Inflammatory Arthritis in Children

when and why it is important to think rheumatology in the young

Dr Navid Adib

Paediatric Rheumatologist

Queensland Rheumatology Services

Background: Definitions

- Arthritis

Inflammation at or near a joint

Usually lasting more than just a few days

Chronic arthritis if ≥ 6 weeks (e.g. JIA)

- Synovitis

Synovium is the site of inflammation

There **may** be fluid accumulation (effusion)

The range of motion (ROM) **may** be limited

Background: Definitions

Enthesitis

Inflammation at tendinous or ligamentous insertion near joints or bones

Inflammation in joints

- Transient synovitis
    - Unknown frequency
    - Usually after URTI
    - Boys 2-4x more common
    - Mostly described as “irritable hip”, but can happen in any joint
    - Lasts 7-10 days
    - May recur in some cases; in the same joint or in the contralateral side (hip, knee)
    - Some elevation in ESR/CRP
    - Immune mediated and not septic arthritis

Transient synovitis

- Signs and symptoms
    - Reduced ROM
    - Pain
    - disability
- Investigation
- Treatment: rest, control pain (NSAIDs), ?steroid injection if persistent
- **Red flags**
    - **Septic child (high fevers >38.5°, elevated CRP/ESR ?range)**
    - **Non-weight bearing, or ++spasm/++ reduced ROM**
    - **Very young age (<1 y.o.)**
    - **Not resolving after 2 weeks**

Juvenile Idiopathic Arthritis (JIA)

- Arthritis*, ≥ 6 weeks, <16 y.o., no other cause for arthritis (e.g. IBD, Down S.)
- ILAR classification system
  - Systemic Arthritis
  - Oligoarthritis
    - Persistent (fewer than 5 joints cumulative count, ≥ 6m)
    - Extended (5 joints or more, ≥ 6m)
  - Polyarthritis RF neg. (5 joints or more, <6m)
  - Polyarthritis RF pos. (5 joints or more, <6m)
  - Psoriatic Arthritis (psoriasis, nail dystrophy/pitting, 1st deg relative with pso)
  - Enthesitis Related Arthritis (male ≥ 6yo, HLA-B27+, 1ST deg relative AS/IBD)
  - Undifferentiated (unclassifiable)

Systemic Arthritis

- Probably auto-inflammatory disease (not autoimmune), IL-1, IL-6
- ANA, RF, HLA-B27 *usually* negative
- Not associated with uveitis
- Characterised by
    - Usually “sick”, but relatively well between fevers
    - Fevers (at least 2 weeks, 3 days quotidian)
    - Evanescent rash (?salmon pink)
    - Lymphadenopathy, hepatosplenomegaly
    - Serositis (ascites, pericardial, pleural effusion)
    - Hepatic derangement (LFTs, synthetic function (including coagulopathy)

Case 1 systemic arthritis

- Female 10yo, Kabuki syndrome
- Fevers, rash
- Joint pains and reduced mobility

Treatment of systemic arthritis

- Steroids (IV, or oral medium to long course, intra-articular)
- Cytotoxics (methotrexate, cyclosporine A)
- Biologics (IL-1 Anakinra), IL-6 Tocilizumab)
- Cenakinumab
- Sub-cut Tocilizumab

Oligoarthritis

- High association with ANA (≥1:80)
- Highest association with chronic anterior uveitis (CAU)
- Knee most common presenting joint
- Treatment
    - IAS
    - ?methotrexate (recurrent cases, persistent uveitis)
    - ?Biologics (recurrent cases, refractory uveitis)
- Usually best outcome*

Case 2 Oligoarthritis

- DH, 3yo male
- s/b GP and referred to LCCH, difficult referral and appointment process, long delay before seen
- Not systemically unwell
- Unable to walk, started bum-shuffling
- Seen at the clinic; in wheel chair, unable to weight bear
- Grossly swollen R knee, also both ankles
- Reduced subtalar joint ROM

Oligoarthritis

- Investigation results
- Arranged intra-articular steroid injections
- Commenced methotrexate treatment
- Referral to physiotherapist
- **Referral for uveitis assessment**

Oligo walking video

Oligo walking video 2

Oligoarthritis

- Review at the clinic
- No uveitis
- Now can mobilise by walking again
- Pains improved, no gelling or morning stiffness
- Persistence of fixed flexion deformity 15 deg.
- Referred for serial casting

Oligo walking video 3

Chronic Anterior Uveitis

- Presence of inflammatory cells in the anterior chamber of the eye
- Painless condition; younger children will not reliably report
- May have photophobia
- Visual acuity affected, not refractory error
- May show injection, irregularity of the pupil
- Advanced cases with glaucoma or cataract

Band keratopathy

Uveitis treatment

- Steroid drops (weak to strong types)
- Cycloplegics (Homatropine<atropine)
- Systemic treatment
    - Oral/IV steroids
    - Cytotoxics: methotrexate, cyclosporine
    - Biologics: Adalimumab or infliximab
- Intra-ocular
    - Steroid depot (triamcinolone)
    - methotrexate

Polyarthritis

- Greater number of joints results in
    - greater disability
    - Greater likelihood of chronic inflammation
    - More difficult procedure (longer GA, larger steroid dose, cervical spine)
    - Less favourable structural outcomes
- Medicare rebated biologic treatment
    - At least 3 months on methotrexate (20mg/sqm)*
    - Concomitant steroid Rx, or hydroxychloroquine/sulfasalazine (“triple therapy”)
    - 4 large joints, or 20 large and small joints inflamed **simultaneously**

Polyarthritis case

Psoriatic arthritis

- May have psoriasis, or develop this later
- History of psoriasis, or psoriatic arthritis in first degree relative
- DIPJ involvement
- Onycholysis, nail pitting
- Arthritis mutilans

Places to look for psoriasis

Navel

Severe nail and paronychial inflammation

Dactylitis, nail dystrophy

Enthesitis Related Arthritis

- Axial skeleton involvement (SIJs to proximal)
- Large joint involvement (especially hips)
- May have no arthritis (enthesitis only)
- Acute anterior uveitis
- Inherent treatment difficulties
    - Steroid and methotrexate resistance
    - SIJs access for steroid injection
    - ?NSAIDs for spondyitis

Acute Anterior Uveitis: Hypopyon

Arthritis In The Context Of Other Diagnoses:

- Inflammatory Bowel Disease Related Arthritis
    - Often large joints (especially hips)
    - Axial skeleton
    - Management difficulty

Arthritis In The Context Of Other Diagnoses:

- Arthritis related to infection
  - Septic Arthritis
    - Staph, Haemophilus, Gonococcal, Tuberculous, Brucella
  - Viruses:
    - Rubella, Parvovirus, Alpha viruses (e.g. Ross River), Mumps, HIV
  - Spirochetes (Borrelia burgdorferi in Lyme Disease)

Arthritis In The Context Of Other Diagnoses:

- Postinfectious arthritis (Arthritogenic bacteria)
    - Enteric Bacteria: Campylobacter, Salmonella, Shigella, Yersinia
    - Chlamydia, Mycoplasma, Giardia, Cryptosporidium
    - ?HLA B27 related

Arthritis In The Context Of Other Diagnoses:

- Reactive arthritis
  - Reiter's Syndrome: Arthritis, Conjunctivitis, Urethritis (Gonococcal, chlamydial).

Arthritis In The Context Of Other Diagnoses:

- Post Streptococcal Reactive Arthritis
- Rheumatic fever

Arthritis In The Context Of Other Diagnoses:

- Immune deficiency
    - congenital immunodeficiency syndromes
        - Selective IgA deficiency
        - Common Variable Immunodeficiency
        - X-Linked Agammaglobulinaemia

    Often non-erosive and mild

    More often large joints

    Mycoplasma infection erosive arthritis

Arthritis In The Context Of Other Diagnoses:

- Haemoncological disorders
  - Haemophilia
  - Leukaemic joint involvement (chloroma)
    - ++ pain and disability
    - Night pain

Arthritis In The Context Of Other Diagnoses:

- Connective Tissue Disease (CTD)
    - Systemic Lupus Erythematosus
    - Overlap syndromes (Note RF positive)
    - Juvenile Dermatomyositis
    - Coexistent with Morphea/Linear Scleroderma

Arthritis In The Context Of Other Diagnoses:

- Systemic Vasculitides and related syndromes
  - Henoch Schonlein Purpura
  - Kawasaki Disease
  - Polyarteritis Nodosa (PAN)
  - Relapsing Polychondritis

Arthritis In The Context Of Other Diagnoses:

Rare syndromes with arthritis

- CINCA (Chronic Infantile Neuro Cutaneous and Articular) Syndrome
- SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis) Syndrome
- Recurrent Fever Syndromes
    - FMF: Familial Mediterranean Syndrome
    - HIDS: Hyper IgD Syndrome (Dutch Fever)
    - TRAPS: TNF-α Receptor Associated Periodic Fever Syndrome (Familial Hibernian Fever)

Treatment of arthritis

- Treat to target
- Involve multidisciplinary team:
  - Physiotherapist
  - Occupational therapist
  - Nursing support
  - Social worker
  - Psychologist
  - Pharmacist
  - Music therapist
  - School at hospital
- Biopsychosocial model of care

Treat to target-Avoid “pyramid” approach

- Completely resolve joint/entheseal inflammation (induction)
    - Steroid injection/infusion
    - Rarely oral course
- Simultaneous commencement of **appropriate** maintenance agent
    - Methotrexate
    - Other cytotoxics (Leflunomide, Azathioprine)
    - Adjuvant medications (Hydroxychloroquine, Sulfasalazine)
- Surveillance
    - Regular follow up appointments
    - Blood screening tests (medications, disease activity)
    - Joint steroid injections
    - Biologics (to be added on, not replaced with)

Do NSAIDs work?

Methotrexate

- Given as low dose (15mg/sqm/wk)
- Oral or subcutaneous (IM hurts!!)
- Slow onset 2-3 months
- Most children tolerate it well
- Others report:
    - Feeling unwell the day after
    - May have nausea or vomiting
    - Rarely mouth ulcers
- Need blood monitoring 1-2 monthly (FBC, ELFTs)
- Safe to handle (pill crusher) if not pregnant

Steroid injection into joints

- Long acting steroid (Triamcinolone acetonide/hexacetonide)
- Preferably under GA
- May use X-ray guidance or ultrasound
- Usually provides 2-3 months relief (sufficient for mtx to become active)
- Onset usually few days
- Larger joints will require larger dose
- HPA suppression rarely a problem

Biologics

- Approaches
    - TNF-α blockers
    - IL-6 blockers
    - IL-1 blockers
    - JAK inhibitors

TNF-α (cachexin, cachectin)

- Cytokine (cell signalling protein), regulation of immune cells
- Pro-inflammatory molecule via IL-1 and IL-6 signal, pyrogen
- Apoptotic cell death, cachexia
- Inhibit tumorigenesis and viral replication
- Predominantly from activated macrophages, but also
    - Neutrophils
    - CD-4 lymphocytes
    - Natural killer cells
    - Mast-cells
    - Eosinophils
    - Neurons

Conditions associated with TNF-α

- Alzheimer’s disease, major depression
- Psoriasis, inflammatory bowel disease
- Rheumatoid arthritis, ankylosing spondylitis, JIA

TNF-α Blockade

Key Actions Attributed to TNF-α

Rituximab selectively targets CD20-positive B cells

- B cell depletion occurs via three proposed mechanisms:
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Apoptosis

Human microbiome

Golden Compass?!

Dust

Microbiome and arthritis

- Organisms which live on and inside our body
- GI tract dry weight 2kg
- Usually in harmony
- Probably have a role as “gate keepers”
- ?role in conditions such as:
    - Obesity
    - Diabetes
    - Arthritis
    - Inflammatory bowel disease

Microbiome

- Child birth
- Antibiotics use
- Diet, ?
- Can they be used for treatment of different conditions

Take home messages

- NSAIDs are not disease modifying but merely symptomatic treatment
- Using cytotoxics requires familiarity and patient surveillance
- Any child/young person with joint symptoms not resolving after 2 weeks **must** be referred for evaluation
- If concerned about a case (contracture, significant joint swelling, loss of function)

PLEASE PICK UP THE PHONE AND CALL US!!