Cryopyrin-associated
Autoinflammatory Syndromes

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Disclosures

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  – None

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  – None

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  – None

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Learning Objectives

• signs & symptoms of the 3 phenotypically heterogeneous but overlapping cryopyrin associated autoinflammatory conditions
• genetics of the cryopyrinopathies (CAPS) and their underlying autoinflammatory pathobiology
• potential patient outcomes of the cryopyrinopathies and recognized treatment

Cryopyrin-associated Autoinflammatory Syndromes

• Familial cold urticaria syndrome (FCAS)
• Muckle-Wells syndrome (MWS)

• Neonatal-onset multisystemic inflammatory disease (NOMID)
• Chronic infantile neurological cutaneous articular syndrome (CINCA)

3 overlapping phenotypes
- FCAS/MWS
- MWS/NOMID

increasing clinical severity
Clinical Spectrum of CAPS

<table>
<thead>
<tr>
<th>FCAS</th>
<th>MWS</th>
<th>CINCA/NOMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold triggering</td>
<td>Rare cold triggering</td>
<td>No cold triggering</td>
</tr>
<tr>
<td>Recurrent episodes of fever</td>
<td>Recurrent episodes of fever</td>
<td>Recurrent episodes of fever</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Urticaria</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Arthrogryposis</td>
<td>Arthrogryposis/severe artropathy</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Conjunctivitis, eye inflammation</td>
<td>Conjunctivitis, episcleritis, optic atrophy</td>
</tr>
<tr>
<td>+/- Aseptic meningitis, deafness</td>
<td>+/- Aseptic meningitis, deafness</td>
<td>Chlorac neuromuscular</td>
</tr>
</tbody>
</table>

Cryopyrin-associated Autoinflammatory Syndromes

- **Familial cold urticaria syndrome (FCAS)**
  - exposure to sudden drops in temperature
    - Brief episodes of fever (<24 hours), urticarial rash
    - arthralgia, myalgia, conjunctivitis

- **Muckle-Wells syndrome (MWS)**
  - attacks of few weeks, <36 hours, +/- changes in ambient temperature
    - fever, urticarial rash
    - arthritis, headaches (aseptic meningitis), myalgia
    - bilateral progressive sensorineural hearing loss (often in 2nd decade)
    - Conjunctivitis, episcleritis, uveitis
    - +/- LAD, HSM
Cryopyrin-associated Autoinflammatory Syndromes

- Neonatal-onset multisystemic inflammatory disease (NOMID)
- Chronic infantile neurological cutaneous articular syndrome (CINCA)
  - Fever, persistent urticarial rash appearing shortly after birth
    - diffuse erythema without pruritus
    - chronic aseptic meningitis (neutrophilic CSF), progressive mental retardation
    - papilledema, chronic nerve atrophy, optic neuritis
  - frontal bossing, long bone epiphyseal overgrowth (osteopathy)
  - growth delay
  - bilateral progressive sensorineural hearing loss
  - +/- LAD, HSM

CINCA/NOMID – Clinical Findings

- neutrophilia in the blood and tissues
- nonpruritic rash, unresponsive to antihistamine

Aksentijevich et al., 2002
Otolaryngologic and Audiologic Manifestations

- 57 CAPS patients seen at NIH
- prospective study 2003-’09
- 31 NOMID, 11 NOMID/MWS, 9 MWS, 6 FCAS
- Comprehensive data
  - clinical manifestations
  - audiologic phenotype
  - FLAIR MRI of brain and inner ear


pure-tone conduction thresholds

Air conduction thresholds (3 freq pure-tone ave) plotted against age

Axial FLAIR-MRI post gadolinium enhancement @ basal turn bilateral cochleae
Cryopyrin-associated Autoinflammatory Syndromes

- CIAS1/NLRP3 gene (NOD-like receptor family, pyrin domain)
- located on locus 1q44 (chromosome 1q) of NLRP3
  - encodes cryopyrin (CIAS1; Cuissant et al. 1999)
    - Cryopyrin part of a multi-protein inflammasome complex
      - triggered by “cellular danger” (infection and/or metabolic dysregulation)
      - regulates the production of IL-1beta
- Cryopyrin mutations
  → abnormal cryopyrin structure (expressed in peripheral leukocytes and chondrocytes)
  → Abnormal inflammasome activity
  → Increased IL-1 beta production

Cryopyrin-associated Autoinflammatory Syndromes

- Cryopyrin’s distinct motifs
  - pyrin domain
  - central nucleotide binding site domain (NBS; NACHT subfamily)
  - c-terminal domain containing 7 leucin-rich repeats
Cryopyrin-associated Autoinflammatory Syndromes

- Inflammasome

Zeft AS, Spalding SJ. CCJM; 2012
Cryopyrin-associated Autoinflammatory Syndromes

• > 90 NLRP3 mutations have been identified (http://fmf.igh.cnrs.fr/infevers/)
  • Majority within exon 3 (encodes NLR binding domain of cryopyrin)

• No consistent correlations between disease severity and
  – the domain in which the mutation occurs
  – the specific residue mutated
  – the conservation of amino acids

Cryopyrin-associated Autoinflammatory Syndromes

• autosomal dominant Mendelian inheritance
• variable genotype-phenotype correlation
• using conventional sequencing, disease associated mutations in 60% of patients, suggests genetic heterogeneity
• Somatic, nongermline NLRP3 mutations
  – Ex: Arostegui JI et al 2010 described clinical case of NOMID with a novel heterogeneous variant (p.D303H) detected in 30-38% of circulating leukocytes, absent in healthy controls and parents
    → de novo true disease causing mutation
  – Also detected in epithelial cells (nonhematopoetic cell lineages)
• Suggests mosaicism
CAPS Epidemiology

- Cuissant et al 201 defined the spectrum and prevalence of NLRP3 mutations in France
- Retrospective review (2001-’09)
- 800 analysis of NLRP3 gene at 3 French labs which provide testing
  → 135 cases (55 probands, 33 multiplex families)
- Prevalence in France 1/360,000

Cryopyrin-associated Autoinflammatory Syndromes

8 yo boy FCAS (overlapping features of MWS)
- negative mutation analysis in CIAS1/NLRP3, PYCARD, CASP1
- mild hypothermia
  → enhanced IL-1b expression by monocytes reversed by anakinra
- LPS stimulation monocytes produced high IL-1b, IL-6, and TNFa compared to controls

Hedrich et al. Rheumatol Int; 2012.
Cryopyrin-associated Autoinflammatory Syndromes

TREATMENT

• Familial cold urticaria syndrome (FCAS)
  – May not require treatment (warmer climates)

• Muckle-Wells syndrome (MWS)
  – IL-1 inhibition (anakinra, riloncept, canakinumab)

• Neonatal-onset multisystemic inflammatory disease (NOMID)
• Chronic infantile neurological cutaneous articular syndrome (CINCA)
  – IL-1 inhibition (riloncept, canakinumab) offers symptomatic relief and long term control of the disease

Interleukin 1 Inhibition

• anakinra (IL-1 receptor antagonist)
• riloncept (“IL-1 Trap”)
  – dimeric fusion protein
  • ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component and IL-1 receptor accessory protein linked to the Fc portion of human IgG1 bind and neutralize IL-1

• canakinumab (human antiIL-1 monoclonal binds IL-1b)
  – dosing in CAPS driven by phenotype severity
  • Caorsi et al 2013
    – Reviewed canakinumab dosing and clinical response in 13 CAPS patients (7 NOMID, 4 MWS, 2 MWS/NOMID)
Cryopyrin-associated Autoinflammatory Syndromes

FCAS
- progressive improvement in attack frequency & severity
- minimal amyloidosis risk

MWS
- good prognosis when treated with IL-1 antagonists; low risk for sensorineural hearing loss, amyloidosis
- untreated ~25% amyloidosis (renal, peripheral neuropathy)
  - Hawkins PN et al. Arthritis & Rheumatism 2004

NOMID
- high risk for sensorineural hearing loss, amyloidosis, growth delay, CNS sequelae, unless recognized and treated early

10 year old boy

- Lifelong inflammatory episodes characterized by
  Cold temperature exposures trigger
  - non-pruritic urticaria
  - skin biopsy mixed perivascular inflammatory cells in the superficial dermis suggestive of an early phase urticarial response
  - distal cyanosis
  Fevers to 39C
  - +/- NSAID response
  - feet discomfort after fever spike

Conjunctivitis

Headaches
- Mild self resolving, not warranting CNS imaging

Articular symptoms
- arthralgias throughout first decade
- small joint and LE large joint arthritis (no radiologic changes)

Poor weight gain

Cryopyrin-associated Autoinflammatory Syndromes

Fm Hx: mother similar symptoms, waned in 20’s

audiology testing - within normal limits

urine analysis micro - no proteinuria

Table.  Dose dependent response to anakinra

<table>
<thead>
<tr>
<th>Anakinra Age (years) (mg/kg/day)</th>
<th>WBC (10^3/ml)</th>
<th>Platelets (10^3/ml)</th>
<th>ESR (mm/h)</th>
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<tr>
<td>1.6 –</td>
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<td>2.9 –</td>
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<td>4 –</td>
<td>8</td>
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<td>9.3 0.9</td>
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<td>9.8 0.3</td>
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<tr>
<td>10.1 1</td>
<td>8</td>
<td>335</td>
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<td>7</td>
<td>302</td>
<td>9</td>
</tr>
</tbody>
</table>
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Mutation Analysis

• heterogeneous change (A→G) in CIAS gene
  – can result in threonine to alanine substitution at amino acid position 436 (T436A) in the cryopyrin protein

• perinatal genetic testing
  – identical nucleotide missense substitution in the mother, not the father

Cryopyrin-associated Autoinflammatory Syndromes

Improved symptoms within days of anakinra (1 mg/kg)
  – energy level improved
  – rash less frequent
  – arthritis and conjunctivitis resolved

Symptomatic and laboratory dose-dependent response noted
Cryopyrin-associated Autoinflammatory Syndromes

2 other mutations that would cause different amino acid substitutions at this site (Thr43iie; Thr436Asn) have been reported in patients with CINCA syndrome

- Hull et al. 2003

Examples of:

- poor phenotype genotype correlation

- phenotypic heterogeneity including incomplete penetrance among family members carrying identical mutations
  • Likely an effect of modifier genes or environmental factors in the phenotypic expression of CAPS

Cryopyrin-associated Autoinflammatory Syndromes

• Questions