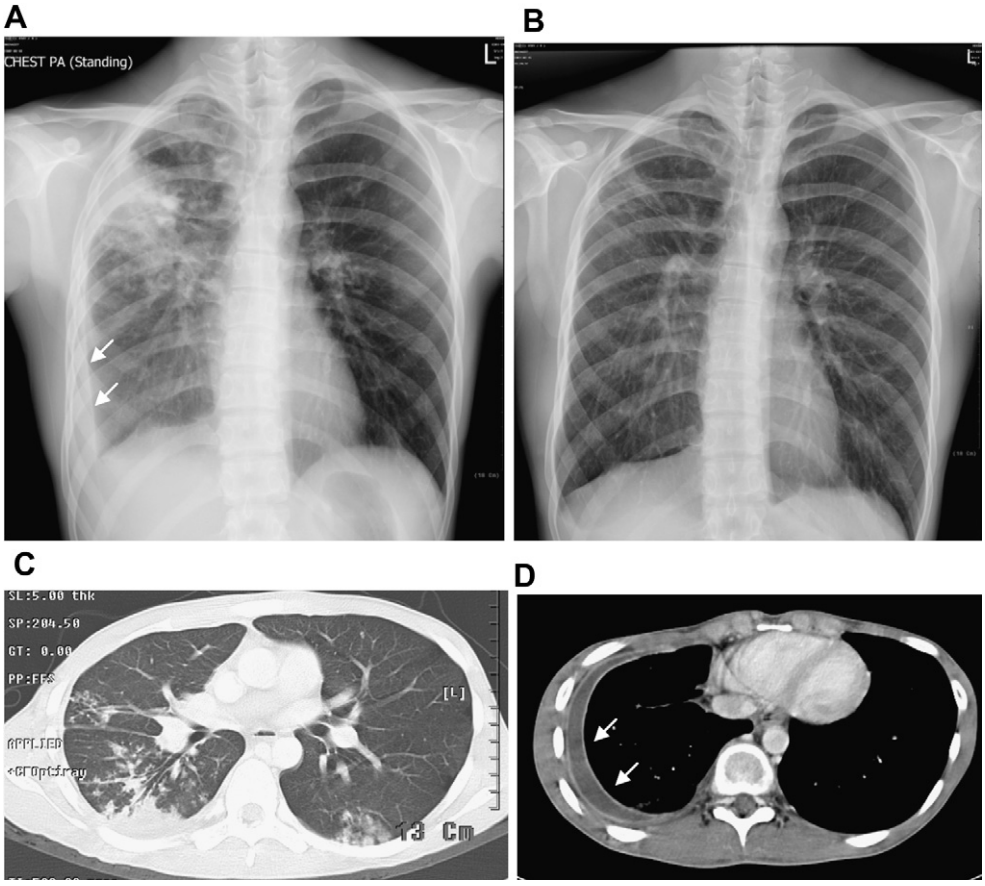

Figure 6 Secondary pulmonary tuberculosis (TB) with pleural effusion. A 17-year-old male visited the emergency department having had a 3-day fever. He had a chronic cough for 3 months. His grandfather was diagnosed with pulmonary TB 6 months earlier. (A) On admission, chest radiograph showed right upper lung patches with parapneumonic opacities (arrows). Computed tomography (CT) showed right apical lung cavitations, (C) right upper lung bronchiectasis with multifocal consolidation and "tree-in-bud" opacities, and (D) local pleural thickening and effusion. Pleural fluid was positive for *Mycobacterium tuberculosis* in TB-PCR analysis. (B) Follow-up radiographs 6 months after complete anti-TB treatment showed complete resolution.

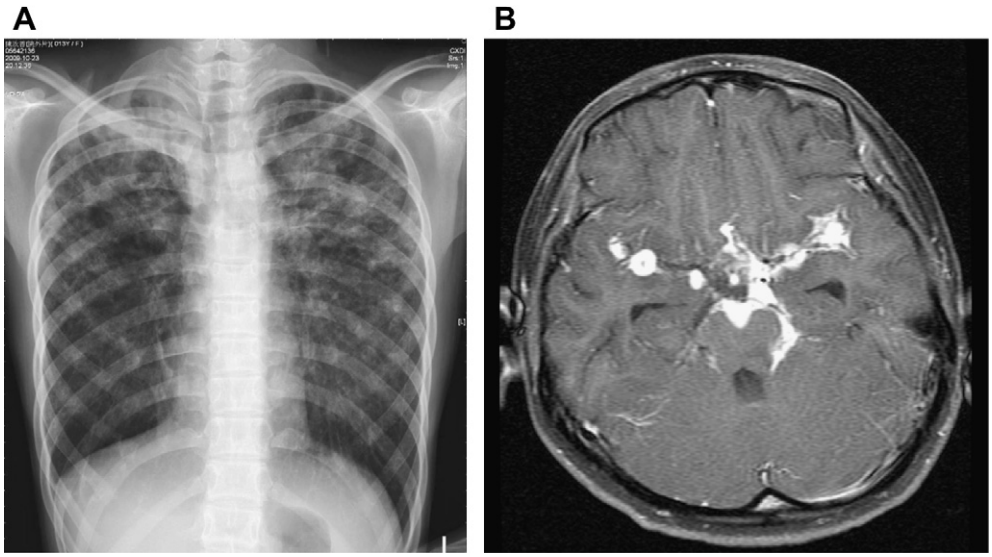

Figure 7 Tuberculosis (TB) involving the central nervous system (CNS). A 14-year-old girl was diagnosed with pulmonary TB 2 months before admission. She visited our emergency department because of neck stiffness and fever for 3 days. (A) Chest radiographs at admission showed patchy, poorly defined consolidation for the upper lobes, which are characteristic of secondary pulmonary TB. Sputum smears were heavily positive for acid-fast bacilli and culture positive for *Mycobacterium tuberculosis* thereafter. Magnetic resonance imaging (MRI) 2 months later showed cerebritis at left basal ganglia, left thalamus, left cerebellar peduncle, left midbrain, and left pons. (B) T2-weighted MRI showed the presence of granuloma, a so-called "paradoxical response".

almost 90% of children with CNS TB (Fig. 7). The most common findings include hilar or mediastinal adenopathy, pulmonary infiltrates, and miliary disease. TB meningitis is characterized by a cerebrospinal fluid analysis with pleocytosis, high protein, and hypoglycorrhacia.[47] AFB stains are positive in only 10—30% of patients, and culture yield is somewhat higher (30—70%) if 5—15 cm^3 of cerebrospinal fluid is cultured.[48] Gastric aspirates cultures are positive in approximately 10% of children with TB meningitis.[41,46] Tuberculomas and meningitis may coexist in up to 10% of cases. The clinical and neuroimaging features of tuberculoma are variable and may pose a diagnostic challenge in the absence of systemic TB or tuberculous meningitis.[49] They appear radiographically as hyperdense, rim-enhancing lesions ranging from 1 cm to 5 cm in maximum dimension. Whereas adults commonly have multiple supratentorial lesions, single infratentorial lesions are more common in children.[50] Tuberculomas can also either develop or enlarge paradoxically after the initiation of antimycobacterial therapy. A paradoxical response is defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions not attributable to the normal course of disease, in a patient who initially improved with antimycobacterial therapy (Fig. 7). Up to 10% of patients with CNS TB report paradoxical responses, and this number may be as high as 30% in HIV-infected patients.[51,52]

Conclusions

Only 5—10% of immunocompetent children progress from TB infection to disease. Risks of progression to disease are dependent upon host factors such as patient age and immune status. The most common sites of infection are the lung and superficial lymph nodes in children. Rapidly progressive forms of disease include CNS involvement and disseminated (miliary) TB; later complications include skeletal and renal disease. Childhood TB is associated with relatively lower culture yields than in adults; the diagnosis is often based on a positive skin test, epidemiological risk factors, and clinical presentations.

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