P1073: Immune Reconstitution Inflammatory Syndrome (IRIS) – Wide Spectrum and Severity in Children

Mark F Cotton[1], **Hilda Mujuru[2], Raziya Bobat[3], Boniface Njau[4], Avy Violari[5], Vidya Mave[6], Charles Mitchell[7], James Oleske[8], Bonnie Zimmer[9] and Savita Pahwa[10]**

[1] KID-CRU, Pediatrics & Child Health, Stellenbosch University, Tygerberg, South Africa, [2] UZ College of Health Sciences, Pediatrics & Child Health, Harare, Zimbabwe, [3] University of KwaZulu- Natal, Pediatrics & Child Health, Durban South Africa, [4] Kilimanjaro Christian Medical Centre, Moshi, Tanzania, [5] Perinatal HIV Research Unit, Pediatrics & Child University Witwatersrand, South Africa, [6] BJ Medical College, Pune, India, [7] University of Miami, Pediatric Immunology, Miami, FL, USA [8] Dept Pediatrics **New Jersey Medical School/Rutgers**, NJ, USA [9] Frontier Science & Technology Research Foundation, Amherst, NY, USA [10] Miami Center for AIDS Research & Microbiology and Immunology, University of Miami Miller School of Medicine, FL., USA

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Introduction

Antiretroviral therapy (ART) in HIV-infected patients leads to CD4+ T cell recovery & restoration of immune responses to pathogens

- IRIS may develop – characterized by "excessive" inflammation
- Disease processes – usually an infection (also malignancy, auto-immune disease)
- Anatomical systems – skin, lymph nodes, pulmonary, central nervous system (can be any)
- Onset – usually within 3 to 6 months of initiating ART
- **Types of presentation:**

1. Paradoxical – apparent worsening of a disease process, usually an infection, either being treated or quiescent
2. Unmasking – 1st appearance on ART

- Hallmark of IRIS – occurs after initiating ART

IRIS in children: -

Only 2 prospective studies

- Only 1 longitudinal in Thailand - (Puthanakit et al, 2008)
  - N = 153
  - Mean age 7.9 ±2.8)y
  - 19% developed IRIS (non TB mycobacteria – most common)
- 1 cross-sectional in Uganda (Orikizira et al, 2010)
  - N = 162
  - Median age 6 (IQR 2.5 – 11) years
  - 38% had IRIS – (TB most common 25% – unmasking similar to paradoxical; skin conditions – 11.1%)

Several retrospective studies

- Nested in prospective studies with retrospective IRIS identification (Smith et al, 2009)

In Sub-Saharan Africa –BCG & TB IRIS most common

- Bacille Calmette Guerin (BCG) immunization to all newborn infants
- TB endemic

Methods

Design

Prospective observational study of children < 6 years of age
5 sites in sub-Saharan Africa & 1 in India.
Public ART programs

Objectives – to describe

- Incidence, spectrum and severity of IRIS
- With special emphasis on TB and BCG IRIS

Methods

- All cases of potential IRIS evaluated by IRIS committee
- Enrollment: Dec 2010 – June 2013

Sites

- 4 in South Africa – Tygerberg, Soweto, Johannesburg
- 1 in India (BJ –Pune)

Inclusion criteria

- HIV-infected (2 tests, 1 in accredited laboratory)
- All infants & children≥4w ≤72m about to start ART
- If <12m, must have had BCG

Exclusion criteria

- Investigator- e.g. if malignancy
- Not yet on ART

Results

Demographics

N= 203	No IRIS	IRIS 38 (18.7%)	P-value
Age (y)	1.3 (0.6 2.3)	0.66 (0.3 1.8)	0.025
Male	85 (52%)	22 (58%)	0.59
CD4%	20 (14 27.5)	16.7 (11.8 22)	0.0176
CD4/mm^3	1147 (633 1082)	838 (223 1259)	0.011
Viral load log$_{10}$/mm^3	5.8 (5.2 6.3)	6.3 (5.8 6.8)	<0.0001
WHO Stage			0.12
1	43 (26%)	4 (10%)	
2	27 (16%)	5 (13%)	
3	79 (48%)	23 (61%)	
4	15 (9%)	6 (16%)	
Weight for age-Z	-1.8 (-3.3 -0.7)	-2.3 (-3.4 -1.3)	0.2
Length for age-Z	-1.5 (-2.4 0.6)	-2.2 (-2.6 -0.9)	0.09
Weight for age-Z	-0.9 (-2.40.01)	-1.1 (-3 0.1)	0.8
Death*	6 (3%)	3 (8%)	0.37

*6 of 9 within 12 weeks of ART

Features of IRIS

Time to IRIS
Median 23 days (IQR: 14 – 38)
Range 8 to 102 days

>1 IRIS episode per subject

- #2 episodes – 6
  BCG + eczema/PTB/oral candida/HPPE/CMV colitis
  Abdominal TB + HPPE
- #3 episodes – 1
  TB, BCG, Molluscum contagiosum

HPPE – HIV-related papular pruritic urticaria

Deaths in IRIS subjects

1# IRIS directly related-

- Paradoxical TB IRIS with vasculitis in 5 year old boy (CD4 10 X 10^9/L; WAZ -0.5)
  - TB confirmed
  - IRIS onset day 12 – increased LN
  - Death day 30

2# IRIS unrelated

1. Presumed candida esophagitis in 2.5 year old girl (CD4 16%; WAZ -6)
   - IRIS onset day 10 + Grade 4 neutropenia (430/mm^3)
   - *S. pneumoniae* sepsis + bilateral hydronephrosis day 20
   - Death day 34 (sudden after improvement)
2. BCG IRIS in 3m girl (CD4 12.7%; WAZ -1.9)
   - Local & regional BCG IRIS day 15
   - Death at 3 months (gastro-enteritis)

Type of IRIS (n = 46)

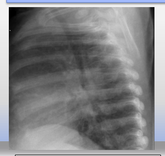
- BCG 21 (46%)
- TB 12 (26%) -
- Dermatological 9 (20%)
  HPPE 4; Tinea capitis 1; eczema 2; zoster 1, molluscum contatagiosum 1
- Candidiasis 3 (6.5%) (esophageal 1; oral 2)
- CMV 2 (4%)
- Cryptococcus 1 (2%)

Both unmasking & paradoxical IRIS have severe morbidity

Case 1: Unsuspected CNS TB granulomas

Prolonged seizures due to unsuspected CNS TB granulomas in infant with PTB (CD4 25% / 2097 per mm^3: viral load log 6.8)

- TB Rx initiated for cough + suggestive CXR
- 6w later ART initiated (Also oral candidiasis & tinea corporis)
- 13 days later, prolonged focal seizure
- CT scan - 2 ring=enhancing lesions



Baseline lateral CXR
Perihilar LN's

Cases 2 & 3: Severe CMV colitis - ICU

1. 16 m infant with grade 4 thrombocytopenia & anemia
   WAZ -2.3; CD4 18%
   Proteinuria noted day 2
   Empiric TB treatment Day 9
   Bloody stools, abdominal distension day 14 requiring inotropes
   CMV viral log 3.4
2. 6m infant with HIV encephalopathy, presumed CMV pneumonitis (Ganciclovir - 14 days)
   CMV viral load 13 657 copies/mm^3 on Day 4
   Bloody diarrhea with shock on day 19 - CMV viral load 5431 copies
   Ganciclovir 21 days

Case 4: Probable intra-abdominal TB IRIS causing biliary obstruction (Cape Town)

8m infant

- HPPE day 13
- Obstructive jaundice day 40
- Infection screen –ve (hepatitis A.B,C, EBV, CMV, RPR
- Mantoux +ve
- Mother's CXR supports PTB (unsuspected, treatment cpmmenced)
- Liver biopsy suggests biliary obstruction – soft tissue mass in porta hepatis (ERCP)
- MRI post 18m – large biliary fluid collection
- Hepato-jejunostomy after 15m after onset obstructive jaundice





Case 5: Multiple intracranial ring-enhancing lesions (TB possible) (Pune, India)

23m infant (CD4 33%; Viral load log 5.6)

- Baseline CXR & Mantoux test negative
- At week 8: vomiting, tonic posturing, decreased level of consciousness
- CSF 700 cells (Neutrophils 85%), protein 20mg/dl, glucose 40mg/dl
- CSF culture –ve for TB, fungi, cryptococcal ag
- Malaria smear -ve
- CXR normal & gastric aspirates –ve for TB culture
- RX acyclovir, ceftriaxone, artesunate, amikacin
- MRI – multiple ring-enhancing lesions – anti –TB Rx initiated
- Patient improved slowly & prednisolone discontinued after 5m

Regional BCG IRIS (Axillary)



Local BCG IRIS



Conclusions

- IRIS common in young children below 6 years of age
- Background of multiple conditions, poor nutrition, severe disease
- More common in:
  - Younger children
  - Lower CD4
  - Higher viral load
- Most resolve
- Unexpected severe morbidity in many systems – TB in abdomen and CNS, presumed CMV colitis

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