Tuberculosis in children

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Abstract

The global burden of tuberculosis (TB) in children remains high. There is increasing attention from clinicians and public health perspectives about this trend, as new occurrence of TB in children is a sentinel event and an indicator of ongoing transmission in the community. The variation in clinical presentations, lack of standardized case definition, difficulty in making diagnosis and subsequent notification made the management and control of tuberculosis in pediatric population very challenging. Over the past decade, there are noticeable advances in our understanding of the disease, diagnostics and management TB in children. This article provides an overview and update on the epidemiology, natural history, clinical manifestations, various diagnostic tests and treatment of TB in children.

Keywords childhood; diagnosis; management; paediatric; tuberculosis

Epidemiology

The scale of the problem

The estimation of TB incidence in children has always been challenging. This is due to the fact that most cases occur in developing countries where affected children remain undiagnosed due to poor healthcare access. In addition, the lack of definitive diagnostics in TB in children, the highly variable presentation, and low rate of positive culture and smear, and non-vigilance in reporting TB cases to public health authorities made an accurate assessment of incidence of childhood TB more difficult. However, there is increasing attention to TB in children as most children are infected by household contacts who are infected with TB and new occurrence of TB in children is an indicator of ongoing transmission in the community.

The figures are stark. In 2014, there were 9.6 million people infected with TB and 1.5 million people died from TB worldwide. Among these 9.6 million people, 1.0 million were children. The numbers continue to rise. The World Health Organization (WHO) estimated there were 8.7 million cases of TB in 2011. In 2014, 359,000 new and relapse cases of childhood TB were reported, with a 30% increase as compared to 2013. The greatest increases were noted in India and the Philippines.

The reasons for this increase are unclear. However, it is useful to note that in the latest WHO TB report in 2015, an updated methodology was used to estimate TB incidence among children where case notifications rates were adjusted for under-detection and under-reporting. Dynamic modeling was used to statistically estimate the incidence, aiming to achieve a more accurate estimation of incidence of TB in children in light of the above factors.

Where in the world?

South-East Asia, in particular India, Indonesia and China, and Western Pacific Region, accounted for 58% of the global TB cases in 2014. Africa is the place with highest incidence rate per population, and accounted for 28% of the whole world's TB cases. A small number of cases were reported in Americas and European countries. Although the notification rates were slightly decreasing in most western regions, there were still concerns on the increase in numbers of immigrants from endemic areas and ongoing transmission in the community particularly in large metropolitan cites. In 2014, 58,008 TB cases were reported in European countries. Romania, Poland and United Kingdom were the top three countries where around 50% of cases were reported. Overall 26.8% of cases were foreign in origin and in some European countries up to 80% of cases were foreign-origin TB cases. The rate of TB in children remained less than five cases per 100,000 populations in European countries. Similar trends were seen in United States. There were total of 9,412 reported cases of TB in 2014 with an annual decline of 2.2% in incidence rate. 66% of all reported cases were foreign-origin cases.

Natural history

Almost all TB infections in children are contracted by inhalation of droplet particles generated from another infected person with pulmonary TB. When the airborne droplets reach the terminal airways and alveoli, they are contained initially by the host's innate immunity with macrophages and carried by lymphatics to regional lymph nodes in immunocompetent patients. The Ghon focus is the primary lesion developed in the lung and is characterized by granulomatous inflammation caused by mycobacterium bacilli and is the feature of primary infection. The typical location of the Ghon focus is in the upper part of the lower lobe or lower part of the upper lobe of either the right or left lung, where the lobar fissures locate. This results in enlargement of regional lymph nodes and in association with the Ghon focus, they are called Ghon complex or primary complex. At this stage, children usually have non-specific respiratory symptoms or are asymptomatic.

The progression from primary infection to disease is signified by development of symptoms and signs of TB. The understanding of the natural history of TB is largely contributed to by literature during the pre-chemotherapy era and this gives us important insight into the disease spectrum and clinical manifestation. The rate of progression from primary infection to active disease is markedly different between children and adult. For children under 1 year of age, the rate of progression is up to 30–40%, while the risk is at 24% for children aged between 1 and 5 years old. The risk of progression drops beyond 5 years of age and increase again during adolescence. This forms the classically described bimodal pattern. In children, the majority of cases (>90%) progress to active disease within one year after primary infection, in contrast to a much longer time interval, sometimes up to decades, in adults. The clinical manifestation also varies

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according to the age at which the infection becomes active. Progressive disease in infants and younger children tends to result in haematogenous dissemination, causing significantly advanced disease such as miliary disease or meningitis. When approaching adolescence, the presenting phenotype mimics adult-type reactivation disease, as characterized by cavitatory lung lesions and associated pulmonary changes. There are ongoing studies into the pathogenesis of tuberculosis which provide insights into such a switch of clinical phenotype as age progresses.

Latent TB infection

Latent TB infection (LTBI) means TB infection in an individual without evidence of active TB disease. LTBI is diagnosed in children with a positive tuberculin skin test or interferon gamma release assay, and active disease being ruled out by absence of symptom, normal physical examination and normal chest radiography. Infrequently chest radiography may show evidence of healed infection like pleural thickening or calcified non-enlarged regional lymph nodes. Universal screening for LTBI in children is not recommended due to high false-positive result. Instead, testing for LTBI is indicated in children with household exposure or close contact with patients suffered from TB disease, and children who plan to start immunosuppressive treatment as such treatment may increase the risk of TB reactivation.

Clinical manifestations

Pulmonary tuberculosis

Pulmonary TB and associated intrathoracic lymphadenopathy are the most common presentations of TB in children. The clinical symptoms in children are often non-specific and overlap with many other chronic diseases. The common symptoms in children with pulmonary TB include prolonged nonproductive cough, intermittent low grade fever, constitutional symptoms including weight loss or failure to thrive. However these symptoms are non-specific and they are not different from features of other forms of lung diseases. Wheezing secondary to endobronchial obstruction by intraluminal granuloma or extrinsic compression from adjacent lymphadenopathy has been reported to be a great mimicker of asthma but is not commonly encountered in the UK.

There are many diagnostic scoring symptoms attempting to improve clinical identification of potential cases but they remain unrevealing and imprecise. Pulmonary TB usually involves the right upper and middle lobe and left upper lobe where ventilation is the greatest. This can take the form of a primary complex with associated lymphadenopathy while calcification and cavitatory lesions are not common. Pleural involvement is secondary to direct invasion of the pleural cavity, resulting in pleural effusion and occasional empyema. Frontal and lateral views chest radiography is one of the very useful and essential tools for diagnosis of TB in children. However the chest radiography findings in children are also highly variable and can be non-specific. The most common radiological findings are that of hilar or subcarinal lymphadenopathy (Figure 1), in the absence of significant parenchymal changes. When approaching adolescent age, the classical adult radiological pattern with cavitatory lesions and upper lobe infiltrates dominates (Figure 2). Chest computed tomography (CT) offer superiority towards delineation of parenchyma, lymphadenopathy, endobronchial lesions and cavitation.

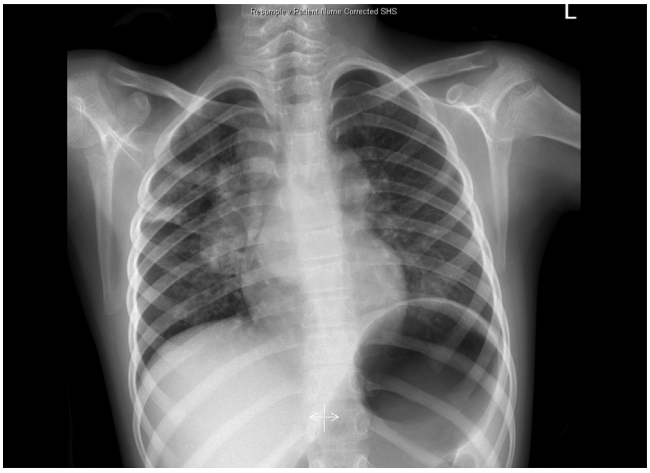

Figure 1 Chest radiography of hilar lymphadenopathy in a child with tuberculosis.

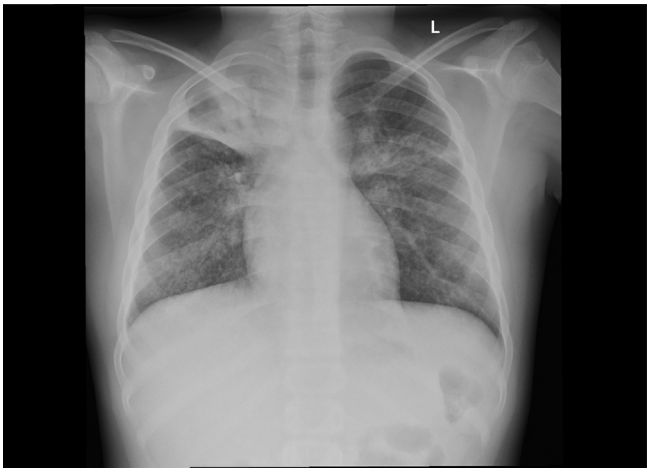

Figure 2 A cavitatory lung lesion in an adolescent with tuberculosis.

However, CT is not recommended for routine evaluation of TB in children due to its high radiation dose.

Extrapulmonary tuberculosis

Extrapulmonary manifestation of tuberculosis in children involves a wide range of phenotypes.

Tubercular adenitis: Tuberculosis lymphadenitis is the most common form of extrapulmonary tuberculosis. The lymph nodes are usually located in the lymphatic drainage areas of a pulmonary focus. They are usually painless, fixed, chronic and occasionally fistulating involving the cervical, supraclavicular, submandibular and preauricular regions. Where clinical suspicion of TB exists, lymph nodes which persist for more than 4 weeks, are greater than 2 cm in size and fail to respond to first-line antibiotics are suggestive of TB adenitis.

Tuberculosis meningitis: Tuberculosis meningitis is the second most common extrapulmonary manifestation of TB in children. It usually occurs in infants and children under 5 years old. The main presenting clinical features are altered consciousness, focal neurological signs, fever and seizures. In younger infants, the