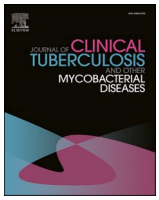
Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 33 (2023) 100392

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube



Morbidity and mortality in tuberculosis associated immune reconstitution inflammatory syndrome in children living with HIV: A narrative review

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ARTICLE INFO

Keywords:
Child/children
Tuberculosis
Immune reconstitution syndrome
TB IRIS
Mortality

ABSTRACT

Tuberculosis-associated immune reconstitution syndrome (TB-IRIS) is an increasingly recognized complication of children living with HIV who are receiving treatment for active tuberculosis (TB). The purpose of the study was to appraise available evidence of morbidity and mortality related to TB IRIS among the paediatric population. A non-systematic review of the literature was conducted by retrieving records from Scopus, PubMed and Google Scholar). Four specific research questions assessing the risk factors (age, undernutrition, extrapulmonary TB and degree of immunosuppression) for TB-IRIS were discussed. The search yielded 370 articles, subsequently screened for eligibility according to the inclusion criteria. The majority of the articles were adult studies. Six studies were identified: Three retrospective and three prospective studies. The majority of the studies were conducted in TB/HIV-endemic countries. Only one study addressed mortality due to TB-IRIS as an outcome. A total of 6 mortalities related to TB-IRIS were reported. Advanced immunosuppression is universally agreed as an established risk factor for mortality in TB-IRIS in children. The severe presentation was more common in children with extrapulmonary tuberculosis. There is a paucity of data available on mortality in HIV-infected children with TB-IRIS. Future research is needed to assess the predictive factors of morbidity and mortality in HIV-infected children with TB-IRIS especially in low resource and high endemic countries.

1. Introduction

Before the COVID-19 pandemic, tuberculosis (TB) was the leading cause of mortality by a single infectious agent, surpassing HIV/AIDS, and was the commonest cause of morbidity and mortality in people living with human immunodeficiency virus (HIV). In 2021, an estimated 1.6 million deaths were reported with 187 000 of them occurring in HIV-positive people. 11% of these deaths involved children [1]. TB and HIV interact synergistically by increasing the risk of acquiring active TB and accelerating HIV disease progression. TB risk is increased by 2-fold during the early phase of HIV infection and progresses to more than 20-fold once severe immunosuppression sets in. HIV may influence the clinical phenotype of TB whilst TB infection increases HIV replication [2]. Diagnosing TB in HIV-infected children is challenging due to the overlapping clinical features and limitations in the pre-existing diagnostic investigations. In addition to the paucibacillary nature of *Mycobacterium tuberculosis,* positive yield in children is low due to difficulties in sputum expectoration, invasive method of gastric sampling and long incubation period on culture medium [3]. Although a chest radiograph is a useful tool to aid diagnosis, HIV might influence TB interpretation on imaging due to HIV-associated respiratory disorders such as lymphoid interstitial pneumonitis or bronchiectasis [4].

TB/HIV co-therapy in children involves the administration of both anti-tuberculous (ATT) and anti-retroviral therapy (ART). Apart from drug-drug interactions, this combination may trigger a phenomenon known as immune reconstitution inflammatory syndrome (TB-IRIS). TB-IRIS is described as an abnormal, exaggerated immune response against Mycobacterium tuberculosis that frequently occur in HIV-infected patients [5]. TB-IRIS is classified either as paradoxical IRIS, ART-associated TB or unmasking TB-IRIS depending on the sequence of ATT and ART administration and site of TB at ART initiation. Paradoxical TB-IRIS may be subdivided further into CNS TB-IRIS as clinical manifestations and management in this subgroup differs [6]. Clinical manifestation of TB-IRIS varies from localized manifestation such as lymph node enlargement to systemic manifestation such as disseminated Bacillus Calmette Guerin infection. In one systematic review, the majority of TB-IRIS in children present as unmasking TB [7]. This narrative review aims to appraise available evidence on the spectrum of TB-IRIS in HIV-affected children, highlighting the morbidity and mortality related to TB-IRIS and the contribution of risk factors namely age,

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https://doi.org/10.1016/j.jctube.2023.100392

Available online 9 August 2023

undernutrition, extrapulmonary TB and degree of immunosuppression in the clinical progression of the disease.

2. Methodology

2.1. Study selection

Only articles related to paediatric patients less than 18 years old, confirmed HIV positive with TB-IRIS as measured outcomes were screened. Articles published in other languages than English were excluded. Publications found through a manual search of references and in authors' libraries are subjected to the same inclusion criteria. After the exclusion of duplicate citations, each title and abstract were screened. When abstracts did not include sufficient information to determine whether the article met the inclusion criteria, the article was reviewed in full.

2.2. Data sources and search

Literature reviews were conducted on paediatric TB-IRIS by using electronic databases SCOPUS, PUBMED and Google Scholar. Reports of interest were identified using the terms "TB-IRIS," "HIV," "tuberculosis," "immune reconstitution inflammatory syndrome," "mortality,' "child/children," as well as all MESH terms and abbreviation relating to these terms.

2.3. Definition of paediatric TB

Clinical forms of TB were classified anatomically into pulmonary TB, extrapulmonary TB (EPTB) and both pulmonary and extrapulmonary TB and according to degree of severity as proposed by Wiseman et al. Severe TB may occur as disseminated (haematogenous bacillary spread), uncontrolled (local or peripheral tissue necrosis secondary to an imbalance between disease and host control) or complicated when there is the presence of compression/infiltration on adjacent organs [8].

2.4. Clinical staging in HIV-infected children

HIV-infected children are categorized according to WHO clinical staging stages 1, 2, 3 and 4 [9]. Another classification applies HIV infection stage based on age-specific CD4 count or percentage [10].

2.5. Case definition of TB-IRIS

In general, diagnosis of IRIS is made based on the time frame after initiation of ART, response to ART and exclusion of alternative diagnoses. The following general criteria are applied to diagnose TB-IRIS [11]:

a. initial improvement of TB-related symptoms and/or radiographic findings after adequate anti-TB treatment for a certain period
b. paradoxical worsening of TB symptoms and/or radiologic findings at the existing or at new locations during or after TB treatment
c. absence of conditions that reduce the efficacy of anti-TB drugs e.g. poor adherence, drug malabsorption or drug toxicity
d. exclusion of other possible causes of deterioration

The clinical features of each type of TB-IRIS may be summarised in Table 1.

3. Results

The search yielded 370 articles, subsequently screened for eligibility according to the inclusion criteria. The majority of the articles were adult studies. Only 6 articles were identified for final review after the exclusion of duplicates and incompatible study designs (Table 2). Many paediatric studies measured mortality following TB/HIV co-infection in children receiving ART but did not specifically address the possibility of TB-IRIS. The final articles selected were three retrospective and three prospective cohort studies. In total, 130 cases of TB-IRIS were reported with 6 deaths. The studies either enrolled ART naïve or children already on ART at the point of study. Except for one study from the United Kingdom, the remaining were from African countries and Peru which are designated by WHO as among the 30 countries with a high burden of TB/HIV infection. The age of enrolled children varied across studies as different inclusion criteria were applied. On average, the basal CD4 % preceding IRIS were low/borderline of immunosuppression which was consistent among the studies despite the children being on ART. The majority of the peak IRIS event occurred during the first month of treatment. Children who died of IRIS have severe forms of TB and the majority were involving extrapulmonary TB. Established risk factors such as advanced immunosuppression was supported by these studies. Meanwhile, the population enrolled in the United Kingdom is older and the median time to development of IRIS was longer.

Table 1
Clinical classification of TB-IRIS [6,11,12].

	Paradoxical IRIS	Unmasking IRIS	CNS TB-IRIS
Definition	Recurrent, new or worsening symptoms after a period of clinical improvement	Latent or subclinical infection disease manifestations with associated inflammatory markers following ART	CNS manifestations e.g. new or worsening meningitis and/or features of raised ICP
Temporal relationship with ART	ART initiation precedes clinical deterioration	ART initiation precedes clinical deterioration	ART initiation precedes clinical deterioration
Timing from ART initiation	Within 3 months after ART initiation	Within 3 months after ART initiation	Acute CNS-IRIS: < 1 year after ART Chronic CNS-IRIS: > 1 year-10 years after ART
Common site of involvement	Pulmonary and lymph nodes	Commonly involves the lung e.g. pulmonary TB complicated by ARDS or BOOP, disseminated TB	Central and peripheral nervous system
Prognosis	Good, self-limiting	–	Poor with mortality between 13 and 30%

CNS: central nervous system, ICP: intracranial pressure, ARDS: acute respiratory distress syndrome, BOOP: bronchiolitis obliterans organizing pneumonia.

4. Discussion

Development of TB-IRIS complicates management in TB/HIV co-infection as its presentation mimics various conditions such as drug toxicity, HIV disease progression, the emergence of new infections such as opportunistic infections, non-adherence to medications and the possibility of multidrug-resistant TB. The condition might be under-recognized or underrepresented due to the absence of definitive diagnostic tests and various adult-adopted definitions used. The majority of the studies mentioned in this review were from high-burden countries except for one study conducted in the United Kingdom. Articles retrieved were examining TB-IRIS-related morbidity and mortality in children and available evidence on the impact of age, nutritional status, anatomical location of TB and degree of immunosuppression as predictive factors on the development of TB-IRIS.

The affected children reviewed in this study were either diagnosed

Table 2
Characteristics of studies on Paediatric TB-IRIS.

Study & location	Study design	CD4%	Age at diagnosis of IRIS in years, median (IQR)	Weight-for-age (<2 SD)	Developed IRIS, n (%)	The median time of IRIS from ART	IRIS related morbidity *severe morbidities are listed	Mortality, n	Risk factors for IRIS
Cotton et al[13] 2019 Sub Saharan Africa, India	Prospective	Median 16.7 (IQR 11.8–21.7)	0.7 (0.3;1.8)	Median −1.91 (IQR −3.19; −1.15)	38 (18.8)	21 days (IQR 13.5;55)	17 cases reported Paradoxical TB in lung parenchyma and cervical lymph node Unmasking CNS TB granulomas Unmasking abdominal TB Possible unmasking TB granuloma Others: paradoxical cryptococcal meningitis, unmasking CMV colitis, paradoxical CMV colitis and pneumonitis	1 Extensive vasculitis skin disease	Current TB treatment Age < 1 year Lower CD4 count Elevated plasma HIV RNA
Van Rie et al [14] 2016 South Africa	Prospective	Median 15.5 (IQR 9.7–21.7) -	0.3 (1.8;5.4)	41.4%	2 (1.9)	14 days	7 cases were reported, and only 2 agreed by the expert panel as IRIS. Both have paradoxical TB-IRIS	None	Not analyzed
Orikiiriza et al [15] 2010 Uganda	Prospective	A majority (70%) have pre-ART CD4% < 15%	6 (2.5–11)	39%	38	11.5 weeks (IQR 3.5–20)	Total 62 cases 20 PTB 2 Disseminated TB 3 BCG lymphadenitis Others: Dermatology e. g. pruritic popular eruption, molluscum contagiousum, Kaposi sarcoma, verruca planus, extensive taenia Infection: unmasking cryptococcal meningitis, unmasking Hib meningitis, encephalitis, acute bacterial pneumonia, varicella zoster ENT: otitis media	None	Male, pre-ART CD4% of < 15%, $CD8^+$ absolute count < 1000/μL, cough.
Gkentzi et al [16]2014 United Kingdom	Retrospective	Median 15 (IQR 8–21)	6.6 (2.3–10.2)	Not analyzed	8 (5.9)	7.5 weeks (mean 9.1 weeks, range 2–20 weeks)	8 cases 4 BCG-related (local ulceration, lymphadenitis) 1 pulmonary TB 1 MAI infection 1 combined TB/MAI 1 cutaneous herpes simplex	2 mortalities: 1 disseminated MTB + MAI 1 disseminated MAI	Increment in CD4 count at 12 months after initiating ART
Wang et al[17] 2009 Peru	Retrospective	8.9 SD ± 5.6	Median 5.7	78%	18 (20)	6.6 weeks (range 2–32)	18 cases (11 unmasking and 7 paradoxical) 4 MTB 1 BCG lymphadenitis 6 Varicella zosters	None	Higher baseline viral load and any indicators of malnutrition

(*continued on next page*)

Table 2 (*continued*)

Study & location	Study design	CD4%	Age at diagnosis of IRIS in years, median (IQR)	Weight-for-age (<2 SD)	Developed IRIS, n (%)	The median time of IRIS from ART	IRIS related morbidity *severe morbidities are listed	Mortality, n	Risk factors for IRIS
							6 Herpes simplex labialis		
Walters et al [18] 2014 South Africa	Retrospective	Median 21.0 IQR (9.0–26.0)	Median 0.6 IQR (0.35–0.87)	−2.73 (-4.32 to −1.69)	23 (4.7%)	Median 1.0 (IQR 0.5–2.1) months	23 cases (4 severe cases) 2 meningitis 1 disseminated TB 1 pericardial TB	3 (insufficient information)	Risk factor for TB-IRIS: starting ART at < 1 year Risk factor of mortality: weight-for-age Z score < − 2 predicted death

CMV, Cytomegalovirus; HiB, Haemophilus influenzae B; ENT, Ear nose throat; BCG, Bacille Calmette- Guerin; MAI, Mycobacterium intracellulare complex;

with TB-IRIS or initiated ART that precedes the development of TB-IRIS within the first decade of life. Half of the studies have a median age of less than 12 months old and in three studies [13,14,18], younger children were found to be at higher risk to develop IRIS. Where information is available, these children acquired HIV through mother-to-fetal transmission. A study from International Epidemiology Databases to Evaluate AIDS (IeDEA) reported that 80% of children initiated on ART were already in advanced clinical/immunologic staging with almost one-third having no known WHO staging or CD4 value [19]. All of the respondents presented with stages 3 to 4 of the WHO classification with equivalent stage 3 by CDC classification. Both groups constitute the advanced immunosuppressed state [20]. This is reflective of possible factors such as poor antenatal ART coverage, lack of awareness and reduced access to diagnosis and treatment. As children are a good reservoir for TB infection, they may develop TB disease or TB become unmasked once they are severely immunocompromised. Diagnosing TB at this stage is challenging due to overlapping clinical features of TB with advanced HIV or failure to establish a diagnosis due to the paucibacillary nature of the organism on laboratory investigation.

In the context of malnutrition, the relevant studies were using a standardized definition of undernutrition being weight for age less than −2 SD. A study by Wang et al reported a high risk of TB-IRIS if one of the indicators of malnutrition (undernutrition, wasting or stunting) were present. Another study by Walters et al reported malnutrition as a significant predictor of death but not specific for TB-IRIS. It is not a surprising finding as malnutrition is an established association in HIV and all the children being studied were severely immunocompromised. The pathophysiology of malnutrition causing the development of TB-IRIS requires more understanding. Anatomical classification of TB was also described in IRIS with a higher incidence in extrapulmonary and disseminated TB [13,15,16,17,18]. These two forms of TB were classified as severe due to their higher bacillary load. Initiation of ART during early antimicrobial treatment may precipitate IRIS due to an exaggerated inflammatory response secondary to large amounts of mycobacterial antigen being released. Mortalities reported in this review were due to disseminated infection by Mycobacterium tuberculosis and Mycobacterium intracellulare.

There are several limitations in this review. The studies appraised were using various adult-adopted criteria to define TB-IRIS in children due to the absence of validated paediatric case definitions. The various inclusion criteria applied and objectives result in heterogeneous outcomes among the studies. There was limited information available on the morbidities and mortalities related to TB-IRIS. Fatalities were seen in disseminated TB however the case description was not explored thoroughly to identify possible risk factors.

5. Conclusion

IRIS is common in dual HIV and TB infection. More prospective studies are needed to establish case fatality rates in countries where TB-IRIS is common and its predictive factors. Attention should be diverted to the at-risk population e.g. young children with undernutrition or children with extrapulmonary TB. Recognizing the risk for the development of paradoxical TB-IRIS is important to facilitate better recognition and counseling when treatment is initiated meanwhile vigorous screening for TB is crucial to reduce the incidence of unmasking TB-IRIS. More data is needed on the incidence of CNS TB-IRIS in the paediatric population.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Funding

This study was self-funded in conjunction with the fulfillment of the author's postgraduate Diploma Degree in pediatric infectious disease.

CRediT authorship contribution statement

Haslina Hashim: Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration.

Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The author wishes to widen our genuine appreciation to the University Sultan Zainal Abidin, particularly the Faculty of Medicine for the given countless support.

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