Systemic Juvenile Idiopathic Arthritis and Other Autoinflammatory Diseases

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Understanding Systemic JIA as an Autoinflammatory Syndrome
Major JIA Subtypes

Defined within 6 mo of JIA onset:

- Pauciarticular
- Polyarticular
- Systemic

Outcome is based on disease course after 6 months.
Systemic JIA

- Also known as Still’s disease in adults
- 10% of all JIA, but >50% with severe or life-threatening disease
- No age or sex predilection – can occur from infancy into adulthood
- At onset, clinically distinguished from other forms of JIA by presence of “extra-articular” or systemic features
Criteria for Diagnosis of SJIA

- Arthritis in ≥1 joint for at least 6 weeks with or preceded by fever of at least 2 weeks duration that is daily (“quotidian”) for ≥3 days and is accompanied by at least one of the following:
  - Evanescent (transient) rash
  - Generalized lymphadenopathy (swollen lymph nodes)
  - Hepatomegaly and/or splenomegaly (enlarged liver or spleen)
  - Serositis - pleuritis or pericarditis (fluid around lungs or heart)

* Exclusion criteria include:
  - Psoriasis or history of psoriasis in a 1st degree relative
  - HLA B27-positive arthritis in boy >6 yr of age
  - HLA B27-related disease or history in a 1st degree relative
  - RF positivity
Arthritis of SJIA

- 1/3 of pts have only arthralgia at disease onset with frank arthritis developing later
- Maybe pauci- or poly- articular at onset, but number & severity of affected joints often increases over time
- Both large and small joints may be involved & usually symmetric: jaw, neck, wrists, hands, hips, knees most often affected
“Quotidian” (Daily) Fever Pattern in SJIA

- Typically, fever spikes to >103° 1-2 times daily with rapid return to ≤37° without antipyretics
- Sustained fever of >103° for >24 hr suggests another diagnosis or development of macrophage activation syndrome complicating SJIA
Rash of SJIA

- Almost always accompanies fever spikes
- Usually discrete “salmon pink” patches of different sizes
- Often on trunk and extremities, but also on face, palms & soles
- Evanescent & migratory – rarely fixed
- Elicited by rubbing, scratching (Koebner’s phenomenon)
- Maybe be urticarial or pruritic (resemble hives or itchy)
Rash of SJIA
Koebner Phenomenon in SJIA
SJIA Disease Course

- Mean period of disease activity is 6 years
- Variable Course of Arthritis:
  - **Monocyclic, Relapsing/Remitting or Chronic**

  40%: Initial systemic illness followed by recovery without further flares

  10%: Multiple flares of arthritis & fever/rash over time with periods of wellness in-between, flares sometimes triggered by infection

  50%: Persistent arthritis (systemic features resolve with biologics)
Lab Findings in SJIA

Reflect an inflammatory state similar to that in infection:

- Elevated wbc (white blood cell count): often 3-5x normal with left shift (increased neutrophils, normal lymphocyte count)
- Elevated platelet count: usually 2-4x normal
- Increased inflammatory markers (CRP, ESR, ferritin)
- Anemia
- Low albumin (main blood protein)
- Increased liver function tests (hepatitis)
- Increased “pro-inflammatory” cytokines: IL-1β, IL-6, IL-18

Unlike other forms of JIA which are autoimmune:

- Autoantibodies are negative: RF, CCP Ab, ANA
- Autoreactive T cells are not found
- No defined HLA association
Risk Factors for Poor Outcome in SJIA

- Less than 6 years of age at diagnosis
- Persistent disease for >5 years
- Persistent systemic features:
  - prolonged fever, rash, serositis (fluid around heart & lungs)
  - requiring chronic corticosteroids >6 months after diagnosis
- Hip involvement
- ESR >50, significant anemia, platelet count >600,000 after 6 months of disease
Prognosis of SJIA

• 85% patients require treatment beyond 1 year from diagnosis
• 10% develop macrophage activation syndrome - a life threatening complication
• In the pre-biologic era, 50% developed cartilage destruction, bony erosions & joint deformities

But Prognosis is Better in the Biologic ERA!
What is Macrophage Activation Syndrome (MAS)?

- Severe, potentially life threatening complication of SJIA
- Characterized by inappropriate phagocyte activation & production of pro-inflammatory cytokines (IL-1, IL-6, IL-18) leading to:
  
  - Sustained fever – rather than quotidian (daily spikes)
  - Pancytopenia (all blood cell lines very low: wbc, rbc, platelets)
  - Hepatitis – liver inflammation, possibly liver failure
  - Coagulopathy (bleeding disorder)
  - Encephalopathy (brain effect)
Hemophagocytosis is Hallmark of MAS

MAS can be confirmed by presence of hemophagocytosis:

• activated tissue macrophages engulfing own blood cells on bone marrow or liver biopsy

However, biopsy is not necessary to make diagnosis of MAS
Macrophage Activation Syndrome

- 10% SJIA patients develop MAS – not seen in other types of JIA
- Another 30-40% of SJIA patients have hemophagocytosis on tissue biopsy without overt MAS on lab tests
- Still a clinical/laboratory diagnosis - tissue evidence of hemophagocytosis is not required to make diagnosis of MAS
- Infectious trigger IS NOT REQUIRED for development of MAS in SJIA
- Responds best to biologics that inhibit IL-1β or IL-6 rather than TNFα
Is the Underlying Immune Cause of SJIA Similar to Other JIA Subtypes?

Remember:
Other JIA Subtypes are Considered Autoimmune Diseases

- Abnormal “adaptive immunity”
- Autoantibodies (ANA, RF, CCP Ab) may be seen
- Detectable antigen-specific T cells in synovial fluid
- JIA susceptibility linked to specific HLA antigens
- Known genetic predisposition: RF⁺ poly JIA - increased risk in relatives
- Good treatment response to TNFα inhibitors (biologics) suggests role for activated T cells in pathogenesis of JIA subtypes other than SJIA
Autoimmunity is Due to Defective Adaptive (Antigen Specific) Immune Responses

- Complex antigen-specific immune responses involving activated T & B cells
- Based on specific SELF - NON-SELF antigen recognition
- Active lifelong tolerance to SELF proteins is critical
- “Specific Memory” is hallmark (basis of vaccination)
- Slow to develop (over days-weeks)
- Cytokines required – more TNFα than IL-1
- Absent T & B cells leads to immunodeficiency
Cytokines are Protein Messengers that Convey Information Between Cells via Specific Cell-surface Receptors.
Autoimmunity

- T&B cell-mediated responses against self proteins culminating in systemic or organ-specific diseases
- Maybe triggered by environmental factors in genetically susceptible individuals
- Breakdown of tolerance to SELF is key
- Involves loss of regulatory T cells, increased autoreactive T & B cells, imbalance between “pro-inflammatory” & “anti-inflammatory” cytokines

Autoimmune system mistakenly attacks self, damaging healthy cells and organs, causing disease

Immune system mistaken attacks self, damaging healthy cells and organs, causing disease

- IFNG
- TNFα
- IL-1
- IL-6
- IL-18, etc
- IL-4
- IL-10
- TGFβ
- IL-1RA, etc

Anti-inflammatory

Pro-inflammatory
Innate Immunity Is Different

- Is the immediate protective response by body to infection or injury
- Nonspecific & primitive – first line of defense
- Mediated by:
  - myeloid cells (phagocytes: neutrophils, eosinophils, monocytes, macrophages)
  - pro-inflammatory cytokines (IL-1β, IL-18, IL-6) that recruit phagocytes to sites of tissue injury
- Leads to **inflammation** with goal of tissue repair
Innate Immunity:
Phagocyte driven
Rapid response (hours)

Adaptive Immunity:
Lymphocyte driven
Slow response (days)

from Dranoff G, Nature Reviews Cancer 4:11-22, 2004
Autoinflammatory Syndromes are Caused by Abnormal Innate Immunity

- Characterized by unexplained & exaggerated innate immune responses with inappropriate activation of phagocytes & excessive production of IL-1β, IL-6 in the absence of infection
- Manifested by recurrent bouts of unprovoked systemic inflammation without activation of the adaptive immune response
- Therefore NO:
  - Specific autoantibodies
  - Antigen-specific T cells
  - Infectious trigger
  - IgE-mediated allergy
  - Immune deficiency
- Some are inherited as single gene defects involving phagocyte activation pathways called hereditary periodic fever syndromes
Characteristics of SJIA
More Typical of Innate Immune Response

- Systemic features - fever, rash, pain
- Elevated acute phase reactants (ferritin, ESR, CRP)
- Increased neutrophils rather than lymphocytes
- Increased plasma levels of IL-1, IL-6, IL-18
- Flares controlled by inhibition of IL-1 & IL-6 rather than of TNFα
- Lack of autoantibodies or antigen-specific T cell responses

Autoinflammatory
not
Autoimmune
Possible Roles of IL-1, IL-6, IL-18 in Pathogenesis of SJIA

- IL-1β is responsible for many of the systemic features of SJIA
- IL-6 correlates with arthritis (number of involved joints & severity) as well as osteoporosis and growth retardation of affected children
- IL-18 is associated with MAS & may be a “biomarker” for SJIA activity

Suggests Innate Immune Defect
Two Subsets of SJIA based on Cytokine Profiles

- **IL-6 dominant subset:** more arthritis

- **IL-18 dominant subset:** more likely to develop MAS

Treatment of SJIA before Biologics

- NSAIDs, aspirin
- Glucocorticoids
- Methotrexate
- Cyclosporine
- Thalidomide
- Cyclophosphamide
- Hematopoietic Stem Cell Transplant
Our “New” SJIA Therapies: Biologic Response Modifiers

Recombinant drugs that specifically target IL-1 & IL-6

- **Anakinra:** Anti-IL-1β receptor antagonist
- **Rilonacept:** Soluble IL-1β receptor:Fc fusion protein (IL-1-trap)
- **Canakinumab:** Anti IL-1β monoclonal antibody
- **Tocilizumab:** Anti-IL-6 receptor (IL-6R) monoclonal antibody

* Not FDA approved treatments for SJIA
Benefits of Cytokine Inhibitors (Biologics)

Most SJIA patients respond to IL-1 & IL-6 inhibitors:
- Effective in controlling pain & swelling, improving severity of arthritis
- Normalize laboratory values
- Risks of growth retardation & osteoporosis reduced
- Treat MAS

A role for TNFα inhibition remains in patients with persistent arthritis without systemic features (chronic subset):
- May retard radiographic progression of JIA
- Long term use may reverse erosions & cartilage damage
Current medication usage patterns
CARRA Registry sJIA Patients

Percent Current Use

2010  2011  2012

- All DMARDs
- All Biologics
- All GC
- DMARD only
- DMARD & Biologic
- Biologic only
- GC Biologic & DMARD
- GC & DMARD
- GC only
- Biologic

CARRA
Other Autoinflammatory Disorders Include Hereditary Periodic Fever Syndromes (HPFS)

- Classic autoinflammatory diseases
- Single gene defects involving phagocyte activation pathways: FMF, HIDS, TRAPS, MWS, FCAS, CINCA/NOMID, PAPA, Majeed syndrome, cyclic neutropenia
- Mutations in HPFS genes are seen in SJIA pts that develop MAS (especially MEFV)
Autoimmune & Autoinflammatory Disease Spectrum

Proposed Treatment of SJIA with Systemic Features at Onset
Proposed Treatment of SJIA without Systemic Features