CLINICAL

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN CHILDREN

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Paradoxical deterioration due to immune reconstitution inflammatory syndrome (IRIS) occurs in up to 21% of children initiating antiretroviral therapy. Mycobacterial diseases are the most common, with BCG-vaccine adenitis predominating in infants and *Mycobacterium tuberculosis* (TB) in older children. The difficulty of diagnosing TB in HIV-infected children and the increasing risk of drug-resistant TB complicate the diagnosis and management of both paradoxical IRIS and post-antiretroviral therapy TB. History and clinical assessment remain key strategies in the management of these infants and children. There are no prospective studies investigating diagnostic criteria and therapeutic strategies in children.

Immune reconstitution inflammatory syndrome (IRIS) refers to an 'unexpected' and paradoxical clinical deterioration in the period immediately after initiation of antiretroviral therapy (ART). Diagnosis of IRIS relates to the time frame after initiation of antiretroviral therapy ART, response to ART and exclusion of alternative diagnoses. Boulware *et al.* proposed criteria for children.[1] There are fewer data on incidence, prevalence and clinical descriptions in infants and children than in adults. Studies report a prevalence of up to 21% in South African infants.[2] IRIS is commonly associated with mycobacterial infections, mainly bacille Calmette-Guérin (BCG), *Mycobacterium tuberculosis* and non-tuberculous mycobacteria (NTM).[2-5] Other conditions such as skin disease, herpes simplex, cryptococcal meningitis and immune diseases such as Guillain-Barré syndrome are also reported.[1,3] Age and geographical location are important determinants of the risk for each disease. Table I summarises the most pertinent paediatric literature.

M. TUBERCULOSIS IRIS

EPIDEMIOLOGICAL CONSIDERATIONS IN HIV-INFECTED CHILDREN

Tuberculosis (TB) is a common opportunistic infection in HIV-infected African children. Rates of 53.3 cases/100 patient-years are reported in children not on highly active antiretroviral therapy (HAART).[6] High rates of exposure to potentially infectious source cases are well documented in HIV-exposed infants[7] and rates of disease of 1 596 cases per 100 000 HIV-infected infants are documented in Cape Town.[8] Young age and HIV-related immunosuppression contribute to this high disease burden.

Recurrent episodes of TB are well documented and are caused by both relapse and re-infection.[9] In a cohort studied before and after widespread availability of ART, 30% of children with HIV and culture-confirmed TB had received prior TB therapy.[6]

Rates of drug-resistant TB vary between settings. Drug resistance was reported in 17% of HIV-infected children with TB, 6.8% having resistance to both rifampicin and isoniazid.[10] Children with prior TB therapy are at higher risk of resistance.[11] There may be an incomplete therapeutic response to 6 months of standard anti-TB therapy.[9]

Up to a third of children initiating HAART may be on anti-TB therapy.[6,12] Cohort data from low-resource settings indicate that the majority of children still initiate HAART at very low CD4 counts and with significant clinical disease.[13] These children are at high risk for IRIS and incident TB from new exposure to *M. tuberculosis.* With improved access to HAART, an up to 70% reduction in the incident TB can be achieved.[6,14]

DIAGNOSTIC CONSIDERATIONS

The diagnosis of TB in HIV-infected children remains difficult. Signs and symptoms overlap with advanced HIV. Clinical scoring tools have poor specificity in HIV-infected children.[15,16]

Sputum is difficult to collect in young children, and gastric washings are frequently not performed.[17] Culture yields from gastric washings and induced sputa are low in children. Although yields of up to 40%[18] have been reported in research settings, the yield in clinical settings is

lower.[19] In children with a high index of suspicion for TB, microbiological confirmation can be obtained in 55%, increasing to 80% with significant pulmonary infiltration.[16] Chest radiographs are difficult to interpret owing to ubiquitous chronic underlying HIV-associated lung disease. Tuberculin skin tests have a reduced sensitivity despite adjusting the extent of induration from 10 mm to 5 mm.[20] The value of interferon-gamma release assays in HIV-infected children is still under study. Negative results do not exclude TB,[21] and tests are expensive. Although failure of therapy for an opportunistic infection is considered an exclusion criterion for IRIS, IRIS has been diagnosed in adults with inadequately treated drug-resistant TB.[22] As the diagnosis of TB is seldom confirmed by culture and drug sensitivity is often not available, it may be difficult to differentiate IRIS from poor response to treatment and drug resistance. It may not be possible to confirm a response to HAART because of lack of access to virological testing. If events occur soon after initiation of therapy, significant reductions in viral load and clinical responses may not yet have occurred.

THERAPEUTIC CONSIDERATIONS

Current dosages of anti-TB medicines, especially isoniazid and rifampicin, are insufficient in all children; this is probably exacerbated in children with HIV, in whom malabsorption is common.[23-25]

Rifampicin reduces exposure to protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), thereby compromising HAART efficacy. Ritonavir-based HAART, previously recommended for co-treated children on PIs, has been associated with poorer virological outcomes.[26]

POST-HAART TB AND UNMASKING IRIS

Besides the general principles proposed by Boulware,[1] there are no proposed criteria to distinguish true IRIS from incident TB or missed disease prior to HAART initiation. Adult clinicians have suggested that all cases of TB after initiation of HAART should be termed post-HAART TB, with only cases occurring in the first 3 months accompanied by heightened clinical features classified as IRIS.[27] Data from cohort studies report TB rates of 3.4 - 6.2% in African children after initiating HAART[6,28] (Table I). In infants TB-IRIS is thought to be less common than BCG-IRIS.[2] Clustering of these cases in the first 100 days after HAART initiation is reported from cohort studies. In a large Ugandan study, a 2.7-fold increase in risk for TB was observed early after the initiation of HAART.[28] This could be due to inadequate screening procedures, as the converse was noted in a study where active screening was done.[6]

Few studies provide detailed assessment of the severity of disease, an essential component in distinguishing between IRIS, incident TB and disease missed prior to initiating HAART. Zampoli *et al.* described 7 children with post-HAART pulmonary TB IRIS, and 1 with additional extrapulmonary disease.[29] Three (43%) had received therapy prior to the initiation of HAART. Culture was positive in 4 of the 7 cases. Of these, 1 had multidrug resistance, having stopped anti-TB therapy 3 weeks before initiating HAART. All chest radiographs showed significant adenopathy with airways compression, extensive parenchymal infiltration and pleural reactions.[29] Although all IRIS is associated with significant inflammatory response, radiological findings are similar in HIV-infected children not on HAART.[10] Clinicians therefore need to judge the relative severity of these conditions. Exposure to *M. tuberculosis* shortly after initiation of HAART could conceivably present as post-HAART TB IRIS.[30] This is especially relevant in children immunologically primed by receiving BCG at birth.

IRIS caused by both BCG and TB in the same patient is now well documented in two prospective paediatric cohorts. In the NEVEREST study 50% of children with TB also had BCG IRIS.[2] In the CHER cohort, 19% of children with BCG IRIS adenitis also had TB IRIS.[31]

PARADOXICAL IRIS

Delaying the initiation of ART in TB cases with severe immunodeficiency is associated with increased HIV-related mortality.[32] Currently the World Health Organization (WHO) recommends that children with severe immune suppression or stage 4 disease should initiate ART 2 - 8 weeks after the initiation of anti-TB therapy.[33]

The basic diagnostic criteria for IRIS[1] should be met first when diagnosing paradoxical IRIS. The proposed case definitions for TB paradoxical IRIS, although appropriate for well-resourced settings, are problematic in lower-resource settings. This is due to the diagnostic uncertainty of TB in HIV-infected children and difficulty in excluding alternative diagnoses and confirming a response to ART because of inability to measure CD4 counts or viral load, especially in rural areas.

Few data exist on the risk of paradoxical IRIS. The study from Uganda reports only 2 cases of paradoxical IRIS.[27] Zampoli *et al.* recently described the clinical events in 4 children receiving anti-TB therapy for 21 - 59 days before initiation of ART, who subsequently developed TB IRIS between 6 and 105 days later. Skin test conversion was documented in 1 child and was positive at the time of exacerbation in another. Two children presented with deterioration of pulmonary TB, 1 developed local adenitis and another abdominal adenitis. One child died.[29]

There is little information on clinical features and management of neurological paradoxical IRIS in children. In adults these account for 12% of cases of paradoxical TB IRIS.[34] Similarly, intra-abdominal TB IRIS is com-

TABLE I. COMPARISON OF STUDIES ILLUSTRATING ASPECTS OF PAEDIATRIC IRIS

	Smith *et al.*[2] All IRIS	Puthanacit *et al.*[3] All IRIS	Nuttall *et al.*[46] BCG only	Zampoli *et al.*[29] TB only	Walters *et al.*[6] All TB and aspects of BCG
Age (all)	8 months	7.9 years		8 - 121 months	23.5 months
Episodes/children (%)	34 episodes /169 children (21%)	32 episodes/153 children (19%)	21 episodes /331 children (6.3%)	11 cases	10 unmasking TB, 4 paradoxical
Age, cases v. controls (*p*-value)	7 months v. 10 months (0.007)	8.2 years v. 7.8 years (0.50)	5 months v. 27 months (<0.001)		
CD4%, cases v. controls (*p*-value)		3.1 v. 5.5 (0.02)	12.3% v. 12.0% (0.55)	10.3% (cases only)	
Absolute CD4 count, cases v. controls (*p*-value)	741 v. 1 075 (0.0148)				
Log baseline HIV RNA copies/ml, cases v. controls (*p*-value)		5.37 v. 5.37 HIV RNA copies/ml (0.96)	6.1 v. 5.6 (0.001)		
Viral load >750 000 (%)	79% v. 55% (0.044)				
Time to event (mean (range))	16 days (7 - 115)	6 weeks (2 - 21)	34 days (15 - 60)		
BCG	24/34	2/32	21/21		
TB	6/34	3/32		11/11, 4 paradoxical IRIS	14/14
TB and BCG	6/34				
MAC		4/32			
NTM		5/32			
Herpes zoster		7/32			
Herpes labialis	1/34	6/32			
Herpes encephalitis		1/32			
Cryptococcal meningitis		3/32			
Cytomegalovirus	1/34				
PCP	1/34				
Seborrhoeic dermatitis	1				
Bacterial sepsis	2				
GBS		1/32			

BCG = Bacille Calmette-Guérin; TB = tuberculosis; MAC = *M. avium-intracellulare;* NTM = non-tuberculous mycobacteria; PCP = *Pneumocystis* pneumonia; GBS = group B streptococcal disease.

mon in adults, occurring in 37% of cases.[35] Although paediatric cases do occur (Helena Rabie – unpublished data), little is known about the prevalence in children.

It is challenging to exclude drug-resistant TB and failure of TB therapy for other reasons in these children. Resistance was common in an adult series from Cape Town.[22] The case in Fig. 1 illustrates the diagnostic difficulties in a setting of paradoxical IRIS and resistance to TB therapy.

GENERAL EVALUATION

Contact with a source case has been documented in 30 - 54% of HIV-infected children with TB.[6,10] TB can therefore be prevented and detected through a careful history looking for a source case in the household and extended social circle. In older children and adolescents transmission may occur outside the family due to social mobility, and it is likely that a history of contact will be a less sensitive marker to distinguish incident TB from IRIS.

Reviewing adherence to anti-TB therapy and ART is essential to evaluate children with suspected paradoxical TB IRIS. Documentation of suspected contact with a source patient who may have drug-resistant TB is also crucial. In

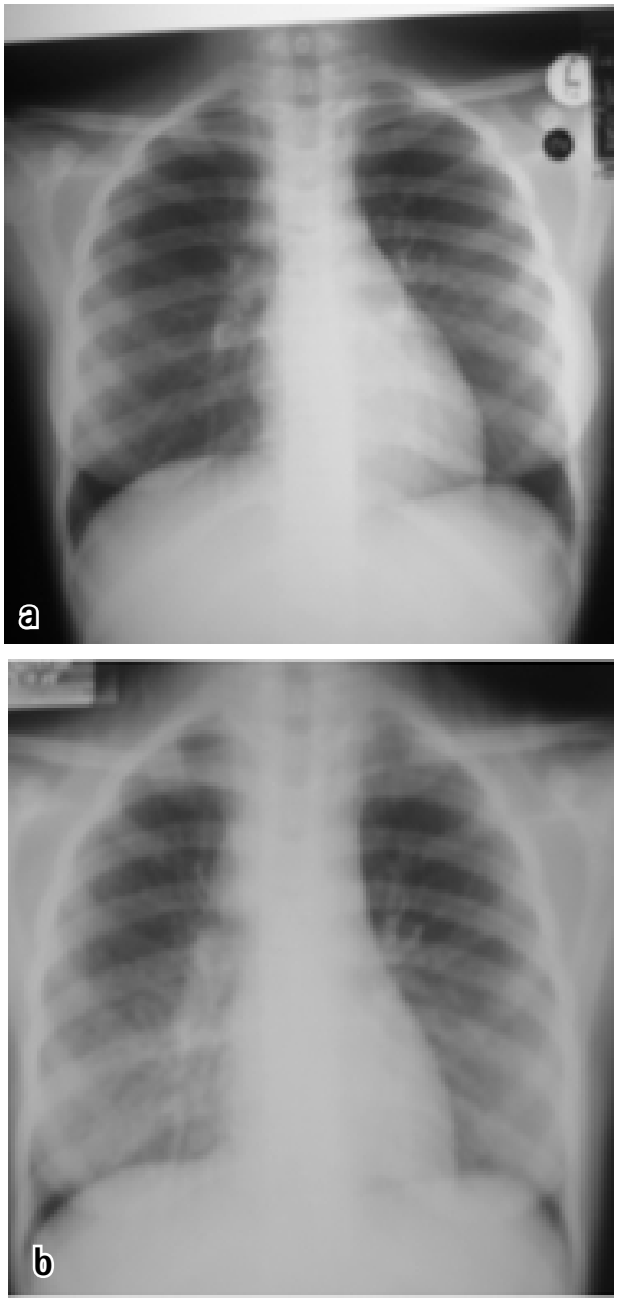

Fig. 1. Drug-resistant TB presenting as paradoxical IRIS in a 12-year-old girl with pulmonary and abdominal TB and severe immune suppression (chest radiograph a). She was sputum smear positive and had a CD4 count of 31 cells/µl. Anti-TB therapy with four drugs was initiated and she responded well, smear conversion taking place within 3 weeks. ART was started 3 weeks after initiation of TB therapy, and 7 days later she developed a high fever, severe abdominal pain and food intolerance. The sputum smear was now positive, and a chest radiograph (b) suggested miliary TB. Steroids were added with some clinical improvement. Rifampicin resistance was confirmed after 48 days on TB therapy and 27 days on ART.

adults diagnosed with paradoxical TB IRIS, resistance is a major clinical confounder.[22] Weight gain on therapy may be an important and measurable clinical marker supporting IRIS rather than clinical deterioration. This information, together with clustering in the first 100 days, may allow for a possible differentiation between incident TB and IRIS in younger children. Culture for *M. tuberculosis* and drug sensitivity testing should be conducted whenever possible. Clinical judgement should guide clinicians as to additional investigations needed to exclude additional diagnoses such as acute bacterial infections, drug reactions and other opportunistic infections or malignancies.

MANAGEMENT

Children are at higher risk than adults of death and hospitalisation in the period immediately after HAART initiation. Mortality of 17.4/100 000 patient-years in the first 3 months of therapy has been reported. Up to 30% require hospitalisation in the first 6 months on therapy. Two-thirds of the admissions are related to bacterial infection and pneumonia.[36,37] Withholding antibiotic therapy and other interventions at initial presentation is therefore very dangerous when TB IRIS is suspected.

As in adults, therapy for TB IRIS includes the anti-TB therapy and continuation of HAART. However, if the IRIS event is life-threatening or likely to cause permanent disability (i.e. TB meningitis with clinical deterioration), HAART may be discontinued temporarily. Children on PIs can stop all drugs simultaneously. There is a significant risk for resistance when stopping efavirenz or nevirapine.[38] Clinicians need to weigh the risk of inducing NNRTI resistance against that of continuing either NRTIs or boosted lopinavir/ritonavir for 7 - 14 days. The safety of these strategies is unknown in this scenario.

Steroids improve outcomes for adults with moderate to severe TB IRIS, but there are no randomised studies in children.[39] As in adults, clinicians must weigh the risk of resistant TB prior to starting steroid therapy. Other modalities used (but not studied) include non-steroidal anti-inflammatory drugs (NSAIDs), thalidomide and leucotriene receptor antagonists.[40-44] Despite the lack of data, it is reasonable to stratify the use of supportive therapy as follows: NSAIDs for mild to moderate disease, and steroids for severe disease. In cases where there is a prior indication, i.e. meningitis, steroids should always be used. It is unclear whether pre-emptive steroids or NSAIDs can prevent IRIS (a trial in adults is underway).

BCG-RELATED IRIS

BCG is the most common mycobacterial IRIS in infants given BCG at birth.[2] Vaccine site ulceration and abscess formation, ipsilateral adenitis and exacerbation of disseminated disease occur.[45] Where ART is delayed until clinically indicated, 6% of all children and 14% of infants experience BCG-related adverse events. In this setting, age at initiation is the most important risk factor.[2,46] When children access therapy early and at a younger age, a low CD4 count is the most important predictor.[45] Although there is a significant reduction in the risk of IRIS with early initiation of ART adverse events are common in these infants also.[31]

The diagnosis of IRIS remains clinical. Where systemic disease is suspected, extensive investigation may be required. Although no prospective studies have been conducted, it is likely that local and regional IRIS requires no specific therapy. However, disseminated disease requires aggressive therapy that should be discussed with an expert. Danish strain BCG is resistant to current standard doses of isoniazid as well as to pyrazinamide and ethionamide.[47] Induction of resistance in inappropriately treated cases with systemic disease has been documented.[48]

NON-TUBERCULOSIS MYCOBACTERIA

One study from Thailand reports on non-tuberculosis mycobacterial IRIS in children. Of 153 children initiating therapy at a median age of 7.9 years, 9 had IRIS caused by non-tuberculosis mycobacteria, 2 with paradoxical deterioration and 7 with unmasking disease. The rate was 5.9 cases per 100.[5] There are no data for South African children, although cases do occur (Helena Rabie - unpublished data).

IRIS INVOLVING SKIN CHANGES

Skin changes are the most common form of IRIS in adults, but there are fewer data in children. Unpublished data from KwaZulu-Natal reported by Boulware in a review on IRIS indicated that 53% of children had a new onset of rash after the initiation of HAART.[1] These included molluscum contagiosum (8%), tinea capitis (20%), warts (16%), impetigo (12%), herpes zoster (5%), and other fungal rashes (24%).[1] Earlier cohorts reported that 11% of children developed herpes zoster. Children at risk were negative for varicella antibody despite a previous history of varicella and had severe immunodeficiency before treatment.[49]

Exacerbation of warts and molluscum contagiosum is commonly seen. If areas such as the face are involved, this disfigurement can be very disruptive and may lead to non-adherence.

OTHER PHENOMENA

Cryptococcus neoformans is common in South African adults[50] but less common in children. In children <15 years of age, the incidence is 1 per 100 000 population.[51] *C. neoformans* IRIS of both the central nervous system and the lungs occurs occasionally.[52]

Guillain Barré syndrome, myocardial dilatation, exacerbation of JC virus progressive multifocal leucoencephalopathy, leprosy, Kaposi's sarcoma, cytomegalovirus, *Pneumocystis* pneumonia (PCP), opsoclonus-myoclonus syndrome, toxoplasmosis and other entities have been reported in adults and in children.[3,41,53-55]

CONCLUSION

IRIS is common in children. BCG is important in infants and TB is more prevalent in older children. Although the morbidity is thought to be low, IRIS may be diagnostically challenging and carry a high morbidity. A higher drug burden may result in decreased therapeutic success, with possible non-adherence and more potential for drug interactions as well. A careful history and clinical review remain important tools in the diagnosis and management of these conditions.

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