Kids With Arthritis: an Under-Represented Population for Naturopathic Intervention

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More Common Than You Think

- One of the **five** most common chronic diseases of childhood
- Occurs more frequently than diabetes or cystic fibrosis

What is JIA?

- Juvenile Idiopathic Arthritis
- Most common childhood arthritis
- Affects nearly 250,000 children in the United States
Symptoms of JIA

- Chronic Synovitis
  - Swelling, limited range of motion of the joint
  - Warmth, pain, stiffness

- Associated signs and symptoms
  - Depends on the JIA subtype
  - Fever
  - Uveitis
  - Rash
  - Hepatosplenomegaly
  - Lymphadenopathy
Considering your DDx

• First step
  • Distinguish arthritis from arthralgia
    • Arthritis: true synovitis and joint swelling
    • Arthralgia: pain in and around joints
Considering your DDx

• Excruciating
  • Pain, swelling, erythema ➔ possible malignancy
• Consider infections
  • Transient is key (under 6 weeks)
  • Rubella, EBV mononucleosis, HBV and HCV, varicella
  • Erythrovirus (Parvovirus B19) – older child with large and small joint polyarthritis, rash present
  • Lyme – large joint arthritis, knee quite common
  • Poststreptococcal arthritis – 7-10 days post-strep
  • Reactive arthritis post gastroenteritis or in sexually active teenagers
  • Recent MMR vaccination
Considering your DDx

- Mechanical Joint Issues
  - Worse with **activity**
  - No signs and symptoms of inflammation
  - Examples
    - Chondromalacia patellae, osteochondritis, Osgood-Schlatter, joint hypermobility, slipped capital femoral epiphysis, Legg-Calve-Perthes
Diagnosing JIA

- Persistent synovitis > 6 weeks
- Patient < 16 years old
- No definitive laboratory test or imaging test to confirm
- Laboratory tests and imaging can help exclude alternative ddx
  - CBC, ESR, CRP, ANA, RF, HLA-B27, radiographs
  - Anti-CCP not yet found to be useful
- Subtype diagnosis based on the following criteria:
  - Patient’s age
  - Number and types of joints involved
  - Presence of other symptoms, i.e. rash, fever, iritis
Subtypes of JIA

- Systemic arthritis (Still’s Disease)
- Polyarticular
- Oligoarticular
- Enthesitis-related arthritis
- Psoriatic arthritis
Subtypes of JIA

- Subtype is determined by how the disease progresses in the first 6 months
### Features of three of the major subtypes of juvenile idiopathic arthritis (JIA)

<table>
<thead>
<tr>
<th></th>
<th>Systemic JIA</th>
<th>Oligoarticular JIA</th>
<th>Polyarticular JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percent of JIA patients</strong></td>
<td>10 to 15</td>
<td>50</td>
<td>30 to 40</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>F = M</td>
<td>F&gt;M</td>
<td>F&gt;M</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Any &lt;17 years</td>
<td>Peak 2 to 3 years, rare &gt;10</td>
<td>Peaks 2 to 5, 10 to 14 years</td>
</tr>
<tr>
<td><strong>Joints</strong></td>
<td>Any number and any joint</td>
<td>Large joints, but rarely hips</td>
<td>Any, usually symmetrical and rare to start in hips</td>
</tr>
<tr>
<td><strong>Fever, rash, lymphadenopathy, hepatosplenomegaly</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Uveitis</strong></td>
<td>Rare</td>
<td>20%, most common in patients who are ANA positive</td>
<td>Less frequently seen than in oligoarticular JIA</td>
</tr>
<tr>
<td><strong>Laboratory abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Leukocytosis</td>
<td>Marked</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>- Anemia</td>
<td>Marked</td>
<td>No</td>
<td>Mild</td>
</tr>
<tr>
<td>- Elevated ESR</td>
<td>Marked</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>- ANA</td>
<td>Absent</td>
<td>Low titer common</td>
<td>Low titer common in younger</td>
</tr>
<tr>
<td>- Rheumatoid factor</td>
<td>Rare</td>
<td>Absent</td>
<td>10 to 20% in those &gt;10 years</td>
</tr>
<tr>
<td>- Elevated ferritin</td>
<td>Marked</td>
<td>No</td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Destructive arthritis</strong></td>
<td>&gt;50%</td>
<td>Rare</td>
<td>&gt;50%</td>
</tr>
<tr>
<td><strong>Response to methotrexate</strong></td>
<td>Poor to moderate</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>Response to biologic drugs</strong></td>
<td>Poor to TNF inhibitors</td>
<td>Excellent to TNF inhibitors and IL-6 inhibitors (although not commonly used)</td>
<td>Excellent to TNF inhibitors and IL-6 inhibitors</td>
</tr>
<tr>
<td></td>
<td>Excellent to IL-1 and IL-6 inhibitors</td>
<td>Poor to IL-1 inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

F: female; M: male; ANA: antinuclear antibody; ESR: erythrocyte-sedimentation rate; TNF: tumor necrosis factor; IL: interleukin.
Complications of JIA

- Leg-length discrepancy and gait disturbance
- Growth retardation
- Osteopenia/Osteoporosis
- Muscle atrophy
- Vision loss, glaucoma, cataracts
- Complications from treatment
- 50% - disease persists into adulthood
Common Treatment Choices

- NSAIDs and Glucocorticoids
  - Naproxen – 20 mg/kg/day
  - Ibuprofen – 40 mg/kg/day
  - Meloxicam – 0.125 mg/kg/day

- Synovitis persists → addition of a DMARD
  - Methotrexate first choice – multiple dosing options – oral, IM, SubQ routes
    - Added earlier for those with seropositive polyarticular type
Common Treatment Choices

- TNF inhibitor Biologics – FDA Approved for JIA in 1999
  - Etanercept, adalimumab, abatacept, and anakinra
  - Malignancy concerns
    - “The development of malignancies was reported in 19 patients with JIA...while receiving a TNF inhibitor, although the total number of children treated with these agents is not known”

The Naturopathic Doctor’s Treatment Goals

Explore underlying triggers
Reduce inflammation and control pain
Improve energy levels and overall vitality
Support healthy growth and bones
Prevent heart disease and diabetes into adulthood
Safely manage prescription side effects
Exploring Underlying Triggers

- **Gut Microbiome**
  - Children with certain subtypes of JRA have dysbiosis
  - Strong connection with HLA-B27
  - History of Caesarian section

- **Oral microbiome**
  - Especially JIA with + anti-CCP
  - Periodontitis
  - Role of *Porphyromonas gingivalis*


Explore Underlying Triggers

- Small study of JIA patients evaluated intestinal permeability using lactulose/mannitol assessment
- **Increased intestinal permeability** found in JIA patients regardless of NSAID administration

Co-occurrence of JIA with celiac disease

According to John Hopkins Arthritis Center,

- There may be a link between food sensitivities and inflammatory arthritis
- Older studies have found “temporary improvement in the signs and symptoms of RA with diet elimination and modification in a controlled study where the symptoms associated with food sensitivities were studied”
- Caution with elimination diets if child is demonstrating growth impairment

• Common cytokine patterns in JIA
  • Elevated TNF-alpha, IL-1, IL-6
    • Induces an increase in Th1 and Th17 cytokine profiles
  • Depressed IL-10


Cytokine-Driven Therapy

- Targeting IL-6
  - Increased IL-6 associated with anxiety, depression, and HPA axis dysfunction
  - IL-6 induces acute phase reactants (ferritin, C-reactive protein)
  - Magnolia officinalis – 400mg qd
  - Resveratrol – trans-resveratrol – 200mg qd
  - Vitamin D
  - Hypericum perforatum – 250mg qd
  - Andrographis paniculata – 400mg qd

- Targeting TNF-alpha
  - Andrographis paniculata
  - Embelis ribes

Cytokine-Driven Therapy

- Targeting IL-1
  - Omega-3 fatty acids – 1,200mg EPA
  - Astragalus membranaceus – 500mg qd
  - Bromelain – 2,500 GDU +
  - Boswellia serrata – 400mg tid
  - Green tea – ½ tsp matcha

- Targeting IL-10
  - Gluten Free Diet

• Post-Lyme Disease Syndrome should be considered
  • Upregulation of TH1, TH-17, IL-17 factors
  • Autoimmune in nature
  • In my experience, a very high amount of my JIA patients have a h/o Lyme

Reduce Inflammation and Control Pain: Botanicals and Nutrients

**Anti-Inflammatories, Pain Relievers**
- Curcumin
- Boswellia
- Bioflavonoids
- Zingiber
- Fish Oil
- Capsaicin topically
- Menthol preparations topically
- Castor oil topically
- Acupuncture

**Sources:**
2012 Study – Clinical Rheumatology

• 27 Juvenile Arthritis patients supplemented with 2 grams of omega-3 fatty acids for 12 weeks

• Measured primary outcomes include Juvenile arthritis disease activity score in 27 joints (JADAS-27) and pediatric American College of Rheumatology (ACR) response criteria, Childhood Health Assessment Questionnaire (CHAQ)

• Also measured levels of pro-inflammatory cytokines

• Results:
  • **significant improvement of active joint count**, number of swollen joints, JADAS-27, CHAQ, TNF-α, and IL-1 levels
  • The pediatric ACR response criteria improved in **92.59%** of the patients
  • **Daily NSAID requirement** decreased
  • Other studies have found that fish oil reduces the chances of DMARD failure
Vitamin D May Be Related to Disease Activity

- Small 2014 study of 47 JIA patients, 61.7% females, mean age 9.3 years old with median follow-up period of 28 months
- Vitamin D levels – 17.7 ng/ml
- 72.3% of the patients had vitamin D insufficiency or deficiency (levels < 20 ng/ml)
- **Significant negative correlation** between the JADAS-27 disease activity score and the vitamin D level
- JADAS-27 score significantly higher in patients with vitamin D level < 15 ng/ml
- Vitamin D may modify disease activity and pain

Improve Energy Levels: Nutrients

- **Nutrient deficiencies** are quite common in people with arthritis
  - folic acid, vitamin C, vitamin D, vitamin B₆, vitamin B₁₂, vitamin E, folic acid, calcium, magnesium, zinc and selenium
  - Mitochondria depend on healthy levels of iron, copper, coQ₁₀, and B vitamins to make ATP from food

*Source: Hudnall M. Illness and Disease Vitamins, Minerals and Dietary Supplements 1999 Minneapolis, MN:Chronimed, 42-44.*
Improve Energy Levels: Lifestyle

- Assess the patient’s:
  - Sleep
  - Stress, Depression
  - Activity level
Support Healthy Eyes

- The risk for uveitis is great especially if ANA + female
- Encourage the patient to follow recommended eye exam schedule
- Symptoms
  - Visual loss
  - Red eye
  - Blurry vision
  - Photophobia

Uveitis – associated with TH1 dominant cytokines

Alpha lipoic acid effective in animal models

Evidence in humans suggests that low antioxidant status may be involved

Consider short term vitamin A supplementation

Consider vitamin D supplementation – low vitamin D may mediate the pathogenesis of uveitis


• **Growth retardation** is a common concern in those with JIA

• Ensure adequate **calories**
  • Promote intake of nutrient-dense foods

• Consider **elemental diets** when needed

• Ensure proper **absorption** of nutrients
  • Consider healthy of small intestinal brush border
Working with Rx Side Effects

• NSAIDs
• Glucocorticoids
• Methotrexate
Support Healthy Bones

- Chronic glucocorticoid use is a risk for osteoporosis or osteopenia
- Calcium (700-1,300mg per day depending on age)
- Vitamin D (800 IU and upwards, depending on blood levels)
- Other nutrients: vitamin K, copper, silicon, protein, boron, lysine
- Limit sodium and caffeine
- Reduce homocysteine levels
- Physical Activity
  - Promote weight bearing activity only until the point of pain
  - Important to discourage sedentary behavior

Reduce Risk of Diabetes and Cardiovascular Disease

- Comorbidities of JIA
- Result of glucocorticoid and NSAID use
- Begin to encourage lifelong healthy habits

Antioxidants in the diet
Sugar control
Healthy weight
Stress management
Proper sleep
Maintain activity
NSAID-Induced Gastroenteropathy

- Study found that a “high percentage of JIA patients” treated with NSAIDs have GI involvement
- Recent animal studies show that quercetin attenuates the damage
  - Dose: 50-100 mg/kg
- Psychological stress may worsen NSAID-induced small intestinal injury by inducing changes in intestinal microbiota and altering gut permeability

- Singh DP, Borse SP, Nivsarkar M. Overcoming the exacerbating effects of ranitidine on NSAID-induced small intestinal toxicity with quercetin: Providing a complete GI solution. Chem Biol Interact. 2017;
Does MTHFR Affect Methotrexate Tolerance?

- **September 2005**
  - 58 JIA patients
  - Better response to MTX in those with A1298C variant
  - C677T variant experienced more frequent adverse events than C677C

- **October 2010**
  - 69 JIA patients
  - C677T MTHFR variant was more frequent in those with adverse MTX effects

- **Feb 2011**
  - 92 JIA patients
  - No association between MTHFR variants and MTX tolerance/adverse events

- **Feb 2016**
  - 196 JIA patients
  - 46% had intolerance to MTX
  - 168 patients were genotyped for C677T and A1298C
  - MTX intolerance was not found to be significantly more frequent among those with MTHFR mutations

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Making MTX Work Better?

- **Prescribe** fish oil** along with MTX**
  - 1,000mg omega-3 fatty acids per day to protect against MTX-induced hepatotoxicity
  - Reduced rates of DMARD failures with doses up to 5,000mg/day

- Silybum marianum
  - Reduced hepatic fibrosis from MTX in animals
  - Study used 600mg/kg silymarin

- Thiamine pyrophosphate
  - Dose studied in animals was 25 mg/kg
  - Reduced MTX hepatotoxicity

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MTX may worsen intestinal permeability
Mitigated by Glutamine in vitro

Talia - 7 year old female

- Presented with left knee swelling and pain x 6 months
  - Severity 7/10

- Left knee plain film – unremarkable

- Left knee arthrocentesis – unremarkable

- PMHx: Lyme disease at 3 yo, treated with amoxicillin

- Patient had no other associated signs/symptoms

- Patient was taking no daily Rx at this time, ibuprofen 200mg prn
  - Digestion was normal with regular bowel movements, denies abdominal pains, reflux, gas, bloating.
  - Labor and Delivery was unremarkable – vaginal delivery, nursed x 9 months
Case 1 – 7 yo female

- Diet:
  - Breakfast - banana, cheerios, cornflakes, cinnamon toast crunch, apple slices, water
  - Lunch - at school - pizza, macaroni and cheese, pasta, mozzarella sticks, water
  - Afternoon snack - chocolate milk, cookies, candy, cucumbers, hummus
  - Dinner - vegetables with lentils, chicken nuggets, pizza, tortilla wraps with turkey cold cuts, water
Case 1 – 7 yo female

- Physical Exam:
  - Noted edema and erythema of the left knee with restricted flexion and extension
  - No tenderness to palpation noted
Case 1 – 7 yo female

- Lab results:
  - Celiac panel – negative
  - MTHFR – C677T heterozygous
  - Homocysteine – elevated 12.5 umol/L
  - Vitamin D - 12 ng/mL
  - ANA +, RF -
  - IL-1beta - heterozygous variant
  - IL-6 and TNF-alpha – no variants detected
  - +IgG casein, egg white/yolk, gliadin, gluten, sesame seed
Case 1 – 7 yo female

• Protocol
  • High EPA Liquid – 1 tsp providing:
    • Total omega-3 fatty acids: 3425 mg
    • Total EPA: 1915 mg
    • Total DHA: 1005 mg
  • Bromelain, Boswellia, Curcumin, Quercetin combination formula – 1 cap tid providing:
    • Boswellia serrata Gum Extract - 600 mg
    • Bromelain - 300 mg
    • Curcuma longa Rhizome Extract - 600 mg
    • Quercetin dehydrate - 300 mg
  • Vitamin D – 5,000 IU daily
  • Methyl Support – 2 caps daily providing:
    • B6 – 20mg
    • 5-MTHF – 1.2mg
    • Methylcobalamin – 1.2mg
Case 1 – 7 yo female

- Dietary Prescription
  - Elimination diet of gluten, egg, and dairy x 6 weeks
  - Anti-inflammatory diet of Mediterranean style provided
Case 1 – 7 yo female

• 3 month follow up
  • L knee swelling resolved
  • Pain reduced to 3/10 severity and only after gym class
  • Gluten exposure 1 time at birthday party → noted swelling the next day
  • No changes made to the protocol at this time

• 5 month follow up
  • L knee swelling and pain resolved
  • Pain reduced to 0/10 most days unless overactive
  • Were able to reintroduce dairy with no reaction
  • Continue to eliminate egg, dairy
  • Labs re-ordered at this time
Case 1 – 7 yo female

- 6 month follow up – lab results:
  - Homocysteine – 9.2 umol/L
  - ANA +, RF --
  - ESR – 2 mm/h, CRP - <0.10 mg/dL
  - Vitamin D – 63 ng/mL
- Plan
  - Discontinue vitamin D
  - Discontinue methylation support
  - Attempt dietary challenges of gluten and egg separately
  - Reduce doses of anti-inflammatory support
    - Fish oil reduced to ¼ tsp per day, BCQ reduced to 1 cap bid
Case 1 – 7 yo female

- 12 month follow up
  - Flares of left knee pain still continuing with activity only
  - No swelling noted
  - Family brought all foods back into the diet
- Plan
  - Continued counseling regarding elimination diet
  - Added Probiotics at this time – 50 billion organisms, multi-strain of Lactobacillus and Bifidobacterium populations to support gut function
  - Daily use of fish oil and curcumin liposomal preparation
    - 500mg bid before and after school
    - ½ tsp daily of fish oil
Case 1- 7 yo female

- 16 month follow up
  - No consistent flares of L knee
  - Continues protocol
  - Continue to struggle with full elimination diet
    - Joint pains clearly correlated to level of activity and food intake
Case 2 – 10 yo female

- Amy – 10 year old female; has a twin brother
- Diagnosed with ANA - oligoarticular JIA 3 years before her first visit
- Anterior uveitis x 1 year; not well controlled with Rx
  - Her uveitis had returned before the first visit; rheumatologist wanted to increase MTX dose
  - Amy had transaminitiis in response to increased MTX dose 1 year prior
- R knee involvement x 3 years
  - Pain, swelling, morning stiffness x 90 minutes, severity 3/10 with Rx
- PMHx: Lyme at 4 yo, treated with amoxicillin; h/o multiple antibiotic exposures due to recurrent otitis media; vaginal delivery, formula fed x 1 y
- ROS: regular stomach aches and IBS-like symptoms
- Rx: MTX 20mg SC weekly
  - Was on 6 months of Adalimumab 20mg in the 6 months before seeing me
    - Worked very well to control uveitis and knee pain
    - Parents were not comfortable continuing
    - Uveitis was back → they didn’t know what to do
Case 2 – 10 yo female

• Diet:
  • Breakfast - waffles, cereal, fresh squeeze citrus, bacon
  • Lunch - pasta, lasagna, chicken nuggets
  • Dinner - pasta, chicken, macaroni and cheese
  • Veggies - corn, carrots, celery, beans
  • Snacks - cheese sticks, cheese crackers, sometimes chocolate milk
Case 2 – 10 yo female

- Physical examination:
  - Edema and restricted flexion/extension of the R knee
  - No other joint involvement noted
Case 2 – 10 yo female

- Lab Results:
  - Vitamin D – 22 ng/mL
  - Homocysteine – 8.5 umol/L
  - ANA -, RF -
  - MTHFR – heterozygous C677T variant detected

- Stool Microbiology
  - Suboptimal beneficial bacteria
  - Low butyrate and total SCFA
  - Elevated fecal sIgA
Case 2 – 10 yo female

- Protocol
  - Vitamin D – 5,000 IU daily
  - High EPA liquid fish oil – 1 tsp
  - High dose, multi-strain probiotic – 50 billion organisms
  - Carnosine eye drops – use 3 drops per eye bid
  - Replace folic acid with 5-MTHF – 1mg
- Dietary elimination
  - No IgG testing due to Rx
  - Recommended full dairy and gluten elimination x 6 weeks to evaluate changes in joint pain and uveitis
  - High antioxidant foods and omega-3 containing foods discussed
Case 2 – 10 yo female

- 4 month follow up
  - R knee pain improved, severity 0-1/10
  - Swelling resolved, improved ROM
  - Last eye check was 5 weeks before our follow up – no inflammatory cells noted
  - Had NOT made dietary changes/eliminations
  - Ordered updated lab testing
Case 2 – 10 yo female

- Updated lab results at 5 months out:
  - ANA –
  - CRP <0.10 mg/dL; ESR 6 mm/h
  - Vitamin D – 61 ng/mL
  - Homocysteine – 7.4 umol/L
- Plan:
  - Vitamin D – 2,000 IU until the spring (it was still winter in CT)
  - Continue all other supplements
  - Dietary encouragement for GF/CF diet
Case 2 – 10 yo female

• 7 month follow up:
  • No uveitis on last eye check 2 weeks prior
  • No R knee involvement; no other joint involvement
  • Rheumatologist reduced follow up to 1 x per year maintenance
  • Last Rheumatologist appointment – took her off MTX
  • Eliminate dairy from the diet only x 2 months; did not eliminate gluten
Case 2 – 10 yo female

- 12 month follow up
  - 5 months off methotrexate
  - Uveitis and R knee involvement – none
  - Continues gluten free diet and fish oil, probiotics, eye drops
  - Spent this visit discussing a generally anti-inflammatory diet of Mediterranean type with a focus on reduction in grains