

2009 Pediatric Conference

Juvenile Idiopathic Arthritis for the Primary Care Practitioner

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'Specially for Children
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Outline

- Review Definitions and Classification of JIA
- Systemic Onset JIA
 - Macrophage Activation Syndrome
- Oligoarticular/Polyarticular JIA
 - Uveitis
- Spondyloarthropathy

Definitions

- Arthralgia = pain in a joint
- Arthritis = swelling of a joint/
synovial hypertrophy
limited range of motion
pain/tenderness with motion
warmth of a joint
redness of a joint

Acute vs. Chronic Arthritis

According to the Arthritis Foundation there are >100 diseases associated with arthritis.

ACUTE

- Lasts < 6 weeks
- Pain is prominent symptom
- Often associated with infection/injury
- Consider septic arthritis

CHRONIC

- Lasts > 6 weeks
- Swelling and stiffness are prominent sx's
- May be noticed incidentally at time of illness

EPISODIC ARTHRITIS: Autoinflammatory disorders, IBD-associated arthritis

Juvenile Rheumatoid Arthritis

Juvenile Idiopathic Arthritis

- Most common chronic rheumatic disease of childhood
- Prevalence $\sim 1/1000$
- Really a group of diseases
- Formerly thought of as “disease of children”
- Now known that for many, disease can persist into adulthood \rightarrow significant functional impairment

JRA: Juvenile Rheumatoid Arthritis

Classification Criteria developed by the American College of Rheumatology in 1970's

- Age at onset <16 years
- Arthritis in one of more joints
- Duration of disease 6 weeks or longer
- Onset type defined by type of disease in first 6 months:
 - Systemic-onset: characteristic fever/rash
 - Oligoarthritis: ≤ 4 inflamed joints (AKA Pauciarticular)
 - Polyarthritis: >4 inflamed joints
- Exclusion of other forms of arthritis

JIA: Juvenile Idiopathic Arthritis

Classification Criteria developed by the International League of Associations for Rheumatology in 1990's

- Systemic
- Oligoarthritis
 - Persistent (≤ 4 joints affected after first six months)
 - Extended (>4 joints affected after first six months)
- Polyarthritis (rheumatoid factor negative)
- Polyarthritis (rheumatoid factor positive)
- Psoriatic Arthritis
- Enthesitis-related arthritis
- Undifferentiated Arthritis
 - Fits no other category
 - Fits more than one category

Case Presentation I

- 4 year old boy is hospitalized for fever of unknown origin for the last month; ID work up has been negative
- While the fevers were around the clock initially, he now tends to have fevers only in the late afternoon
- During this time he also gets a red rash on his trunk, arms, and inner thighs; the rash disappears when the fever is gone
- He has started complaining of chest pain when lying down

Case Presentation I

- On physical exam he is febrile to 102 degrees and is tachycardic; he is fussy
- Skin exam shows small, slightly raised pink macules on his trunk and arms
- His knees and ankles are swollen bilaterally
- Echo shows mild pericardial effusion

Systemic Onset Juvenile Idiopathic Arthritis

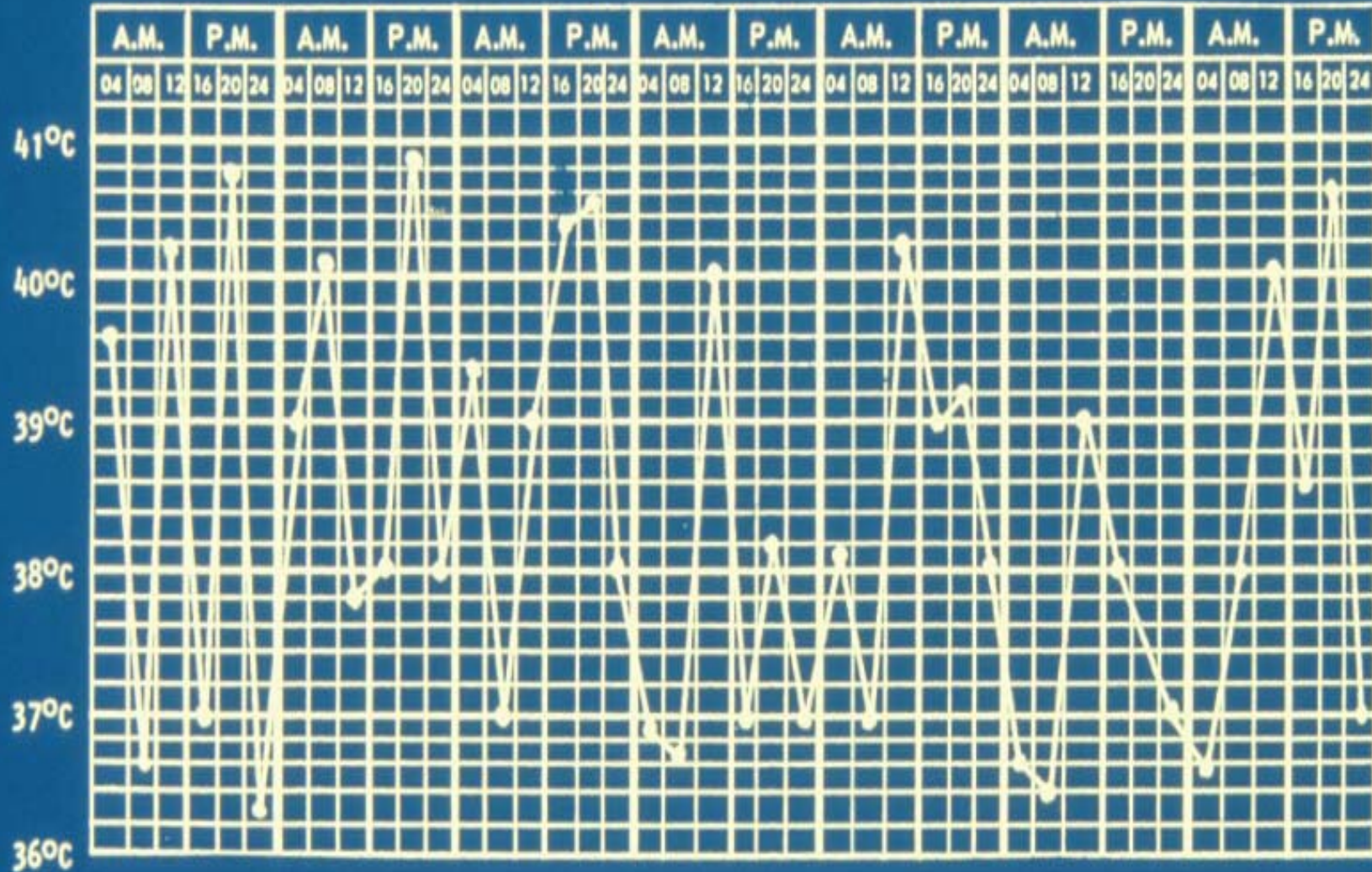
SoJIA: Epidemiology

- Boys and girls affected equally
- Accounts for ~10% of JRA cases
- Peak age 1-5 years?

SoJIA: ILAR Criteria

- Arthritis (any number of joints)
- Fever x 2+ weeks that is quotidian x at least 3 days
- One or more of the following:
 - Evanescent rash
 - Generalized lymphadenopathy
 - Hepatomegaly and/or splenomegaly
 - Serositis

SoJIA: Characteristic Fever



SoJIA: Characteristic Rash

- Salmon pink
- Evanescent
- Typically present at time of fever
- Non-pruritic (classically)

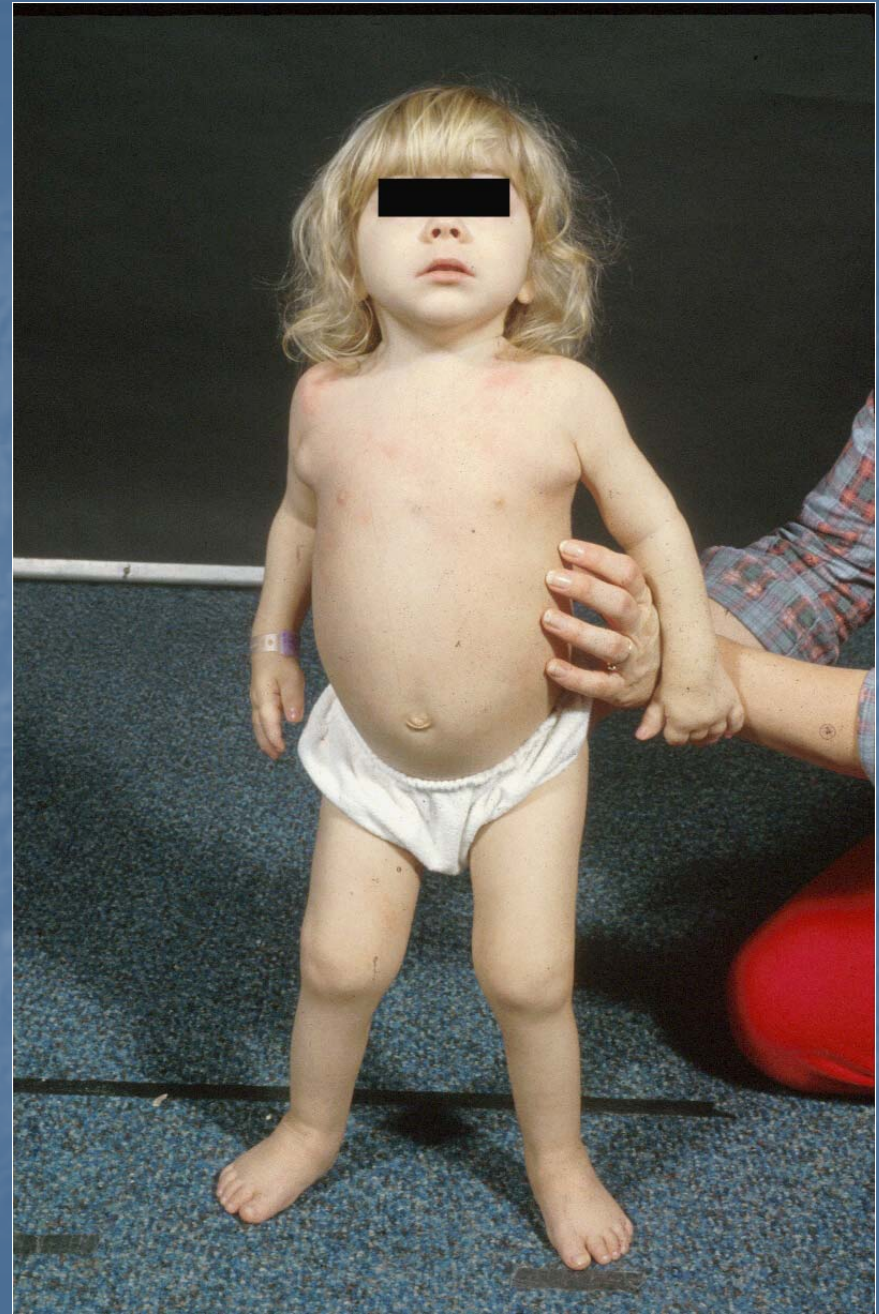
SoJIA: Characteristic Symptoms

- Serositis
 - Pericarditis/Pleural Effusions
 - Chest pain that is worse when lying down, dyspnea
 - PE: diminished heart sounds, tachycardia, tachypnea, friction rub
 - CXR: enlarged cardiac silhouette
 - EKG: low voltage, ST-segment elevation, diffuse T wave inversion

SoJIA: Characteristic Symptoms

- Lymphadenopathy
 - May raise the question of lymphoma as diagnosis
- Splenomegaly
 - Typically early in disease
- Hepatomegaly
 - Less common than splenomegaly

- Arthritis
 - Knees
 - Elbows
 - MCPs
 - Ankles
- Axillary Lymphadenopathy
- Prominent Abdomen – Hepatosplenomegaly
- Evanescent rash?



Picture from Dr. Murray Passo

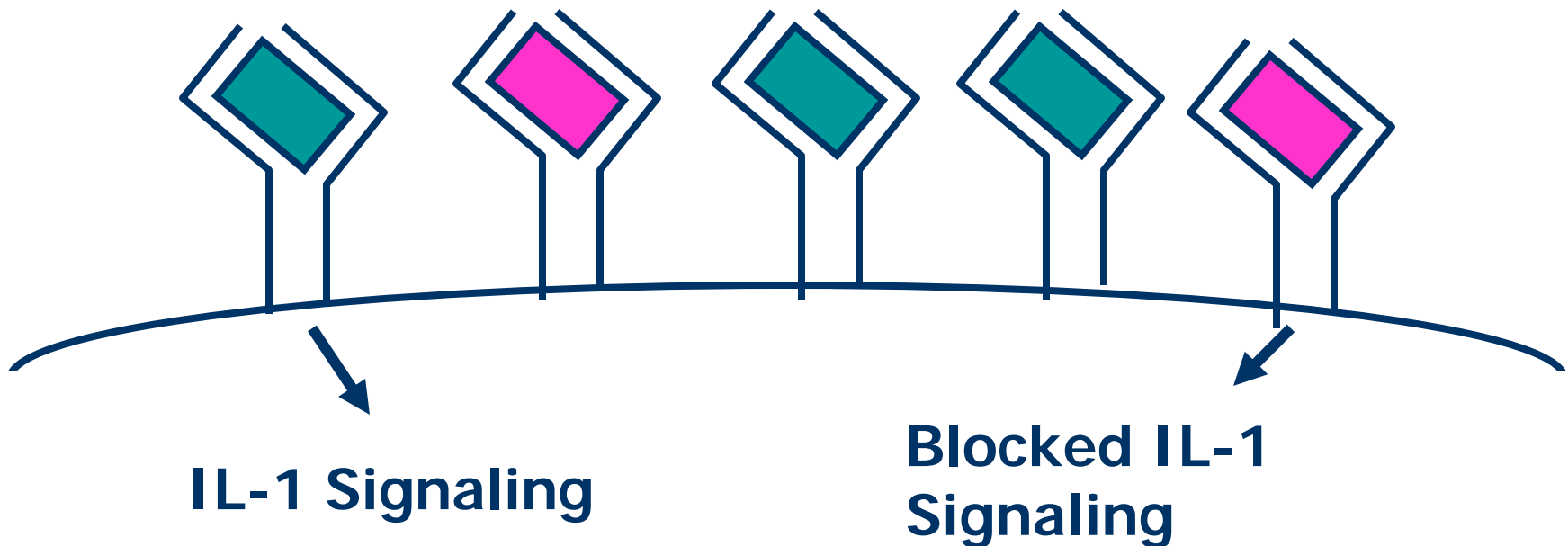
SoJIA: Diagnosis

- Presence of arthritis is key to making diagnosis
- Systemic symptoms may be present for weeks to months before arthritis manifests
- Differential Diagnosis: Infection, Malignancy, Vasculitis (Kawasaki's Disease), ARF, Connective Tissue disease
- Laboratory Evaluation: Abnl CBC (↑ WBC, ↓ RBC, ↑ Plt), increased inflammation, increased ferritin

SoJIA: Treatment

- Fever, Rash, Arthritis
 - Naprosyn first line therapy
- Fever, Rash, Arthritis, Serositis
 - Indocin first line therapy
- Fever, Rash, Arthritis, Serositis, and Sick
 - Steroids first line therapy (after malignancy ruled out)
 - Involve Peds Rheum before starting if possible
- Second line therapy: Methotrexate, Anakinra

SoJIA: Biologic Therapy



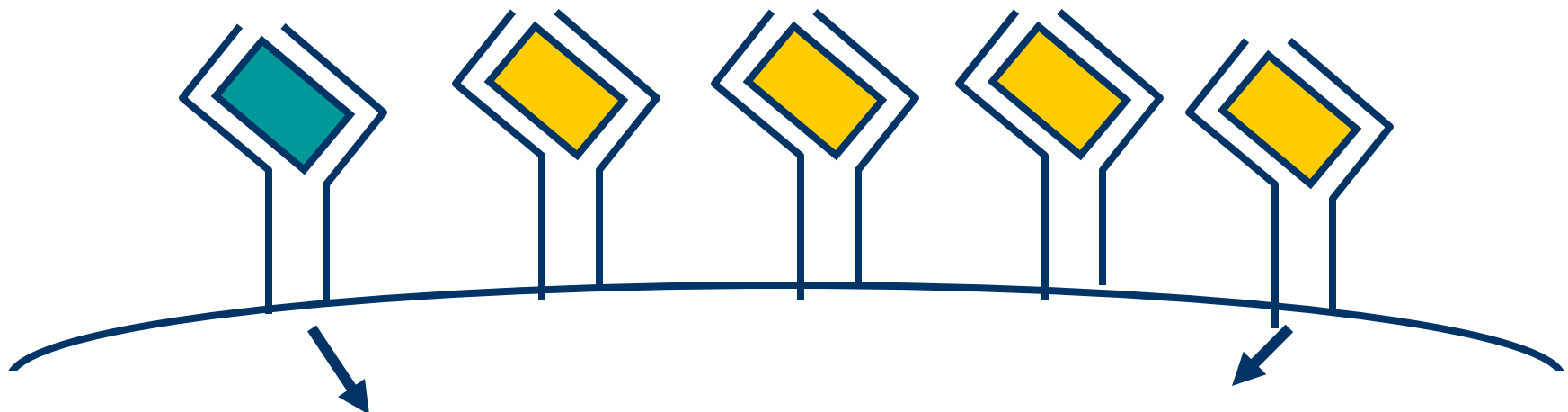
SoJIA: Biologic Therapy



IL-1

Anakinra

(synthetic IL-1Ra)



IL-1 Signaling

Blocked IL-1
Signaling

SoJIA: Biologic Therapy

- Anakinra (Kineret) is given by injection daily
- Anakinra blocks IL-1 signaling
- If patient has fever from intercurrent illness, we instruct patient to hold Anakinra until afebrile x 48 hours, on antibiotics x 48 hours (if appropriate), and they've "turned the corner"

SoJIA: Complications

Macrophage Activation Syndrome

- Potentially lethal complication; occurs in ~5-8% of cases of SoJIA
- Most often associated with SoJIA, but can also be seen in lupus, other rheumatic conditions
- Similar to Hemophagocytic Lymphohistiocytosis (HLH)
- Triggers: Mono, other infections, drugs, ??

SoJIA: Complications

Macrophage Activation Syndrome

- Fever
- Hepatosplenomegaly
- Hepatic failure with encephalopathy
- DIC
- Cytopenias
- Labs: ↑`d AST/ALT, ↓`d platelets, prolonged PT/PTT, ↑`d ferritin (>10,000), paradoxically low ESR, low fibrinogen, ↑`d D-dimer, ↑`d triglycerides
- Dx: bone marrow biopsy showing phagocytosis of blood cells

SoJIA: Complications

Macrophage Activation Syndrome

- Treatment
 - High dose steroids (oral or pulse)
 - Cyclosporine

Case Presentation II

- 14 year old female presents with 2 month history of swollen and stiff fingers; she is having trouble straightening her arm while playing the violin
- She reports significant fatigue – during the lunch hour she is taking naps in the empty orchestra room

Case Presentation II

- Physical exam shows swelling and decreased range of motion of her bilateral wrists, elbows, 2nd, 3rd, and 4th MCP, and 2nd and 3rd PIPs.
- Lab evaluation shows a normal CBC, ESR 68, and RF 1700.

Polyarticular JIA

Poly JIA: Epidemiology

- ~40% JRA
- Girls > Boys
- RF positive group late childhood/adolescent

Poly JIA: ILAR Criteria

- Arthritis in five or more joints in first 6 months
 - RF positive: positive RF on at least two occasions, separated by 3 months
 - RF negative: negative RF
- Exclusions
 - Psoriasis
 - HLA-B27 positive boy >6 years of age
 - HLA-B27 disease in patient or first degree relative: AS, ERA, SI and IBD, Reiter's, acute anterior uveitis
 - Presence of systemic features

Rheumatoid Factor Positive Poly JIA

- ~5% of JIA
- Suggests more aggressive, erosive disease
- Onset typically in adolescence
- Symmetric joint involvement
- Rheumatoid nodules
- Rheumatoid vasculitis

Poly JIA: Diagnosis

- Chronic Arthritis >4 joints
- Labs: check ANA, RF (and/or CCP), CBC, ESR
- Eye Exam: screen for uveitis

- Differential Diagnosis: infection (parvo, TB, GC, Lyme), SLE or other connective tissue disease, hemophilia, malignancy, sickle cell anemia, sarcoid, other arthritic syndromes

Poly JIA: Treatment

- First Line: Naprosyn (10mg/kg/dose BID) for 4-6 weeks → 80-90% patients will need more aggressive therapy
- Second Line: Methotrexate
 - +/- Steroid treatment
- Second Line: TNF inhibitors
 - Can be synergistic with Methotrexate
- Second Line: Orencia

Methotrexate Therapy

- Anti-inflammatory doses used
- Suppresses immune system
 - Hold temporarily if febrile/bacterial illness
 - Hold indefinitely during EBV/CMV infections
 - No live vaccines
- Metabolized by liver
 - No alcohol
- Frequent Labs (Q 2-3 months)
 - WBC count
 - Liver enzymes, kidney function

Methotrexate Therapy

- Possibly teratogenic
 - Females should not become pregnant and males should not father a child unless they've been off MTX for 3 months
- Nausea common (~20% patients)
 - Take Friday nights → sleep through nausea; doesn't interrupt school if some nausea on Saturday
- Folic Acid supplementation
 - Helps prevent nausea, mouth sores, protect liver

TNF Inhibitors - Biologic Therapy

- Suppresses Immune System
 - Hold temporarily for febrile/bacterial illness
 - TB testing required before starting
 - No live vaccines
- Frequent Labs
 - CBC with diff, ESR
- Injection site reactions common
 - Usually peak around 3rd dose then improve

Case Presentation III

- 3 year old girl presents with swollen right knee and limp
- Parents noticed the knee after she fell down two weeks ago, although were surprised by this finding as the fall was minor
- Thinking back, they wonder if she was limping slightly before then; her gait has seems more unsteady lately
- She does not complain of pain, but seems stiff in the morning for a couple of hours the last two weeks

Case Presentation III

- On physical exam
 - right knee is swollen with synovial hypertrophy; small fluid wave is seen; she is unable to fully straighten her leg
 - Left thumb MCP is also swollen with decreased range of motion
- Labs show she is ANA positive
- Ophtho exam reveals flare and keratic precipitates in anterior chambers of her eyes bilaterally

Oligoarticular JIA

Oligo JIA: Epidemiology

- ~60% JRA
- Girls > Boys
- Peak age 1 – 3 years

Oligo JIA: ILAR Criteria

- Arthritis in four or fewer joints in first 6 mos
 - Persistent: Never more than four joints involved
 - Extended: More than four joints involved over time
- Exclusions
 - Psoriasis
 - HLA-B27 positive boy >6 years of age
 - HLA-B27 disease in patient or first degree relative: AS, ERA, SI and IBD, Reiter's, acute anterior uveitis
 - Presence of systemic features
 - Presence of rheumatoid factor on 2 occasions

Oligo JIA: Diagnosis

- Chronic Arthritis ≤ 4 joints
- Labs: check ANA, RF, CBC, ESR
- Eye Exam: screen for uveitis

- Differential Diagnosis: septic arthritis, infection (TB, GC, Lyme), trauma, hemophilia, malignancy, sarcoid, pigmented villonodular synovitis, other arthritic syndromes

Oligo JIA: Treatment

- First Line: Naprosyn (10mg/kg/dose BID) for 4-6 weeks – 80-90% patients will need more aggressive therapy
- Second Line: Steroid joint injections
- Third Line: Methotrexate
- Fourth Line: TNF inhibitors

**Chronic Asymptomatic
Uveitis Associated with JIA**

JIA-Associated Uveitis

- Patients at increased risk:
 - Oligo JIA
 - Females < 7 years of age
 - ANA +
- Asymptomatic initially
- Typically bilateral
- 10% of patients develop uveitis before onset of arthritis
- Uveitis typically diagnosed within 7 years of JRA diagnosis
- Course of uveitis does NOT parallel course of arthritis

JRA-Associated Uveitis Treatment

- Local Topical Therapy
 - Steroid Eye Drops
 - Short Acting Mydriatic/Cycloplegic Eye Drops
- Local Injectable Therapy
 - Periocular Steroid Injections
- Systemic Steroid Therapy
- Methotrexate, TNF Inhibitors

JRA-Associated Uveitis Complications

- Cataracts (13-58%)
- Glaucoma (3-27%)
- Band Keratopathy (5-56%)
- Posterior Synechiae (8-75%)
- Vision Loss (10-38%)

Complication rates compilation of 8 studies involving 376 children as cited in article by Reiff et al (2001)

Case Presentation IV

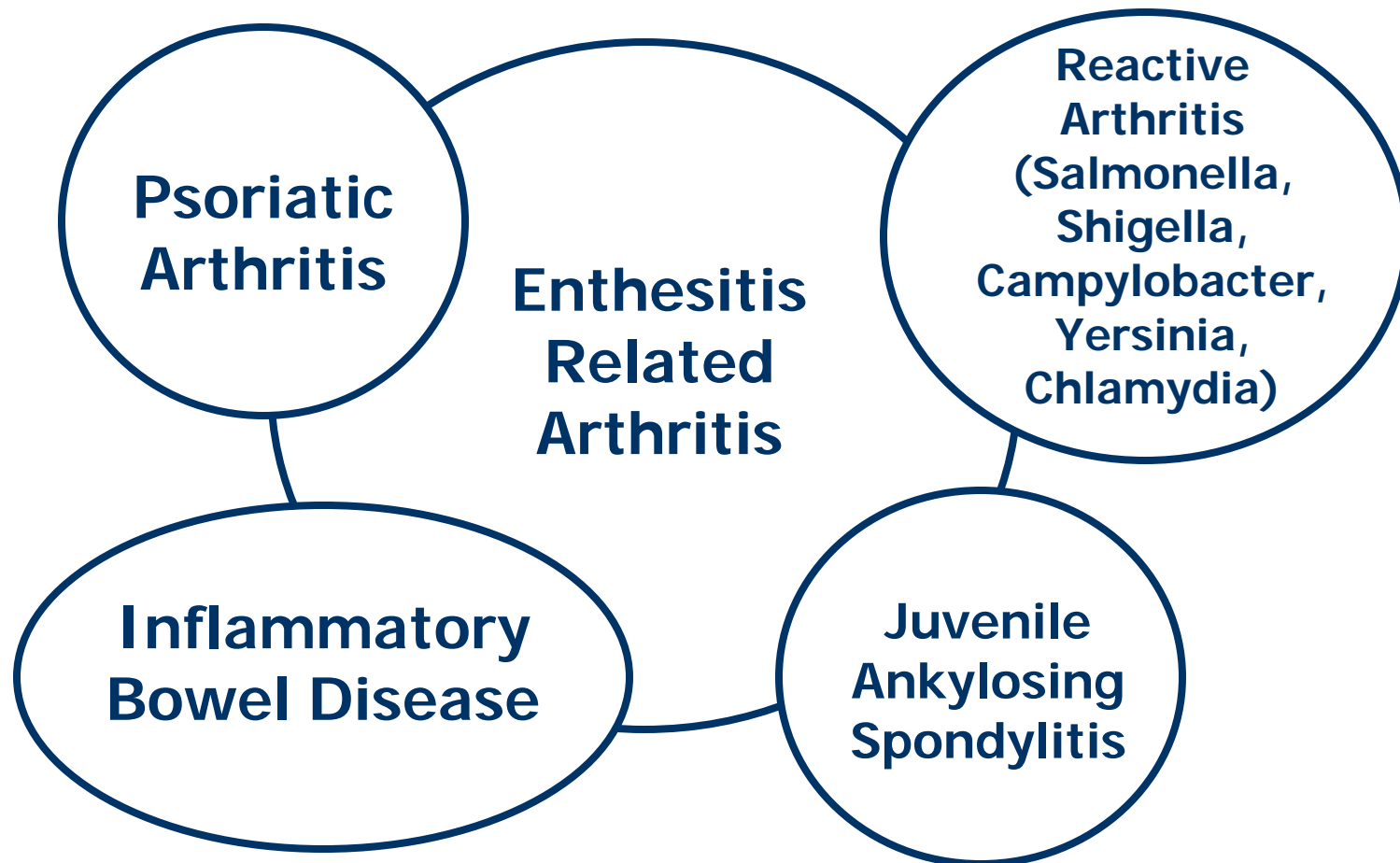
- 16 year old boy presents with 3 week history of left knee swelling
- He also reports pain on the bottom of his feet for several years; it is worsening
- His uncle has had several episodes of acute anterior uveitis

Case Presentation IV

- Physical exam shows swollen left knee with synovial hypertrophy and fluid wave
- He has pain at the plantar fascia on the calcaneous as well as the metatarsal heads
- Lab results show that he is ANA -, RF -, but HLA-B27 positive.

Spondyloarthropathy

Spectrum of Enthesitis-Related Disease



Spectrum of Enthesitis-Related Disease

- Seronegative (RF- and ANA-)
- Sacroilitis (radiographically)
- Peripheral arthritis (typically lower extremity, asymmetric arthritis)
- Enthesitis
- Familial aggregation (HLA-B27)

Ankylosing Spondylitis

- New York Criteria for Diagnosing AS
 - Requires presence of significant SI joint involvement on x-ray
 - On average, it takes over 6 years of symptoms before SI joint involvement is apparent on x-ray

Enthesitis-Related Arthritis: ILAR Criteria

- Arthritis and enthesitis
- Or
- Arthritis or enthesitis with at least two of the following:
 - SI joint tenderness and/or inflammatory spinal pain
 - Presence of HLA-B27
 - Family History of HLA-B27 related disease in a first- or second-degree relative
 - Acute anterior uveitis
 - Onset of arthritis in a boy > 8 years of age
- Exclusions: psoriasis or systemic features

Arthritis

- Lower extremities
- Isolated hip disease not unusual
- Tarsitis – pain and decreased motion of midfoot
- Toes commonly involved, but finger joints are not
- SI joint involvement, spinal involvement

Enthesitis

- Inflammation of tendons/ligaments at their attachment sites to bones
- Common sites:
 - 2 o'clock, 6 o'clock, and 10 o'clock positions around patella
 - Tibial tuberosity
 - Achilles tendon attachment site at calcaneus
 - Plantar fascia attachment site at calcaneus
 - Heads of the metatarsals
 - Base of 5th metatarsal

Osteochondroses

- Injury in primary or secondary ossification center
- May be normal developmental variant
- Results in pain
- Boys > girls
- Typically only one site affected at a time

Osteochondroses

- **Osgood-Schlatter:** tibial tuberosity
- **Sinding-Larsen-Johansson:** inferior pole of the patellan (AKA jumper's knee)
- **Sever's Disease:** calcaneal apophysis
- **Kohler's Disease:** tarsal navicular bone
- **Freiberg's Disease:** second metatarsal head
- **Thiemann's Disease:** phalangeal epiphyses

Enthesitis-Related Arthritis: Treatment

- First Line Therapy: NSAIDs
- Second Line Therapy: Methotrexate or Steroid Injections (not as effective)
- Second Line Therapy: TNF blockers

Spondyloarthropathy Associated Disease

Acute Anterior Uveitis

- Unilateral
- Painful
- Redness
- Tearing
- Photophobia

JIA Outcomes

- Mortality Rate: ~1%
 - 60% mortalities in SoJIA
 - Majority related to infection
- Systemic JIA
 - ~50% monocyclic/polycyclic course
 - ~50% persistent course, polyarticular joint disease
- Oligo JIA (in general, best outcome)
 - ~50% monocyclic/polycyclic course
 - Significant morbidity can be associated with uveitis

JIA Outcomes

- Poly JIA
 - RF negative – variable
 - RF positive – chronic, often destructive course
- Spondyloarthropathy
 - Variable course
 - Disease limited to peripheral arthritis, better outcome
 - Disease involving SI joints, spine, more chronic/progressive course

Take Home Points

- JIA is more than just one disease
- Arthritis is a clinical diagnosis; presence of ANA or RF does not make or break the diagnosis, but rather helps with prognosis
- NSAIDs are first line therapy; need to be scheduled, sometimes for 4-12 weeks before full anti-inflammatory effects will be seen

NSAID Therapy

- Naprosyn is almost always my first-line therapy for arthritis
 - Twice daily dosing
 - Approved for JRA
 - Available in liquid formulation
- Avoid in fair-skinned, blonde haired children
 - Side Effect of Pseudoporphyria more likely

NSAID Therapy

Alternative NSAIDS

- Mobic
 - 0.125 mg/kg/day (max 7.5 mg) once daily
- Relafen
 - 30 mg/kg/day (max 2000 mg) once daily
- Diclofenac
 - 2-3 mg/kg/day ÷ TID (max 150 mg/day)
- Celebrex (not if sulfa allergic)
 - 10-25 kg 50 mg po bid
 - >25 kg 100 mg po bid



PSEUDOPORPHYRIA

Picture from: Schäd *et al. Arthritis Research & Therapy* 2007 9:R10 (dio:10.1186/ar2117)

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