Pediatric Non-Infectious Uveitis Medical Therapy: The MERSI Perspective

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Pediatric Uveitis

• Only 10% of uveitis
• Yet, 33% of legal blindness from uveitis

Challenges

- Deliped IV
- Established serology new uveitis
- Limited Rx options in children
- Difficult examinations
- Risk of amblyopia

Ocular Complications

- 71 patients with JIA-associated uveitis at the Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Percentage of one or more complications:
- 67% (132 eyes) at presentation
- 81.6% at 3 months
- 89.4% at 6 months
- 93.4% at 1 year
- 96.3% at 3 years

- Childhood uveitis is significant for numerous complications, many of which are vision-threatening
- Complications increase with duration of disease

POX

- 10 y.o. female
- 4 year hx of bilateral uveitis
- Tx with top steroids-regional steroid inj
POX

- Glaucoma OU
- PRP OU
- Ahmed Valve Sx, OS
- Post-Sx cataract formation OS
- Poorly controlled uveitis OU, with many flares

Meds

- PF, TID OU
- CSA drops TID OS
- Cyclogyl qd OS
- Cosopt BID OS

On presentation

- VA: 20/50 OD, HM OS
- IOP: 26 OD, 19 OS
- SLE:
- OD: 2+ vitreal cells
- OS: white cataract, an Ahmed valve, tube eroding through the cornea, throughout much of the extent of its implantation tract, with its opening implanted into the corneal stroma

On presentation

- Mother requested steroid-sparing Rx, eg. Methotrexate
- The child’s “uveitis specialist” ridiculed this “reckless” idea
- Pediatric ophthalmologist suggested urgent valve tube revision (risk of endophthalmitis)
- Glaucoma specialist, who installed the valve, denied revision ("too risky" in a eye with "no vision potential")

Pt picture

B-scan & UBM

- B-scan: unremarkable
- UBM: open angles OU

What would you suggest?
What would you want for your child?

- Leave as it is? (eye is quiet)
- Extract cataract?
- Extract cataract and revise valve?
- Continue with steroid therapy?
- Begin steroid-sparing IMT?

Our approach

- Operated immediately
- Preserved the valve
- Repaired the corneal defect with tutaoplast
- Removed the mature cataract
- Performed PPV (disclosed healthy ON & macula)
- Reinstalled the tube through the superotemporal sclerostomy site
- Left the eye aphakic, given the history

Immediately post-op OS

- Comfortable eye
- VA CF@4ft OS; 20/50 OD
- PF sq 1 h
- IOP 5mmHg
- D/C Cyclogyl, Cosopt
- Started MTX 10mg/week
**Last F/U (4/2003)**
- Comfortable eye
- VA 20/50 OD, 20/50 OS (contact)
- MTX 10mg weekly, PF QID OU
- IOP: 21 mmHg OD, 20 mmHg OS
- Taper topical steroid to full discontinuation
- OD now has 3+ vitreal cells
  - Increase MTX or propose PPV, OD?

**7/28/03**
- Pars plana vitrectomy, OD
- 7/29/03: 20/30 OD

**8/26/03**
- 20/25 OD; 20/60 OS
- IOP: 16 OD; 18 OS
- Meds: Methotrexate, 10mg/week, Cosopt OD bid

**Predictors of Poor Visual Prognosis**
- Increased severity of nodular disease at presentation
  - Active inflammation (AC flare $\geq 1+$, cell $\geq 0.5+$)
  - Active inflammation of anterior uveitis
  - Presence of posterior synechiae
  - Abnormal IOP
  - Uveitis onset before/concurrent to arthritis
  - Shorter interval from onset arthritis to uveitis
  - Prolonged referral to uveitis specialist
  - Male sex

**Use of ADEQUATE THERAPY (IMMUNOMODULATORY DRUGS)**
- Reduces the risk of some ocular complications
- Reduces the risk of visual impairment
- Reduces the risk of blindness

**Visual Outcomes**
- Hospital for Sick Children, Toronto, Canada, 2007
  - 1081 JIA patients, f/u 6.9 years
  - 142 (13.1%) JIA-uveitis
  - 37.3% (53) ocular complications
    - Time interval from arthritis Dx to uveitis Dx shorter
    - Use of oral prednisone greater
  - Visual outcomes
    - 87% VA $\geq 20/40$
    - 5.7% VA $\leq 20/200$

- MERSI, Boston, MA, USA, 2006
  - 89 JIA-uveitis patients, f/u 2.96 y
  - Visual outcomes
    - 73% VA $\geq 20/40$
    - 9% VA 20/50-20/200
    - 18% VA $\leq 20/200$

- John Hopkins, Baltimore, Maryland, USA, 2007
  - 75 JIA-uveitis patients, f/u 3 y
  - Visual outcomes
    - 50% VA $\geq 20/100$
    - 30% VA $\geq 20/200$

- Bascom Palmer, Miami, FL, USA, 2004
  - 148 children with uveitis (including JIA-uveitis)
    - Visual outcomes $\leq 20/200$
      - 33.3% at 1 month
      - 40.5% at 6 months
      - 56% at 2 years
      - 69.6% at 5 years
Combination of 3 tertiary care centers
127 children with uveitis (20.9% JIA-uveitis)

- Visual outcomes < or = 20/200
  - 9.23% at presentation
  - 6.52% at 1 year
  - 15.35% at 5 years
  - 7.69% at 10 years

Smith et al, Ophthalmology 2009

Reasons for disparity on the visual outcomes between tertiary care settings in JIA-uveitis
- Rheumatologists referrals
- Pediatricians referrals
- General ophthalmologists referrals
- Different aggressiveness on uveitis Rx (medical and surgical)
- Different approaches for glaucoma and CME Rx (medical and surgical)
- Genetic consideration

Visual Outcomes

Objective, quantitative, non-invasive, in vivo
Measurement correlates to aqueous humor protein levels
Not simply a sign of blood-aqueous break-down
May be a dynamic sign of disease severity
Possible relationship between laser flare values and ocular complications at baseline and over time
Poor visual outcomes

Laser Flare Photometry in JIA-U

- Early diagnosis / pediatrician / referral to uveitis specialist
- Early after JIA onset
- Early general ophthalmologist referral to uveitis specialist
- Mandatory vision screening for pre-school children
- Reassessment of current screening guidelines

How can we modify the Poor Prognosis in JIA-associated Uveitis?

1 Early Diagnosis

- Increased severity of ocular disease
- Higher chance of scatter & cataract
- Systemic complications
- Restricted vision
- Absent uveitis onset before/concurrent arthritis

2 Identification for high-risk children at presentation

JIA-Associated Iridocyclitis

- Predictors of poor visual prognosis
  - Severity of disease at presentation
  - Male sex
  - Shorter interval from onset arthritis to uveitis
  - Elevated alpha-2 globulins, HLA-DR 5
  - Long-term prognosis guarded
  - Significant visual impairment in 15%, blindness in 5%
  - Proportion with active disease at presentation unchanged despite screening guidelines
  - Need for increased surveillance and early treatment

Therapeutic Approach

- Elimination of active inflammation
- Appropriate antimicrobial medication
- Limited tolerance for steroids
- Early implementation of steroid-sparing immunomodulatory medication

3 Complete elimination of active inflammation

- Limited tolerance for steroids
- Early AND aggressive introduction of effective steroid sparing IMMUNOMODULATORY THERAPY especially for high-risk children before complications develop
- REFER !!!!
**Stepladder Algorithm**

- Aggressive topical steroids, cyclopia
- Periocular steroid; general anesthesia as required
- NSAIDS (tolmetin, naproxyn)
- Brief (3 months) systemic steroid therapy
- Immunosuppressant therapy
- Diagnostic and therapeutic pars plana vitrectomy

**MY**

- 1997 – 19 yo Chinese female with h/o bilateral iridocyclitis from age 12, treated with chronic topical corticosteroids
- “TMJ”
- ANA + 1:1280
- Consult : Dr. Robert Coles, NYC
- Dx: JRA – associated uveitis
- Refer to Dr. Stephen Foster

9/1977
Episodic loss of vision
Gradual clearing over a period of 4-12 days

9/8/1977
Visual acuity 20/200 OD
20/400 OS
No view of retina
Rx - Napsyn, 500 mg bid

10/31/1977
Visual acuity CF @ 16. OD
CF @ 36. OS
AC 3+ cells
Rx 1% Pred acetate q1h
Discussed prednisone
Discussed chemotherapy

11/1/1978
Intravitreal history
Alternative forms of healing - herbalism/holistic, acupuncture

1/5/1979
Pars plana lensectomy/vitrectomy OD
Papillitis, macular edema, NVD
Recurrent iritis OU w/prednisone taper

3/1/1979
Begin Chlorambucil 8mg/day

Repeat hemorrhages OU
Laser, pan retinal, OD
Visual acuity 20/40 OD
CF @ 40. OS

7/14/1981
Pars plana lensectomy/vitrectomy OS

10/1981
PRP, OS, for NVD

Visual acuity 20/40 OD
20/25 OS
Prolonged wear SCLs
Immunomodulatory Therapy

- Weekly methotrexate (10-30mg/m²)
- Folic acid 1mg daily
- Minimum 2 years after inflammatory quiescence
- Off all steroids
- Azathioprine (3mg/kg/day)
- Mycophenolate mofetil (2-3g/day)
- Cyclosporine (5mg/kg/day)
- Chlorambucil (0.1mg/kg/day)
- Cyclophosphamide (1-2.5mg/kg/day)

- Pulsed intravenous cyclophosphamide
  - 500mg/kg/m² once monthly
- Intravenous immunoglobulin
  - 2g/kg/cycle, once monthly
- Infliximab
  - Variable efficacy; higher dose and more frequent administration required for control of uveitis compared to control of arthritis.

4 Urgent need for therapeutic guidelines

- Multicenter randomized clinical trials comparing immunomodulatory drugs
- Safety and efficacy of early Biologic Response Modifiers (BRMs) in JIA-uveitis versus other Immunosuppressive Agents (MTX, MMF...)
- Better outcomes with less risk?

5 Coordination among ophthalmologists, pediatricians, and rheumatologists

- For uveitis diagnosis
- For effective uveitis management with Immunomodulatory therapy in children