Autoinflammatory Syndromes

Periodic fevers and other (previously) mysterious inflammations

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Autoinflammatory Syndromes

“Periodic fever syndromes” - but attacks are not always at regular intervals, symptoms may be continuous, and fever can sometimes be absent.

“Inborn errors of inflammation” – often present in childhood

Autosomal recessive or dominant inheritance
Spontaneous mutations occur
Penetance is variable (role of other genes)

No role of acquired immunity

Autoinflammatory Syndromes

for this lecture:
Familial Mediterranean Fever (FMF)
Cryopyrinopathies (FCAS, MWS, CINCA)
Hyper-IgD Syndrome (HIDS)
TNF-receptor Associated Periodic Syndrome (TRAPS)

Signs and symptoms
Genetic and molecular basis
Treatments
Autoinflammatory Syndromes

Acquired immunity:
- T and B lymphocytes
- Refinement of T-cell receptor and antibody repertoire based on antigen exposures

Innate immunity (inflammation)
- Neutrophils, monocytes
- Fixed response (migration, degranulation, cytokines, CRP etc.)
- Triggers (microbial etc.)

Case 1: Chloe

10-month old girl, mixed European ancestry
Persistent urticaria-like rash since day 1 of life

Fevers since age 7 months, 3-5 days/wk, evenings
No joint problems, no CNS or developmental abn.
No FH of similar illness.

Normal skeletal Xrays
WBC 27K, ESR 46 mm/hr, CRP 9.5 mg/dl
Skin biopsy – neutrophilic infiltrate
Negative evaluation for infections and neoplasms
Normal ophthalmologic evaluation

?? Systemic JRA before onset of arthritis?
Treated with corticosteroids. Rash persisted.
Fevers responded but flared with tapering dose.

Case 2: Amelia

(stock photo – not patient)
Case 2: Amelia

2 year old girl, mixed European ancestry
One year history of fever lasting about 3 days, every 3-4 weeks
Vomiting with some episodes – required i.v. fluids several times. No severe abd. pain or diarrhea.
Eyes red and watery during episodes, no exudate.
Fussy, fatigued, seems to "ache all over"
No swelling or rash, no mucous membrane lesions.
Between episodes seems healthy and happy.
No FH of similar illness.

Physical examination normal.
ESR 46 mm/hr, CRP 4 mg/dl. Normal quant. lgs.
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Multiple tests for infections negative during episodes.

Familial Mediterranean Fever

Armenian, Arab, Turkish, Jewish, and Italian
Autosomal Recessive: Carrier up to 1 in 8
Duration: 24-72 hrs  Frequency: q week-years
Fever - constant or responsive to antipyretics
Polyserositis – can mimic acute abdomen
Synovitis – often monoarticular
Rash – “erysipelas-like erythema”
Other: Myalgia, scrotal inflammation, aseptic meningitis
FMF
Erysipelis-like erythema
(tender, on foot or lower leg)
Other rashes including purpura

FMF
Labs:
Elevated acute phase reactants
(ESR, CRP, fibrinogen, Serum Amyloid A)
– may persist between attacks
± hypergammaglobulinemia
Absent autoantibodies
Erysipeloid rash histology:
perivascular mononuclear mixed infiltrate

FMF
Common Complication: SYSTEMIC AMYLOIDOSIS
Serum Amyloid A (SAA) deposits in
kidneys, liver, spleen, GI tract,
testes, thyroid, adrenals, etc
Due to prolonged chronic inflammation
Suspect if organ dysfunction,
diagnose histologically.
SAA levels not available in US,
and may not correlate.

FMF
Autosomal recessive
Pyrin (marenostren)
>50 pathogenic mutations * identified
Different manifestations and severity
Some patients are homozygous for same mutation
Some heterozygous for two different mutations
Rarely heterozygous for one mutation (?other unidentified)

Pyrin downregulates inflammation ('off-switch')
Mutations → loss of function → uncontrolled inflammation
**MEFV Gene**

"INFLAMMASOME"

- PYRIN (marenostren)
- Downregulates inflammation
- Mutations → FMF
- Loss of function

**CARD = CASPASE RECRUITMENT DOMAIN**

**Interleukin-1β in inflammation**

**MONOCYTES**

- Pre-IL-1β (inactive) → Caspase 1 (active) → IL-1β

Fever, malaise
Elevated acute phase reactants
Induction of IL-6, TNFα, other cytokines, adhesion molecules, etc
Activation of monocytes, neutrophils, (and T and B lymphocytes)

**FMF Treatment**

- Colchicine – oral, daily
  - From crocus - Inhibits microtubule assembly
  - Prevents or ameliorates acute attacks
  - Prevents or retards amyloidosis

- ± Corticosteroids for acute attacks
- Cytokine inhibitors are generally not effective

- Amelia?
- Chloe?
Autoinflammatory Syndromes

**Cryopyrinopathies:**

**FCAS**

- *Familial Cold Autoinflammatory Syndrome*
- *Familial Cold Urticaria*
- Onset age < 6 mo
- Generalized urticaria-like rash within 30-60 min of generalized cold exposure
- ± Fever, conjunctivitis, headache, arthralgia
- Duration 6-72 hrs (usually <24 hrs)
- Amyloidosis is uncommon
- No other sequelae
- Autosomal dominant

**Muckle-Wells Syndrome (MWS)**

- Onset of attacks - infancy to adolescence
- Duration 12-48 hrs
- Frequency: variable
- May be induced by temperature change, stress

**Symptoms:**
- Fever and malaise
- Urticaria-like rash
- Arthralgia, arthritis
- ± Abdominal pain, conjunctivitis, lymphadenopathy

**Autosomal Dominant**
Cryopyrinopathies: Muckle-Wells Syndrome (MWS)

Urticaria-like rash
Not usually itchy

Labs:
- Acute phase rx
- Hypergammaglobulinemia

Sequelae:
- Bilateral sensorineural hearing loss (SNHL)
- Amyloidosis 25% – Serum Amyloid A
- Kidneys, adrenals, spleen, testes

Cryopyrin (NALP3)

Cryopyrin upregulates inflammation (‘on-switch’)
Mutations → gain of function → uncontrolled inflammation

Cryopyrinopathies

PYD
C
1034
N
LRR
NACHT (NBS)

Multiple mutations * -
Different ones for FCAS and MWS

Cold Induced Autonomic Syndrome 1 (CIAS1) Gene

FCAS and MWS – Mutations in same gene

PROPOSED ROLE OF THE FMF GENE IN INFLAMMATION

“INFLAMMASOME”

Signal

PYRIN (marenostren)

3 types known depending mediator of signal

CARD = Caspase Recruitment Domain

Mutations → FMF
Loss of function

Cold Induced Autonomic Syndrome 1 (CIAS1) Gene

“NALP3 INFLAMMASOME”

Signal

Mutations → FCAS & MWS
Gain of function
Cryopyrinopathies:
CINCA (Chronic Infantile Neurologic, Cutaneous, and Articular Syndrome)
NOMID (Neonatal Onset Multisystem Inflammatory Disorder)

Cryopyrinopathies
CINCA / NOMID

Urticaria-like rash from birth or within first months
Rash is always present, varies in intensity
Fever - intermittent, severe or mild, or (rarely) absent
Arthralgia, arthritis
Chronic aseptic meningitis (HA, vomiting, papilledema)
Anterior or posterior uveitis
Bone deformity (long bones and skull)
Developmental and cognitive deficits
Shortened life span

Cryopyrinopathies
CINCA / NOMID

Rash

Bony Deformities
Cold Induced Autonomic Syndrome 1 (CIAS1) Gene

“NALP3 INFLAMMASOME”

Cryopyrinopathies:
- Rash
- Fever
- Arthritis
- Bone
- Hearing loss
- CNS
- Eye

>60 different pathogenic mutations

Cryopyrin is a major regulator of Caspase-1
Caspase-1 aka ICE (IL-1β Converting Enzyme)

IL-1β – major pro-inflammatory cytokine
Secretyed by monocytes and macrophages
Activation / Secretion requires cleavage by caspase-1

BENCH TO BEDSIDE
Human IL1-receptor antagonist - Anakinra
- sub cu daily
- effective in uncontrolled trials
- no FDA indication

Human Monoclonal anti-IL-1β - Canakinumab
- sub cu every 4 wks
- effective in controlled trials
- FDA indication

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?? Systemic JRA before onset of arthritis?
Treated with corticosteroids. Rash persisted.
Fever responded but flared with tapering dose.

Phenotype: Severe MWS / Mild CINCA
Genotype: CIAS1 gene mutation leading to
T436I in Cryopyrin - previously assoc with mild CINCA phenotype

Treated with anakinra at 17 mo
Rash and fevers responded splendidly
Weaned off steroids rapidly
Now age 5 years and mild learning problems
Hope long term sequelae will not occur –
but other mediators besides IL-1β are not inhibited

Autoinflammatory Syndromes

Hyper IgD Syndrome HIDS
Netherlands & neighbors
Autosomal recessive
Onset median age 6 months
Duration 3-7 days
Frequency variable, ↓ with age
Fever, rash, ± aphthous ulcers
Abdominal pain (serositis), diarrhea, vomiting
Arthralgia, arthritis, lymphadenopathy

Health seems normal between episodes
Sequelae – amyloidosis uncommon (3%)
Hyper IgD Syndrome (HIDS)

**Mucocutaneous Lesions**
- Erythematous macules
- May affect palms and soles
- Sometimes seen: Papular, urticarial, annular, purpuric rash
- Aphthous ulcerations

Skin bx: – Mixed perivascular infiltrate
- Endothelial cell swelling

**Labs:**
- Leukocytosis, left shift
- Elevated acute phase reactants
- Elevated serum IgD (Immature B cell surface Ig)
- Some cases do not have elevated IgD
- Serum IgA may also be increased

**Pathogenesis of HIDS**
- May have nothing to do with IgD

**HIDS is caused by MVK mutations resulting in reduced Mev Kinase activity**

- MVK Gene
- Mevalonate kinase

- Mevalonic aciduria
- Autosomal recessive
  - Very reduced/absent enzyme activity

**HIDS vs Mevalonic aciduria**

- Depends on degree of function of Mev Kinase
- Range of phenotypes between two syndromes depending on which gene mutations present

> 70 pathogenic mutations
- Autosomal recessive

**2001**

- MVK Gene
- Mevalonate kinase

- Mevalonic aciduria
- Autosomal recessive
  - Very reduced/absent enzyme activity
MVK mutations in HIDS - ? Mechanism of action

**MVK Gene**

- Mevalonate kinase

IL-1β &/or TNFα often elevated

? Role of inflammasome

Post-transcriptional geranylation and farnesylation of proteins regulating Caspase-1 activity

Some Mev kinase HIDS mutants are temperature sensitive (↑temp, ↓activity) so ordinary fevers may trigger attacks.

Hyper IgD Syndrome

**HIDS**

**Treatment:**
- Colchicine ineffective (some patients previously deemed “colchicine-resistant FMF” have HIDS)
- Corticosteroids sometimes effective for attacks
- Simvistatin – HMG CoA reductase inhibitor
- Double blind crossover study showed benefit in adults,
  But mevalonic acid decreased and IL-1β increased in vitro.
- Anakinra - IL-1 receptor antagonist
- Etanercept – TNFα receptor–Fc chimera
  Effective – anecdotal evidence

HIDS and IgD

- Some HIDS patients (known mutations in MVK) have normal serum IgD.
- Some patients with HIDS phenotype have high IgD and do NOT have demonstrable MVK mutations - “variant HIDS”.
- Some patients with other genetically proven autoinflammatory syndromes have moderately ↑ IgD.
- IgD may be only a marker for uncontrolled inflammation in some circumstances.

Case 2 : Amelia

**HIDS ?**
Case 2: Amelia

2 year old girl – mixed European ancestry
One year history of fever to 103 degrees, lasting about 3 days, every 3-4 weeks.
Vomiting with some episodes - required i.v. fluids several times. No severe abd. pain or diarrhea.
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Negative testing for MVK gene mutations

Autoinflammatory Syndromes

Leaving the Inflammasome

TNF-Receptor-Associated Periodic Syndrome

TRAPS

“Familial Hibernian Fever”

First report in Irish- Scottish kindred (FHF) 1982
Autosomal dominant.
Later – other European familial periodic fevers (FPFs)
TRAPS
Median onset – age 3 yrs.
Attacks > 7 days, frequency variable.
HUGE variation in phenotype.

Fever can be the sole manifestation
Rash usually present but can be mild, subtle
Serositis – chest and abdominal pain
Arthralgia > arthritis
Migratory pain (limbs, trunk) - rash over affected area
(Not myositis, but panniculitis, fasciitis)
Conjunctivitis or periorbital edema (80%)
Uveitis (uncommon)

TRAPS
Rash – red, macular, blanching,
may migrate centrifugally
Skin biopsy –
perivascular mononuclear cells

Labs:
Elevated WBC and plts, mild anemia
Elevated ESR, CRP, SAA –
often elevated between attacks
Elevated IgG, A, M

Sequela – amyloidosis (10%), more likely with
severe manifestations and certain genotypes.

Gene: TNFRSF1A
Protein: p55 receptor for TNFα
No ethnic or racial predisposition
Autosomal dominant,
penetration very variable
~ 50 pathogenic mutations*
Polymorphism vs mutation:
R92Q and P46L in 1% controls.
Effect of modifier genes?

TRAPS
TNF-Receptor-Associated Periodic Syndrome

TNFα is a potent pro-inflammatory cytokine
Elevated with inflammation from any cause
Systemic effects (fever, malaise, arthralgia, etc)
Local effects – arthritis, uveitis
Binds to surface receptors, activates cells

Alterations in cell surface or intracellular receptors
could cause more prolonged or severe inflammation.
TRAPS

Mutated p55 receptor - defective shedding or intracellular accumulation → stimulation

TRAPS

Treatment:
- Corticosteroids – variable benefit
- TNF inhibitors, to decrease stimulation of abnormal receptors

Etanercept - TNF receptor-Fc chimera marketed for RA, JIA – sub cu 1-2 x weekly
Effective - anecdotal reports, uncontrolled trials
(Other TNFα inhibitors such as infliximab and adalimumab should also be effective)

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TNFRSF, A mutation leading to R92Q substitution in p55 TNF receptor.

Pathogenic mutation with the most variable penetrance and spectrum of symptoms.

Treated with etanercept and had no further episodes for > 2 years – discontinued. Episodes returned after 9 months off etanercept.

Other Autoinflammatory Syndromes

Blau Syndrome (Early Onset Sarcoidosis) - NOD-2/CARD15 mutations
PAPA (Pyogenic Arthritis with Pyoderma gangrenosum and Acne) - PSTPIP-1 mutations
DIRA (Deficiency of IL-1 receptor antagonist) IL-10 Receptor Mutations

? PFAPA
? Behcet's Disease
? Systemic onset JRA

PHAPA
Periodic Fever, Adenitis, Pharyngitis, and Aphthous ulcers
(aka Marshall's Syndrome)
Systemic Onset JIA

Fever
Macular rash
Lymphadenopathy
Hepatosplenomegaly
Polyarthritis
Elevated acute phase

When to consider an autoinflammatory syndrome?

Exclude infection, neoplasm, cyclic neutropenia
Consider family history, ethnicity, provoking factors
Episodes truly recurrent, without explanation
Elevated acute phase reactants and TWBC, plts-
especially between attacks
Age of onset (young). Duration of episodes
Associated symptoms – rash (type), red eyes,
oral ulcers, arthritis, serositis, vomiting/diarrhea
Elevated IgD ± IgA, urine mevalonate during attack
Guidance for genetic testing - narrow the DDx
Easy to collect specimen - buccal swab or blood
but $$$

Autoinflammatory Syndromes

Can be difficult to recognize due to phenotypic variation:
- Different mutations in same gene
- Other genes that modify phenotype

>60% of patients with periodic fevers have
no demonstrable mutations in known genes
- Mutations in regulator genes
- Uncharacterized syndromes
Autoinflammatory Syndromes

Kastner Higgins

Disclaimer: I am not Dan Kastner

or Mike McDermott
or Phil Hawkins
or Anne-Marie Prieur...... etc.

Disclosure:

I have participated in clinical studies of anakinra (Kineret), canakinumab (Ilaris) and etanercept (Enbrel) for treatment of juvenile idiopathic arthritis. These studies were funded by Abbott, Novartis, and Amgen - the manufacturers of these medications.

I have no financial interest in any pharmaceutical company.

Useful Review Articles


