Extra-pulmonary Head & Neck Tuberculosis in Children of the Developed World, an Old Enemy Revisited.

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Introduction

Mycobacterium tuberculosis (TB) is the second most common infectious cause of death globally, after Human Immunodeficiency Virus (HIV).[1] Resurgence in the disease is largely due to HIV co-infection in high-prevalent communities, mostly affecting regions within the developing world.[2] Regions with the highest proportion of cases are in my home country in Africa (31%) and Asia (55%). In contrast, over the last two decades there has been a decline in the rates of TB in developed countries,[3] with the lowest reported cases in the Americas (3%) and Europe (5%).[4] Declining prevalence rates in Canada, where I am currently training, have lead to a lack of experience among physicians, possibly contributing to a low index of suspicion and diagnostic delays.[5] When we were presented with a case of extra-pulmonary TB (EPTB) that I managed with the well-worn algorithms I had learned whist training in South Africa, I was encouraged to organize my thoughts and share them with colleagues via the IAPO manual.

Pulmonary TB makes up approximately 51% of all TB cases.[6, 7] EPTB results from dissemination of the disease to various other parts of the body. Common sites include lymph nodes, central nervous system (CNS), bone, pleura, abdomen and genitourinary tract.[6, 8] As this review is aimed at Otolaryngologists, the focus is mainly on EPTB-related cervical lymphadenopathy.

Childhood TB

The prevalence of TB in children is estimated at < 5% in low burden countries.[4] In Canada, TB in children is largely a disease of Aboriginal and foreign-born children, and Canadian-born children of foreign-born parents.[3] An infected child usually represents a sentinel event within a community, indicating recent transmission from an infectious adult with pulmonary disease. Childhood TB is therefore considered a reflection of TB control in a population.[7, 9]

Children when compared to adults are more likely to develop active TB following exposure.[2, 10] In general, the risk of developing active TB and/or advanced forms of TB following infection, is inversely related to age, highlighted in **Table 1** below.[11] Risk factors include age at exposure, nutritional and immune status, genetic factors, virulence of the organism, and magnitude of initial infection.[6, 9] In addition, EPTB is more common in children than adults, and is reported to occur in approximately 25% of infants and young children under 4 years of age.[12]

Table 1. Prevalence of Pulmonary and Extra-pulmonary TB (EPTB) per age group.[11, 13]

	Risk of disease following primary infection			Comments
	Disseminated tuberculosis/ tuberculosis meningitis	Pulmonary tuberculosis	No disease	
< 1 years	10-20%	30-40%	50%	High rates of morbidity and mortality
1-2 years	2-5%	10-20%	75-80%	High rates of morbidity and mortality
2-5 years	0.5%	5%	95%	---
5-10 years	< 0.5%	2%	98%	"Safe school years"
> 10 years	> 0.5%	10-20%	80-90%	Effusion or adult-type pulmonary disease

Natural history of the disease and clinical features

The pattern of disease is described in **Figure 1**. Following initial exposure and infection, the primary complex is characterized by a lung parenchymal infiltrate and associated regional lymph node enlargement. Most children are asymptomatic at this stage and in the majority of cases the infiltrate and lymphadenopathy will resolve spontaneously.[4, 9] If infiltrates continue to enlarge and progress to primary pulmonary TB, lesions can erode into pulmonary vessels resulting in hematogenous dissemination to the lung (miliary TB) and distant extra-pulmonary sites.

Most EPTB in children is presumed to arise from reactivation of latent infection, acquired during a primary infection that could have occurred earlier, or advancing active pulmonary TB that had spread outside the lung. Disease outside the lung parenchyma usually occurs through lymphatic spread and hematogenous seeding at the time of initial pulmonary infection. Other, more rare sources include ingestion and direct inoculation. The result is either acute extra-pulmonary illness or locally contained bacteria (with the risk of extra-pulmonary disease being reactivated at a later time).

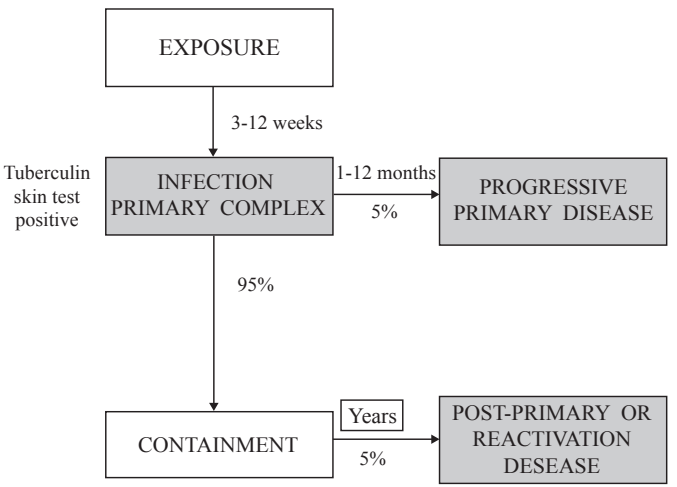

Figure 1. Nature of disease [4]

The majority of children (>50%) with TB disease will be asymptomatic. Of those that develop symptoms most will have pulmonary manifestations, while 25–35% of children will have extra-pulmonary symptoms. [6]

Systemic complaints such as fever, night sweats, anorexia and lethargy occur less often. The commonest symptoms at presentation in children with TB disease are cough in the preceding 3 months, persistent fatigue and weight loss, and the child is asymptomatic. Older children and adolescents are more likely to present with adult-like symptoms such as fever, night sweats, productive cough, chest pain and hemoptysis. [5, 10]

It is important to distinguish latent TB infection (LTBI) from active TB infection. In both there is evidence of TB infection (positive tuberculin skin test (TST) or blood-based immunological assay), however, in the latent infection there is no clinical, radiological or microbiological evidence of disease. [4, 7] Arguably, as there is not a long period of delay from infection to disease in children, it is often seen as a continuum of disease. The distinction of diagnosis into latent and active is for the purposes of management.

Specific Clinical Features of EPTB

Clinical manifestation is variable, the child uncommonly presents with pulmonary symptoms. Cervical lymphadenopathy is the most common form of EPTB in children, with estimates ranging from 60-75% of all EPTB.[6, 8, 12] This typically involves supraclavicular, anterior and posterior cervical, and submandibular nodes.[12] Without treatment, a cold abscess (the absence of an acute inflammatory infiltrate) or chronic sinus formation (often referred to as "scrofula") may develop.[8]

Diagnostic work-up

In general all children who have suspected TB lymphadenitis should have a full TB work-up that includes the following (**Table 2**):

Table 2. TB lymphadenitis should have a full TB work-up that includes.

1.	A detailed medical history that includes • General symptoms of weight loss, fever, malaise, cough, chest pain • Duration of cervical lymphadenopathy, growth, skin changes, drainage • Social inquiry- country of birth, travel to TB endemic regions, contact with people who have visited TB endemic regions • History of BCG vaccination, tuberculin skin test (TST), or chest x-ray if done prior, knowledge of HIV status
2.	Physical examination that includes • General appearance - growth assessment, weight loss, fatigue • Cervical lymphadenopathy – presence or absence of fistula formation, multiple matted nodes, tenderness, if unilateral or bilateral. • Pulmonary – usually asymptomatic, but can have a dry cough, hemotypsis, respiratory distress (especially if military) • Other extra-pulmonary sites: features of meningitis, bone
3.	Chest x-ray – evidence of primary PTB • Tuberculin Skin Test (TST)***** • Interferon-gamma release assays (IGRA)***** • HIV test (should be offered to all presumptive and diagnosed TB patients) • Other common ancillary tests are highlighted in the **Table 3** next page.

***** Ancillary diagnostic tests may be useful in raising the suspicion of TB lymphadenitis before definitive diagnosis, or in supporting the diagnosis of cases with non-diagnostic microbiologic or histologic findings, but are not diagnostic for TB. A negative result does not exclude the diagnosis of TB.

Table 3. Yield of *M tuberculosis* from various tests [2]

Type of specimen	Culture yield (%)	Advantages	Disadvantages
Gastric lavage	40-92	Highest culture yields especially in infants	Invasive procedure Requires three consecutive day early morning samples Requires trained nurse to pass nasogastric tube
Bronchoalveolar lavage	4-43	May be useful with bronchoscopy especially with bronchial obstruction or transbronchial biopsy	Invasive procedure Requires general anaesthetic and specialist facilities Low culture yield
Laringeal swab	27-63	Useful in children who are unable to expectorate	Low culture yield Require physiotherapist to obtain sample
Introduced sputum	20-30	Yield comparable to gastric lavage Safe and well tolerated even in infants	Infection control issues

Diagnostic studies for EPTB:

The importance of obtaining a positive culture cannot be over-estimated, not least to exclude drug-resistant TB. [6, 8]

Excisional nodal biopsy is favored as the method of choice for diagnosis in low endemic regions, having optimal diagnostic sensitivity despite being the most invasive approach. [8] A definitive diagnosis is yielded with culture or polymerase chain reaction (PCR) demonstration of *M. tuberculosis* in the excised lymph node. This also allows distinction from atypical mycobacteria that may also cause lymphadenitis as well as other infective causes like *Bartonella sp*. Culture is the gold standard for diagnosis, however it may take up to 4 weeks to yield results. A positive acid-fast bacilli (AFB) stain result indicates active TB, and has excellent specificity for *M. tuberculosis* in adults, less so in children. Histologic features, such as nonspecific lymphoid infiltrates, non-caseating granulomas, or Langerhan giant cells in areas of extensive caseous necrosis, support a diagnosis of probable tuberculosis in AFB-negative, culture-negative cases. Rare complications of excisional biopsy include postsurgical pain, wound infection, sinus formation, and scar.[8]

In TB-endemic countries **Fine Needle Aspirate (FNA)** has emerged as a first-line diagnostic technique, where the test is reported to be both sensitive and specific.[14] In resource-limited settings as these, it is considered is safer, less invasive, and more practical than biopsy. Notably, in the majority of FNA studies from these regions, the diagnosis of tuberculosis was based on detection of granulomatous inflammation.[8, 11, 15]

Radiologic Imaging

Ultrasound is considered a good first line investigation for cervical neck masses assessment. In addition, it also enables guided fine needle aspiration cytology. The combination of imaging and FNAC as a sensitivity of 92% and specificity 97% in distinguishing benign from malignant nodal disease.[16] Ultrasound findings when compared to metastatic nodes, typically revealed intra-nodal cystic necrosis,

matting and posterior enhancement. There is also a higher incidence of associated surrounding soft tissue edema.[8] Reactive nodes (including those in tuberculous lymphadenitis) demonstrate prominent vascularity confined mostly to the hilum. In contrast malignant nodes demonstrate more peripheral or capsular vascularity.[16]

CT findings reveal that TB lymphadenitis is variable depending on the degree of caseous matter. In the initial phase TB nodes may appear enlarged and attenuated to muscle. Later on in the disease process, with central caseation, the nodes become low density centrally, and frankly cystic, and is associated with a higher incidence of peripheral enhancement.[8, 17] When compared to lymphoma, hey are usually matted together with only minor surrounding inflammatory changes.[8]

Nucleic Acid Amplification (NAA)

NAA is automated real-time nucleic acid amplification technology that detects the presence of *M. tuberculosis* (MTB) DNA. It is also capable of testing for mutations in the *rpoB* gene. Using the Xpert MTB/RIF system diagnosis of TB within 2 hours of testing.[9] Other advantages include simultaneous detection of tuberculosis and rifampicin resistance. *RpoB* mutations identify 95% of resistance to rifampicin (taken as an indicator of multi-drug resistant TB). This is a huge advance in TB diagnostics. The Xpert MTB/RIF system is recommended by the 2014 Canadian guidelines for TB investigation of pulmonary and extra-pulmonary TB in adults and children. The guidelines further recommend that Xpert MTB/RIF may even be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for non-respiratory specimens (lymph nodes and other tissues) from children suspected of having EPTB.

Management

Patients need to be managed by a multi-disciplinary team of medical practitioners, specialist nurses and social workers.[10] Effective therapy, anticipated drug-related issues in regards to toxicity and/or resistance as well as preventative practice for potential contacts, will need to be addressed, and ideally the team would be best overseen by an Infectious Disease Specialist.

Medical Therapy

First-line treatment for extra-pulmonary TB (EPTB) is the same as for pulmonary TB.[8] Previously all doses were extrapolated from adult regimens, but now the World Health Organisation (WHO) has released 2014 TB guidelines, allowing medication to be titrated according to weight and age of child, thereby avoiding toxicity or undertreating.[8] The WHO recommends daily treatment that includes dose-related 6 month course of the following drug therapy outlined in **Table 4**.[2]

Table 4. First Line Drug Therapy Regimen[2]

Medication	Daily Dose**	Intermitent Twice Weekly Dose** †	Available Dosage Forms	Principal Adverse Reactions
Ionized	10-15 mg/kg ‡ (max. 300 mg)	20-30 mg/kg (max. 900 mg)	10 mg.mL suspention 100 mg tablet 300 mg tablet	• Mild hepatic enzyme elevation • Hepatitis • Gastritis • Peripheal neuropathy (see pyriforme below) • Hypersensitivity
Rifampin	10-20 mg/kg (max.600 mg)	10-20 mg/kg (max. 600 mg)	10 mg/mL suspention (reconstttuted shelf life = 1 month) 150 mg capsule 300 mg capsule	• Orange discoloration of secrerions • Vomiting • Hepatitis • Flu-like illness
Pyrazinamide	15-30 mg/kg (max. 2g)	50 mg/kg (max. 4g)	500 mg scored tablet	• Hepatotoxicity • Hyperuricemia • Arthralgia
Ethambutol	15-20 mg/kg § (max. 1g)	50 mg/kg (max. 2.5 g)	100 mg tablet 400 mg tablet	• Optic neuritis with decreased visual acuity and decreased red-green colour discrimination • Gastrointestinal disturbance

The Initial Intensive Phase of 4 months in duration is with all 4 drugs (Rifampicin, Isoniazid, Ethambutol, Pyrazinamide). This is then followed by the **Later Continuation Phase of 2 months** duration with only 2 drugs (Isoniazid and Rifampicin).

The current Canadian National guidelines recommend that in uncomplicated pulmonary disease or single sited lymph node disease, ETH can be omitted in the Initial Intensive Phase.[9] In addition, children with suspected or confirmed TB lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV-negative, can be treated with a three-drug regimen (Isoniazid, Rifampicin, Pyrazinamide) for 2 months followed by a two-drug (Isoniazid and Rifampicin) regimen for 4 months.[9]

Patients with confirmed drug resistance will need second-line drug therapy regimens, depending on the specific drug involved. Monitoring of response to treatment in cervical lymphadenopathy-related EPTB, is primarily based on symptomatic improvement, weight gain and reduction of lymphadenopathy. This can often take months or years. If there is any discomfort in the affected swollen glands, the role of steroid therapy can be discussed, however, this is not routine practice.[8]

It is imperative to treat contacts who are children with symptoms suggestive of TB; children <5 years of age;children with known or suspected immunocompromising conditions (especially those living with HIV); and child contacts of cases with multidrug-resistant or extensively drug-resistant TB (proven or suspected). Children less than 5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated empirically for 6 months.[2, 9]

Conclusion

TB in children is particularly challenging due to its largely asymptomatic presentation, until rapid progression leads to advanced presentation. Furthermore, in low burden communities less awareness may lead to a delay in diagnosis. As such, it is imperative for Otolaryngologists to be aware of this disease and its management. Prompt and accurate diagnosis is important especially for pediatric patients, who more likely present with extra-pulmonary disease and can progress rapidly if not properly treated.

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