Update in the Diagnosis and Management of Juvenile Idiopathic Arthritis

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Objectives
- Recognition of Juvenile Idiopathic Arthritis (JIA)
- Subtypes of JIA
- Common complications of JIA
- Prognosis and outcomes
- General treatment recommendations

What is Arthritis
- Criteria for diagnosis of juvenile idiopathic arthritis
  - Age of onset < 16 yrs
  - Arthritis
    - Swelling or effusion or presence of 2 or more of the following
      - Limited range of motion
      - Tenderness or pain on motion
      - Warmth
    - Duration of symptoms > 6 weeks (some criteria use 3 months)

Take the “R” out of JRA
- ILAR (Juvenile Idiopathic Arthritis)
  - Oligoarthritis
  - P Kensicent
  - ACR (Arthritis, Oligoarthritis, Juvenile rheumatoid arthritis)
  - Polyarthritis
  - Pauciarticular arthritis
  - Polyarticular arthritis
  - Systemic arthritis
  - Enthesitis-related arthritis
  - Psoriatic arthritis
  - Other

JIA
- Incidence 10-20 per 100,000 children
- Prevalence 100-300 per 100,000 children
  - Niagara + Erie County: est. 1000-3000 children
  - > 300,000 children with rheumatic diseases in the U.S.
- Ambulatory care visits for pediatric arthritis and rheumatologic conditions average 830,000 annually

ACR, American College of Rheumatology; ILAR, International League of Associations for Rheumatology

Disclosures
- None
Recognizing JIA

- Retrospective chart review of all referrals to a pediatric rheumatology service (1998-2001)
  - Chief Complaints: (414 children)
    - Musculoskeletal pain: 226 (54.6%) had chronic inflammatory dz
    - Abnormal Lab: 157
      - 12 JIA
    - Joint Swelling: 107
    - Fever: 46
    - Gait disturbance: 38
    - Rash: 34
    - Fatigue: 26
    - Morning stiffness: 15
    - Other: 39
  - 111 had pain as only complaint
  - 1 had a rheumatic disease (spondyloarthropathy)

McGhee et al. Pediatrics 2002

Pain as isolated complaint (n=111)
- Mechanical or overuse syndromes: 81 (73%)
- Psychogenic or amplified pain: 23 (21%)
- Viral arthritis: 3 (3%)
- Toxic synovitis of the hip: 3 (3%)
- SLE: 1 (1%)
- JIA-spondyloarthropathy: 1 (1%)

McGhee et al. Pediatrics 2002

76 Children JIA
- 12 (16%) had pain as a chief complaint
- Pain had a NPV for JIA of 0.95
- 55 (72%) joint swelling
- 33 (40%) gait disturbance
- ANA: 24/90 (27%) with +ANA had a chronic inflammatory dz
- RF: 3/16 (19%) with +RF had JIA
  - All 3 pts had swelling, morning stiffness and fatigue

McGhee et al. Pediatrics 2002

RFRF

Recognizing JIA

- ANA

24/90 (27%) with +ANA had a chronic inflammatory dz

- RF

3/16 (19%) with +RF had JIA
  - All 3 pts had swelling, morning stiffness and fatigue

McGhee et al. Pediatrics 2002

Recognizing JIA

- Pain + other complaints (n=226)
  - JIA (7%)
  - Other rheumatic process (2%)
    - SLE
    - RSD

Malleson et al. Archives of Disease in Childhood 1997

Tan et al. Arthritis & Rheumatism 1997;40:1601

McGhee et al. Pediatrics 2002
Recognizing JIA

ANA

<table>
<thead>
<tr>
<th>Group</th>
<th>ANA Range</th>
<th>ANA median</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE (n=10)</td>
<td>1:360-1:10,240</td>
<td>1:1080</td>
<td>PPV 1.0 ≥ 1:1080</td>
</tr>
<tr>
<td>JIA (n=18)</td>
<td>1:80-1:640</td>
<td>1:240</td>
<td>NPV ≤ 1:180</td>
</tr>
<tr>
<td>Control (n=89)</td>
<td>1:40-1:640</td>
<td>1:160</td>
<td></td>
</tr>
</tbody>
</table>

- 509 new pt referrals, 110 patients + ANA
  - 10 pts had SLE, 1 MCTD, 1 Raynauds
  - 18 pts with JIA
    - All presented with joint swelling and/or gait disturbance
  - 80 pts without inflammatory dx

McGhee et al. BMC Pediatrics 2004

Rheumatoid Factor

- 437 consecutive children tested for RF

<table>
<thead>
<tr>
<th>Rheumatoid Factor</th>
<th>JIA</th>
<th>Non-JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Absent</td>
<td>100</td>
<td>326</td>
</tr>
</tbody>
</table>

- 5% JIA RF (+) and 2% non JIA RF (+)
- All 5 RF +JIA patients were correctly diagnosed prior to sending the lab based on history and PE
- Conclusion: RF is a poor screening test for JIA, supportive diagnostic value only in older children with polyarthritis

Eichenfield et al. Pediatrics 1986; 78:480-484

Recognizing JIA

- ANA and RF are NOT good diagnostic markers for juvenile arthritis
- ANA important for uveitis monitoring
- Can be useful as prognostic indicators

Recognizing JIA

- Non inflammatory joint pain
  - Joint pain without objective signs of joint inflammation
  - Common causes:
    - Benign hypermobility
    - Overuse syndromes
    - Patellar tendinitis
    - Osgood-Schlatter Disease
    - Sever's Disease (heel, dancers)
    - Benign nocturnal pains of childhood “growing pains”
    - Amplified pain syndromes
  - Less common
    - Leukemia
    - Bone tumors/malignancy
    - Legg-Calve-Perthes
    - Slipped Capital Femoral Epiphysis (SCFE)

Recognizing JIA

Benign Hypermobility

- 20% females and 10% of males (10-35%)
- 3-8 years of age
- Joint pain, muscle pain, neuropathic pain
  - Pain later in the day after activities or in the evening
  - Typically no morning symptoms
  - Often located periaxial
- Associated Conditions
  - Marfan Syndrome
  - Ehlers-Danlos
  - Homocystinuria, Sickle’s Syndrome, Osteogenesis Imperfecta, William’s Syndrome, Down Syndrome

Beighton Scale

- Able to touch thumb to forearm
- Hyperextend 5th MCP so its parallel to the forearm
- >10 degree hyperextension of elbows
- >10 degree hyperextension of knees
- Touch palms on floor with knees straight
- (*) common cause of pes planus
Benign Nocturnal Pains of Childhood

- Not related to growth
- 3-14 years of age
- 15-20% of children
- Intermittent dull or aching pain
- Most commonly noted around the anterior tibia
- Pain at the end of the day rarely in the morning
- Typically follows days of increased activity
- Can awaken a child from sleep
- Gait and exam of the joint are normal

Treatment of Hypermobility and BNP

- Reassurance
- NSAIDS as needed
- Heat
- Massage
- OT/PT
  - Hypermobility: strengthening and stabilization of joints, joint protection, low resistance muscle toning exercises

JIA vs leukemia

- Discriminating childhood leukemia from JIA
  - 277 children
  - JRA (206) ALL (71)
  - 75% blast negative at the time of the evaluation
  - Three most important factors that predicted ALL
    - Low WBC (<4 x 10^9/L)
    - Low-normal Platelets (150-250 x 10^9/L)
    - History of night time pain
  - All 3 sensitivity of 100% and specificity of 85% in blast negative ALL

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Recognizing JIA

- JIA
  - Morning symptoms
  - Improves with activity
  - Stiffness/limitation
  - Abnormal physical exam
  - Labs may be helpful

- Non-JIA
  - Evening symptoms
  - Worsens with activity
  - Pain
  - Often normal exam other than laxity
  - Labs typically normal
Types of JIA

<table>
<thead>
<tr>
<th></th>
<th>Oligoarticular</th>
<th>Polyarticular</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>40-50%</td>
<td>20-30%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td># Joints</td>
<td>≤4</td>
<td>≥5</td>
<td>≥1</td>
</tr>
<tr>
<td>Uveitis</td>
<td>20%</td>
<td>5%</td>
<td>Rare</td>
</tr>
<tr>
<td>RF</td>
<td>Rare</td>
<td>Rare*</td>
<td>Rare</td>
</tr>
<tr>
<td>ANA</td>
<td>80%*</td>
<td>40-50%</td>
<td>10%</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Excellent</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
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</table>

*young girls with uveitis
*except older girls

Age at onset of Oligoarticular JIA

Oligoarthritis

- Most common form of JIA (30-50%)
- Less than five joints involved in first 6 months
  - Knee (55-90%)
  - Ankle (25-40%)
  - Wrist (15%)
  - Elbow (2%)
  - Small joints hands/feet (5-10%)
  - TMJ is late finding and unilateral
  - Hip very rare no rule out LCP or SCFE
- Females to male 5:1

- Development of greater than four joints after the first 6 months of disease
- Extension usually occurs in the first 5 years
- Risk for extension
  - Upper extremity joint involvement
  - Small joint involvement
  - Elevated ESR

- Malignancy
- Infection
  - Septic Joint
  - Osteomyelitis
  - Lyme- especially with knee involvement
- Reactive
  - Post-strep
- Spondyloarthropathy

Oligoarthritis

- Complications
  - Leg length discrepancies
  - Bony overgrowth
  - Quadriceps atrophy
  - Uveitis
  - Risk factors for uveitis are female, young age and +ANA

Oligoarthri

- Exten

- Develo

- Risk for ex

- Leg len

- Bony ov

- Quadri

- Uveit

- Risk fac

- Femal
**Uveitis**

- First 2 years after JIA diagnosis greatest risk
- Rare after 4 years
- ≤10% prior to onset of arthritis
- Bilateral (70-75%)
- Anterior disease (80%)
- Chronic anterior uveitis
- Insidious and silent (oligo, poly, psoriatic JIA)

**Uveitis Complications/Treatment**

- 21-80% complications due to uveitis
  - Cataracts (20-65%)
  - Posterior Synechiae (20-50%)
  - Band Keratopathy (15-45%: calcium deposition in Bowman’s membrane)
  - Glaucoma (6-30%)
- Visual Acuity
  - 20/50 to 20/150 (10-15%)
  - 20/200 or worse (20%)
- Treatment
  - Topical steroid drops
  - Methotrexate if unable to wean off drops
  - Infliximab
  - Adalimumab

**Oligoarthritis**

**Treatment**

- NSAIDs
  - Need several weeks to assess full response
  - Initiate for pain relief, anti-inflammatory effects, assess response
  - Liquid preparations available in Ibuprofen (10 mg/kg TID) and Naproxyn (10 mg/kg BID)
- Intraarticular Corticosteroids
  - Often achieve 9-12 months of improvement
  - If incomplete benefit from NSAIDs & IA steroids then move to Methotrexate
  - PT and OT

**Polyarthritis (RF-)**

- 20-30% of JIA
- Mean age of onset is 6-7 years of age
- Bimodal peaks (toddler-preschool and preadolescent)
- Female to male (3:4:1)
- ANA 20-40%
- Uveitis in 5-20%
- Outcomes fall between oligoarthritis and RF(+) polyarthritis

**Age at onset of polyarticular JIA**

![Graph showing age at onset of polyarticular JIA](Image)
Polyarthritis (RF+)

- Least common subtype of JIA (5%)
- Females : Male (9:1)
- Mean age of onset is 9-12 years
- Native American, African American, Latino, South African
- Symmetric upper extremity involvement
- Rheumatoid nodules
- Poorest functional outcome

Polyarthritis DDX

- SLE
- Inflammatory Bowel Disease
- Infectious Related
  - N. gonorrhoeae
- Reactive Arthritis
- Psoriatic Arthritis
- Enthesitis Related Arthritis
- Sarcoidosis

Polyarthritis Treatment

- NSAIDs
- Methotrexate (at diagnosis)
- Intra-articular steroids if few persistent joints
- If incomplete response-> TNF inhibitors
  - Etanercept (Enbrel)
  - Infliximab (Remicade)
  - Adalimumab (Humira)
- PT/OT

Systemic Juvenile Arthritis

- Incidence: 0.5-1.5 per 100,000
  - 5-10% of JIA
- Male: Female 1:1
- No increased frequency at any particular age

Systemic Juvenile Arthritis Diagnosis

- Diagnostic Criteria
  - Age of onset before 16 years
  - Duration of arthritis minimum of 6 weeks
  - Arthritis with or preceded by daily fever of at least 2 weeks duration documented to be quotidian for at least 3 days and accompanied by one or more of the following:
    - Evanescent, non-fixed erythematous rash
    - Lymphadenopathy
    - Hepatomegaly or Splenomegaly
    - Serositis

Systemic Onset Juvenile Arthritis Fever

- Spiking temps >39 C daily or twice-daily, with rapid return to baseline or below baseline
- Any time of day, classically late afternoon & with rash
- Appear & feel ill while febrile, well when afebrile
**Systemic Juvenile Arthritis**

**Rash**
- Salmon-pink, macular, most commonly on trunk and proximal extremities
- Transient and migratory
- Characteristics
  - Can be urticarial, pruritic, Koebner phenomenon
  - Increased with fevers or ambient temperature
  - Majority have at onset of disease

**Explanation**
- Can be urticarial, pruritic, Koebner phenomenon
- Increased with fevers or ambient temperature
- Majority have at onset of disease

**Arthritis**
- Symmetric, Oligo or Polyarticular
- Most commonly wrists, knees, ankles
- **Hips** can be involved early in this subtype
- Can be absent at onset of disease in 1/3
  - Usually develops within months of onset of fever and rash

**Evaluation**
- Anemia almost always present
  - Chronic inflammation
  - Iron deficiency
  - Leukocytosis
- Thrombocytosis (if absent consider other dx)
- Elevated ESR (often >100), CRP, Ferritin

**Serositis/Adenopathy**
- Pericarditis
- Pleural effusions
- Often asymptomatic
- Hepatomegaly is common but mild
- Splenomegaly 30%
- Lymphadenopathy 50%

**Prognosis**
- ~40% monophasic course, few polycyclic, remainder persistent
- Monophasic course
  - Remission off meds for 3 months—high sensitivity & specificity
  - Remission off meds for 12 months even higher specificity 93%
- Non-monophasic course
  - Active arthritis at 3 or 6 months predicts non-monophasic course and longer time to remission
  - Presence of systemic symptoms, steroid requirement, elevated ESR and thrombocytosis at 6 months (even 3 months)

*Singh-Grewal et al. Arthritis Rheum 2006*
**Systemic Juvenile Arthritis**

- **Mild Disease**
  - NSAIDs
  - Prednisone
  - Anakinra (IL-1 receptor antagonist), daily subcut

- **Severe Disease**
  - Pulse methylprednisolone IV x 3 days or oral prednisone
  - Anakinra
  - Tocilizumab (IL-6 receptor antagonist), monthly IV
  - PT/OT

**Spondyloarthropathy**

- **Definition**
  - Juvenile seronegative spondyloarthropathies:
    - Juvenile onset ankylosing spondylitis (JAS)
    - IBD related
    - Reactive arthritis
    - Juvenile psoriatic arthritis (HLA-B27+)

  - Axial skeleton, lower extremities and entheses
  - HLA-B27 (90% in AS)
  - Acute anterior uveitis
  - RF, other autoantibodies infrequent

**Enthesitis Related Arthritis**

- **Enthesitis Related Arthritis (ERA)**
  - Arthritis + Enthesitis
  - or
  - Arthritis or enthesitis + 2 of the following
    1. Sacroiliac joint tenderness and/or inflammatory spinal pain
    2. Boy > 6 years age (male:female 9:1)
    3. Family History of HLA associated disease
    4. HLA-B27 positive
    5. Anterior uveitis usually associated with pain, redness, or photophobia

- **Clinical**
  - Peripheral joint symptoms occur at onset in ~80%, usually distal lower extremities
  - Sacroilitis
  - Hip disease, unilateral or bilateral
  - Tarsitis, small joints toes
  - Least common small joints hands

**Enthesitis Related Arthritis**

- **Clinical**
  - **Enthesis**- site of insertion of a tendon, ligament, joint capsule, or fascia to bone
  - Early manifestation
  - Presence strongly suggests diagnosis
  - Knees, plantar fascia, Achilles, ischial tuberosity, tarsus
  - Pain, swelling and tenderness

- **Clinical**
  - Sacroilitis-
    - Pain low back, tenderness on palpation over SI joint
    - FABER test: flexion, abduction and external rotation hip
    - No radiographic requirements in diagnosis of ERA
    - Widening from erosions->fusion

  - Spondylitis
    - Progression from lumbar spine superiorly
    - Loss of mobility, lumbar lordosis, thoracic kyphosis
    - Modified Schober test
Enthesitis Related Arthritis

Iritis

- Acutely red, painful, photophobic eye
- Unilateral, recurs, usually leaves no ocular residua
- Reported 1-25%

Psoriatic Arthritis

- 5-10% of JIA
- Mean age of onset around 6 years
- Female to male (2:1)
- 50% first or second degree relative with a history of psoriasis
- ANA positive patients (~1/3) at risk for uveitis

Spondyloarthropathy

Treatment

- Often poorer responses to conventional immunosuppressives compared to other subtypes JIA
- NSAIDS
  - Aleve, naproxen, Indocin, Tolmetin
- Steroids
  - Inflammatory in ill patients
  - Intraarticular- worse outcomes
  - Enthesitis- concern rupture tendons
- Methotrexate
  - Great therapy for psoriatic arthritis
  - Has not shown efficacy in axial disease, JAS
  - May be beneficial in peripheral arthritis or enthesitis

Enthesitis Related Arthritis

Prognosis

- Disease course- full remission, recurrent episodes, chronic aggressive
- Remission rates range 17-44%
- HLA-B27 + child with chronic arthritis ➔ 60-75% develop sacroiliitis & spondylitis
- Axial disease occurs within 10 years of disease onset
- Occurrence of severe disability ranges 4-52%
- Arthritis of the hip poor prognostic indicator

Psoriatic Arthritis

- Arthritis and psoriasis
  - Nail changes
  - Dactylitis (30%)
  - 1st degree relative with psoriasis

Treatment

- TNF Inhibitors
  - Efficacy shown in several studies for arthritis, enthesitis, pain, and inflammatory markers
  - Shown to improve sacroiliitis and spondylitis
  - Adult studies shown to slow progression of spondylitis
  - Use early in children- may prevent progression
References