



Post-tuberculosis Sequelae in Children

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Abstract

Tuberculosis (TB) is a global health problem especially in the Indian subcontinent imposing significant physical, psychosocial and economic burden on the society. Most national programs define TB cure as completion of treatment with improvement in clinical symptoms, microbiological and radiological clearance. However, follow up these patients for long-term sequelae or complications has not got adequate attention. Post-TB lung disease, neurological deficits and spinal deformities are some of the post-TB sequelae reported in adults, with scanty data available for children. With this review authors attempt to discuss various post-TB disease manifestations and the risk factors associated with their development in children. They address the need to create awareness amongst physicians involved in managing children with TB and obtain more scientific data in this field.

Keywords Post-tuberculosis sequelae; Complications of tuberculosis in children · Post-tuberculosis lung disease · Childhood TB

Introduction

Tuberculosis (TB) continues to be a global health problem with 10.6 million cases of TB reported worldwide in 2021, which is a 4.6% increase in the prevalence as compared to previous year. As per the WHO Global Report 2022, India accounted for 28% of total global cases. Out of the 10.6 million cases, 1.2 million were children i.e. 10.9% of total incident cases globally [1]. As per the National TB Elimination Program (NTEP) data in 2022, incidence of TB in India was reported to be 228 per 1,00,000 population and TB mortality was 33 per 1,00,000 population [2].

The focus of attention has been early diagnosis of TB (including upfront diagnosis of rifampicin resistance), better TB cure rate and a lower relapse rate. Unfortunately, little attention has been paid to post-TB sequelae in clinical practice and research. Modelling health outcomes of patients with TB found that post-TB sequelae accounted for 47% of the 122 million disability-adjusted life years (DALYs) attributed to total incident TB in 2019. For children, the estimated

proportion of DALYs caused by post-TB sequelae in 2019 was modelled at 49% of the 21 million DALYs [3].

This review summarizes the pulmonary and extra-pulmonary post-TB sequelae specifically in children. Risk factors for development of such sequelae are also discussed.

Overview of Post-tuberculosis Sequelae

Several post-TB sequelae have been reported after treatment completion from a period of few months to years. Pulmonary problems are more common in adults while children seem to have more of extrapulmonary sequelae. A systematic review including 3529 children with TB identified a wide spectrum of post-TB morbidity ranging from long-lasting, disabling somatic to psychosocial impairment [4]. The most common post-TB sequelae are spinal deformities, residual neurological disease leading to permanent disability and long-lasting lung injury. Decreased growth potential or failure to gain weight in post-TB children is well-documented in literature [5]. TB at an early age is associated with lower length-for-age, weight-for-age and body mass index z-scores at 5 y of age in children [6]. Figure 1 shows various post-TB sequelae.

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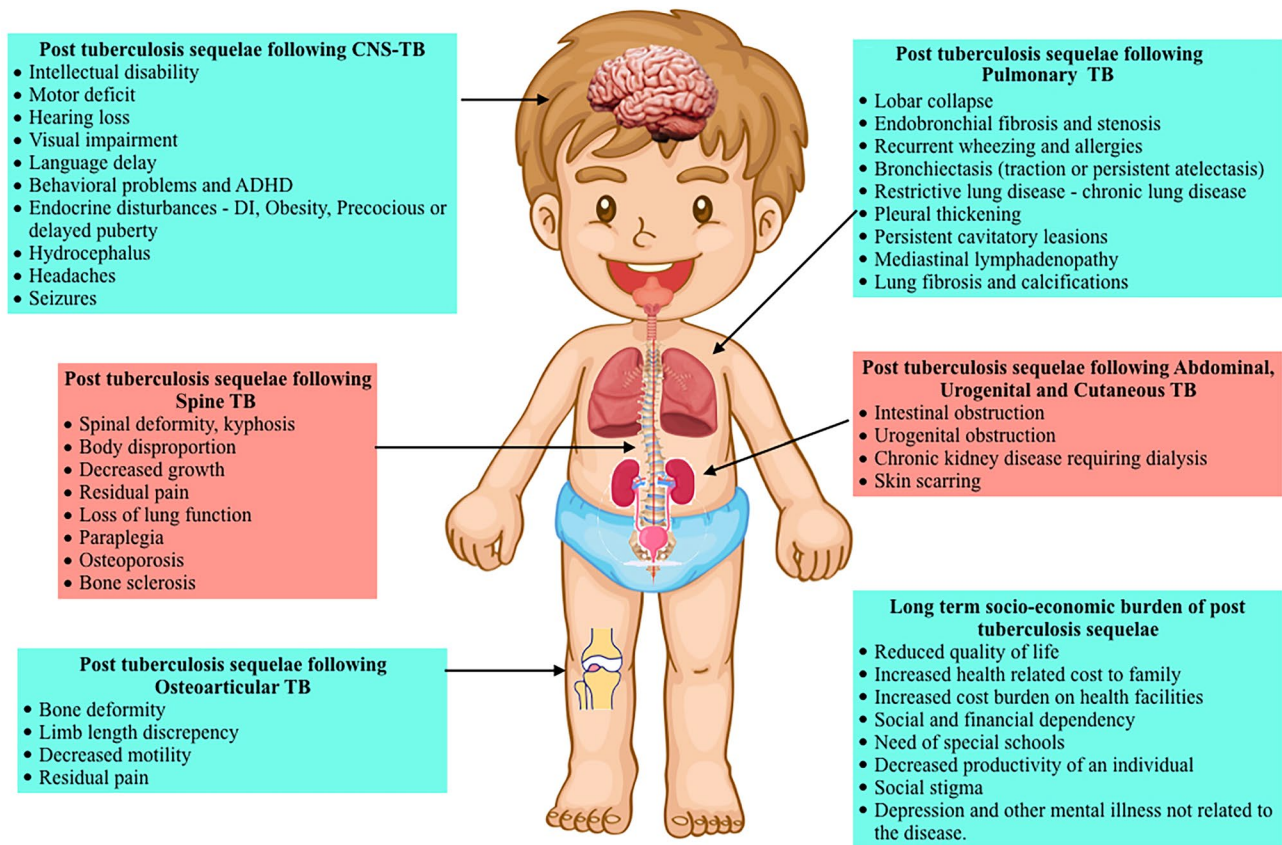


Fig. 1 Overview of post-tuberculosis sequelae in children. *ADHD* Attention deficit hyperactivity disorder, *CNS-TB* Central nervous system tuberculosis, *DI* Diabetes insipidus

Post Pulmonary Tuberculosis Sequelae

Clinical Manifestations

The most common sequelae of pulmonary TB is persistence of lobar pneumonia/atelectasis on follow up radiology [7]. Lobar pneumonia/atelectasis may be due to endobronchial lesions, extrinsic compression by enlarged lymph nodes or residual bronchiectasis. Residual bronchiectasis in adults has been reported in up to 19.7% of TB patients [8]. Residual cavitation is seen in adolescents with destructive type of TB lesions at diagnosis [9]. Post-TB tracheobronchial stenosis is reported in 68% of adults with pulmonary TB despite adequate chemotherapy. In children, 40–50% of patients might have concurrent tracheobronchial stenosis with pulmonary TB [10]. Other complications reported are fibrotic changes in lung parenchyma, mediastinal lymph node enlargement and calcifications and pleural TB related complications like pleural thickening [4]. Some studies have also found significant higher risk of chronic cough [6] and recurrent wheezing at

5 y of age [6, 7]. Possible etiology includes endobronchial disease in younger age group leading to bronchial wall fibrosis and narrowing or extrinsic compression by persistent enlarged lymph nodes. Figure 2 shows radiological images of post pulmonary TB complications while Fig. 3 shows a case of a child with left main stem bronchus following pulmonary TB.

Some data is available on long term lung function in patients with pulmonary TB. Restrictive pattern has been seen in majority of children with impaired lung function [5]. Low FEV1 and obstructive airway disease has also been reported in children and adults with pulmonary TB in follow up [5, 6].

Risk Factors

Demographic factors associated with higher risk of pulmonary sequelae are younger age of presentation and rural population in low and middle-income countries [11]. Rural population has poor access to health care leading to delay in diagnosis and treatment. In addition, increased exposure to indoor smoke and biogas exposure is contributory. These environmental factors

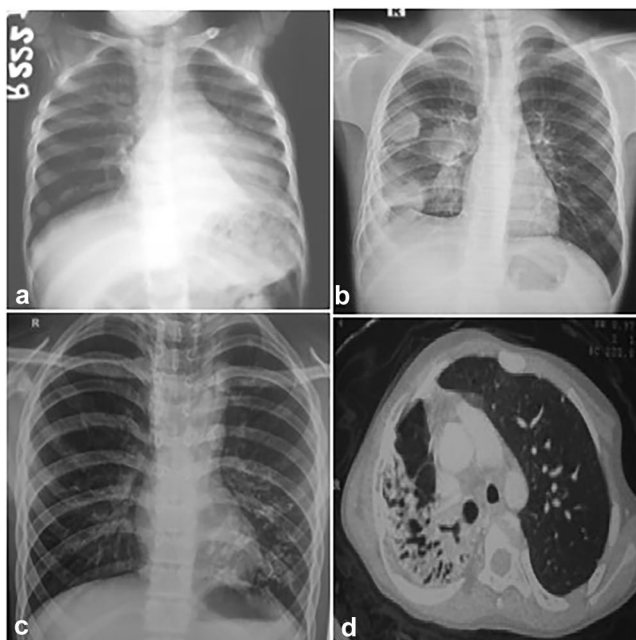


Fig. 2 Radiological images of post-tubercular lung disease in children. **a.** Left lower zone persistent collapse-consolidation. **b.** Right sided pleural thickening. **c.** Calcification in left lower zone and hilar lymph node. **d.** Right lower lobe fibro-atelectasis with volume loss of right lung

have been implicated independently for poor lung outcomes in patients with pulmonary TB [9, 12, 13]. Clinical factors like increased severity of symptoms, worse X-ray findings at the time of diagnosis and long duration of symptoms prior to start of treatment are risk factors for poor lung outcomes at the end of treatment and on 2 y follow up [4, 11, 12, 14]. Multi-drug resistant TB (MDR-TB) is associated with worse clinical outcomes and more extensive lung injury [9, 15]. HIV TB-coinfection is common but it is still unclear whether the risk of sequelae is higher or not. Few studies have suggested a reduced risk of post-TB lung disease probably due to protective

balance between low CD4 counts, impaired immune responses to mycobacterial infection at the time of diagnosis and immune reconstitution for patients on concurrent anti-retroviral therapy (ART) and anti-tubercular therapy (ATT) [4, 9, 16].

Prevention

Early diagnosis, prompt initiation of ATT, ensuring completion of treatment, regular monitoring of clinical response and early detection of MDR-TB are important to prevent development of pulmonary sequelae.

Treatment

Lung rehabilitation by breathing exercises, chest physiotherapy and airway drainage techniques can be employed to treat persistent atelectasis and bronchiectasis. Regular monitoring of lung function is important for prognosis. Bronchoscopic interventions might be required in cases with persistent atelectasis and tracheobronchial stenosis. Opening of the stenotic area with electrocautery or laser and balloon dilatation can restore airway patency. Surgical intervention might be useful in some cases like severely bronchiectatic lung/lobe with recurrent infections or severe tracheal stenosis.

Post Central Nervous System (CNS) Tuberculosis Sequelae

Clinical Manifestations

Children with TB meningitis (TBM) can have many post-TB sequelae which could be motor deficits, sensory problems, seizure disorder, intellectual and behavioral problems and occasionally mortality.

Overall prevalence of neurological abnormalities in children following CNS TB is reported to be as high as 49%,



Fig. 3 A 6-y-old boy suffered from pulmonary tuberculosis and completed 6 mo ATT. Chest X-ray at the end of treatment showed opacification of left hemithorax (**a**). Axial CT chest image at the level of

the carina showed mediastinal shift to left and non-visualization of the left main bronchus (**b**). Axial CT chest image at the level of the ventricles shows complete left lung atelectasis (**c**)

intellectual disability being the most common (21%) [4]. Reported IQ scores in children post TBM ranged from 36 to 102 with low intellectual level in most children [17]. Poor scholastic performance, general behavioral disturbances (anxiety, depression, aggression, attention deficit) and emotional disorder have been reported in children post-TB meningitis [17–19]. Motor deficits following CNS TB with impaired ambulation and seizure disorder was seen in 17.6% and 6.2% children with TBM [4].

Radiologically, persistent intracranial calcifications and hydrocephalus have been reported in various studies associated with focal neurological deficits [20, 21]. Sensory deficit such as vision loss (5.2%), hearing loss (11.4%) and/or speech deficit (5.4%) has been reported extensively as poor outcome in several studies following CNS TB [4, 17, 20, 22]. Hypopituitarism was seen in 20.4% patients, years after completion of TB treatment leading to various hormone deficiencies [21]. Risk of mortality after CNS TB in children is high (upto 20% in some studies) especially in children with stage 3 TBM with significant CSF abnormalities, infarcts and hydrocephalus [23].

Risk Factors

The risk factors for a poor CNS outcome are younger age at presentation (especially <5 y), severe disease at presentation, longer duration of symptoms before treatment initiation and poor socio-economic background [4, 18, 20, 22]. Cerebrospinal fluid (CSF) parameters at diagnosis such as increased CSF protein >100 mg/dL is associated with poorer outcomes [20, 22]. Presence of hydrocephalus and infarct on neuroimaging are also associated with poor outcome despite medical management of raised intracranial pressure (ICP), placement of shunts and steroids [19, 20, 22]. A delay of more than 5 d in placement of shunt in children with hydrocephalus leads to poor motor, sensory outcome and persistent raised ICP [19].

Treatment

Early diagnosis and timely initiation of TB treatment is essential. Early use of steroids is essential and has been shown to reduce mortality and many post-TB sequelae [24]. Ventriculo-peritoneal shunt surgery to decrease persistently raised ICP can reduce motor and sensory disability in children with hydrocephalus. Neuro-rehabilitative measures should be taken to improve quality of life in children with disability.

Post Spine Tuberculosis Sequelae

Clinical Manifestations

Spinal TB causes bone loss and damage to the vertebral bodies leading to disproportionate growth of the spine and kyphosis. TB of dorsal spine almost always produces kyphosis while cervical and lumbar spine shows reversal of lordosis to begin with, followed by kyphosis. Kyphotic deformity can occur even after healing, and its progression has been reported in 41% of children with spine TB in some studies [25]. Children can present with late onset paraplegia due to intrinsic changes in spinal cord [26]. Severe restrictive lung disease can happen in almost 50% children with severe kyphosis [27]. Other reported complications are early complete or partial fusion of vertebral bodies leading to decreased growth, residual sequester, osteoporosis, bone sclerosis and calcification [4].

Risk Factors

Involvement of thoracic spine, multiple vertebrae and presence of paravertebral abscess with positive bacteriology were noted to be significant risk factors in development of kyphoscoliosis and buckling collapse at follow up of 15 y [25, 28]. Younger age, especially infants, is also associated with a worse clinical outcome as vertebral bodies in children are mainly cartilaginous [26, 28, 29].

Prevention

Kyphotic deformity can be prevented by early diagnosis and treatment of TB before kyphosis sets in [30]. Growth in children with spine TB must be monitored until skeletal maturity. Bracing can be quite helpful in preventing vertebral collapse and neurological sequelae. Early involvement of orthopedic spine surgeon is important to improve outcomes.

Treatment

Regular monitoring for progression of kyphosis and lung function is important to plan corrective spinal surgery early and prevent permanent disability. Rehabilitation with physical and occupational therapy should be done regularly. Surgical correction of kyphotic deformity is challenging and is advised only in children with paraplegia or risk of death due to reduced lung function.

Post Osteoarticular TB Sequelae

Children with osteoarticular TB especially involving the hip and knee can lead to many sequelae. The most frequent findings are limb length discrepancy, restricted mobility, residual pain and bone deformity [4].

Urogenital TB

In a large Indian study on urogenital TB in children many sequelae were seen. Chronic renal failure was seen in 20% (7/35) of children at follow up. All 35 children showed cicatrization sequelae with 10 children requiring second-look endoscopic or surgical reconstructions for obstruction and functional impairment [31].

Implications of Post-tuberculosis Disease and Future Perspective

Residual impairment in children has many physical and psychological implications by hampering growth potential and leading to a poor quality of life. There is a need for a more robust follow up post treatment completion. Follow up every 3 mo post treatment for next one year and every 6 mo in the subsequent year is recommended.

Increasing awareness amongst pediatricians and all doctors in the NTEP, caring for children with TB regarding the broad spectrum of post-TB manifestations in children will help in implementing preventive strategies and employing early management measures. This will reduce morbidity due to post-TB sequelae.

There is also a need for prospective studies looking at epidemiology of various post-TB sequelae and risk factors for both pulmonary and extra-pulmonary disease [32]. This is crucial to make necessary policy changes at the national level. With the goal of TB elimination from the country, there is a need for the NTEP to also include post-TB sequelae as a long term outcome measure.

Authors' Contributions Both authors contributed to literature review, designing and writing of the manuscript. AP will act as guarantor for this manuscript.

Declarations

Conflict of Interest None.

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