CAPS for Ophthalmologists

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A newborn with a rash

- Premature birth 34 weeks, hydramnion since 30 weeks
- Urticarial rash, 2\textsuperscript{nd} day of life
- Low grade fever, Splenomegaly
- Limitation mobility left elbow, knees, ankles, with pain
- Swelling of PIP3 left, PIP2 right
- Hyperleucocytosis, thrombocytopenia
- Cholestasis, increased CRP
- Differential diagnosis: infection, inflammation
A newborn with a rash

Urticarial rash
with vasculitis lesions
A newborn with a rash

• Polyarthritis, systemic inflammation, liver involvement
• Suspicion of infection: sepsis, parvovirus B19
• Suspicion of auto-inflammatory disease. Cold urticaria is suggesting CAPS
• Genetic analysis: NLRP3 mutation heterozygote E567K

• Diagnosis confirmed:
  Cryopyrin Associated Periodic Syndrome (CAPS): CINCA

Early diagnosis and early treatment in this patient
Cryopyrinine Associated Periodic Syndrome (CAPS)?

Very simple story

- Chronic inflammatory disease
- Increased basal production of IL-1β
- Diagnosis by genetic testing
- Treatment by agents blocking IL-1β

More difficult story

- Unspecific symptoms
- Heterogeneous phenotype
- Very rare disease
- Lack of awareness in the medical population
- Long-term outcome of severe forms?
Cryopyrine Associated Periodic Syndrome (CAPS)?

A medical success story

1. From the patient to the lab: discovery of the gene
2. From the lab to the patients: very efficacious treatment

A challenge for the future
CAPS for Ophthalmologists

1. What is CAPS?
2. Pathophysiology
3. Diagnosis
4. Therapy
5. Outcome
CAPS for Ophthalmologists

What is CAPS?

Pathophysiology

Diagnosis

Therapy

Outcome
Cryopyrin Associated Periodic Syndrome (CAPS)

A defect in the same gene: NLPR3, autosomal dominant

Clinical expression specific for the different mutations
Cryopyrin-associated Periodic Syndrome (CAPS)

Due to mutations in NLRP3 on Ch1q44

- PYD
- N-terminal
- NACHT
- C-terminal

Increasing disease severity

Skin:
- Cold-induced: Fever
- Urticaria
- Arthralgia
- Conjunctivitis

Skin:
- Fever
- Abdominal pain
- Urticaria
- Conjunctivitis

Musculoskeletal:
- Arthritis
- Hearing loss

Musculoskeletal:
- Arthropathy
- Hearing loss
- CNS involvement:
  - Headaches
  - Meningitis, papilledema

Normal life span

Hearing loss (2nd-4th decade of life), amyloidosis up to 30%

Mental retardation, hearing loss (1st decade of life), short stature, vision loss, joint contractures, unable to reproduce

FCAS: Familial cold autoinflammatory syndrome

MWS: Muckle-Well syndrome

NOMID/CINCA: Neonatal-onset multisystem inflammatory syndrome
  - Chronic infantile neurological, cutaneous and arthritis
Eye involvement

- Chronic inflammation can cause eye redness, pain, and vision impairment\(^1\)
  - Conjunctivitis
  - Anterior uveitis
  - Corneal infiltrates
  - Papilledema and papillitis
  - Posterior uveitis (rare)

- Inflammatory lesions, resulting in permanent damage\(^1\)
  - Band keratopathy
  - Corneal clouding
  - Retinal scarring
  - Optic nerve atrophy

CNS manifestations

- Aseptic meningitis and increased intracranial pressure are common, resulting in headaches\(^1\)
  - Ventriculomegaly and brain atrophy
    - Arachnoid adhesions likely develop due to chronic leptomeningeal inflammation
    - Not observed in patients with milder disease

- Cognitive impairment, ranging in severity (NOMID/CINCA)\(^1\)

- Seizures, stroke, and other vascular occlusive events, often at sites of intravascular catheters\(^1\)

Ophthalmological symptoms

- Conjunctivitis\(^1,3-7\)
- Papilledema\(^4,6,7\)
- Papillitis\(^4,7\)
- Corneal Clouding\(^1,5,6\)
- Corneal Infiltrates\(^5,7\)
- Uveitis\(^4,5,6,7\)
- Iritis\(^6\)
- Hypopyon\(^1,4\)
- Retinal Vascular Sheathing\(^1,3\)
- Retinal Scaring\(^6\)
- Optic nerve atrophy\(^7\)
- Orbital Pain\(^2,3\)
- Optical Disk Swelling\(^3\)

### FCAS

Conjunctivitis (non-infectious) during flares\(^6\)

### MWS

Conjunctivitis (non infectious) during flares, or corneal haze.

### NOMID/CINCA

Papilledema, uveitis, iritis, conjunctivitis. Some with retinal scarring, corneal haze or vision loss.

Muckle-Wells and visual loss (R260W)

Rheumatology 2014;53:1095–1099
CAPS for Ophthalmologists

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From the inflammasome to IL-1β

**Signal 1**

Pro-inflammatory stimulus

- TLR
- NFkB
- proIL-1

**Signal 2**

Gain of function

NLRP3

Caspase-1

proIL-1β → IL-1β
Dysregulation of IL-1β production

Gain-of-function mutations in NLRP3 gene lead to overactive cryopyrin, which promotes inflammasome hyperactivation\(^1-3\)

NLRP3 protein (cryopyrin)

NLRP3 inflammasome activates caspase-1, which cleaves pro-IL-1β into IL-1β\(^3\)

NF-κB activation

IL-1β activates NF-κB in the nucleus, resulting in more pro-IL-1β synthesis\(^3,4\)

IL-1β and Systemic Inflammation in CAPS

Liver¹
Production and release of acute-phase proteins
Accounts for increased ESR

IL-1 induces IL-6 production¹

Endothelial cells¹
Results in rash and IL-6 production

Bone/marrow¹
Increases mobilization of granulocyte progenitors and mature neutrophils
Results in peripheral neutrophilia

Increases platelet production
Results in thrombocytosis

Decreases response to erythropoietin
Results in anemia

Brain¹
Hypothalamus thermoregulatory center
Induces fever

IL-1β

↑CRP; ↑SAA

Bone/joint¹,²
Induces bone resorption and cartilage breakdown in the joint

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A.
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Genetic disease diagnosed at 55 years

- Recurrent polyarthritis since childhood
- Joint pain, moderate fever, fatigue since a long time, jobless because of “weakness”
- Considered as Rheumatic fever since childhood
- Mother with the similar symptoms who died in 2005

- Mutation in the NLRP3 gene: CAPS, Muckle-Wells
- Good response to canakinumab (ILARIS®) 1x/8 weeks
- Actually asymptomatic under treatment
- Renal amyloidosis with slight improvement
NLRP3 mutation: always CAPS?

- 3 years old boy
- Since 6 months of life, fever flares every 3-4 weeks
- Cervical adenitis and pharyngitis
- One flare after a vaccine
- No rash, no arthritis, no neurological or ophthalmological symptoms
- Transitory response to one dose of Prednisone

- Genetic testing: CAPS (V198M), MVK (V377I)
- Clinical PFAPA, mutation for CAPS, and MVK
Mevalonate Kinase Deficiency (MKD)

Accumulation during fever flares

HMG-CoA reductase Statins
Mevalonate kinase (defective in MKD)

Mevalonate

IPP

FPP

GGPP

Squalene

Cholesterol

Dolichol

Ubiquinone

Heme A

Prenylated Proteins

Caspase -1

IL -1

Nuclear cataract
Retinal dystrophy
Retinitis pigmentosa
Monogenic Auto-inflammatory Diseases (MAI)

Test 1: MKD / HIDS (gene: MVK)
- Recurrent fever, early onset, vaccin as a trigger
  - Mevalonic aciduria during the fever flares

Test 2: FMF (gene: MEFV)
- Short flares, 2-3 days, arthritis, serositis
  - Ethnical origin

Test 3: TRAPS (gène: TNFRSF1A)
- Long fever flares, periorbital oedema, myalgias
  - Familial cases

Genetic testing according to the clinical picture
Reimbursement only if ok from the insurance
Specialized consultation to interpret the results recommended
What is PFAPA?

First described in 1987 by Marshall

Recurrent fever flares with ORL symptoms

Diagnosis based on a set of 5 diagnostic criteria
PFAPA: genetic disease?

« Auto-inflammatory »

genetic variants in 25% of PFAPA patients

<table>
<thead>
<tr>
<th>Variant</th>
<th>Expected frequency</th>
<th>Observed frequency</th>
<th>P value</th>
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<tbody>
<tr>
<td>V198M</td>
<td>0.0148</td>
<td>2/57</td>
<td>0.205</td>
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<tr>
<td>Q703K</td>
<td>0.10</td>
<td>9/57</td>
<td>0.145</td>
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<tr>
<td>R488K</td>
<td>0.0028</td>
<td>1/57</td>
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<tr>
<td>All</td>
<td>0.118</td>
<td>12/57</td>
<td>0.029*</td>
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Autoinflammatory disease and genetic variants
Mutation versus polymorphism
High Incidence of NLRP3 Somatic Mosaicism in Patients With Chronic Infantile Neurologic, Cutaneous, Articular Syndrome: Results of an International Multicenter Collaborative Study

Naoko Tanaka\textsuperscript{1,†}, Kazushi Izawa\textsuperscript{1,†}, Megumu K. Saito\textsuperscript{2}, Mio Sakuma\textsuperscript{3}, Koichi Oshima\textsuperscript{4},


\begin{itemize}
  \item germ line heterozygote
  \item mosaicism
  \item no mutation
\end{itemize}
**CAPS: classification criteria**

<table>
<thead>
<tr>
<th>Presence</th>
<th>Score</th>
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<tbody>
<tr>
<td>Urticarial rash</td>
<td>25</td>
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<tr>
<td>Neurosensorial hearing loss</td>
<td>25</td>
</tr>
<tr>
<td>Conjunctivitis</td>
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</table>

<table>
<thead>
<tr>
<th>Absence</th>
<th></th>
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<tbody>
<tr>
<td>Exudative pharyngitis</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
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Cut-off \( \geq 52 \)

**Autoinflammatory disease**
- Diagnosis on clinical criteria
- Genetic confirmatory, but not exclusive

**CAPS**
- AUC (TS) = 0.99
- AUC (VS) = 0.99

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>VS</th>
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<tr>
<td>Sens</td>
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<td>96</td>
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<tr>
<td>Spec</td>
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<td>92</td>
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</table>
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Anti-IL-1 medications

- Canakinumab
- Rilonacept
- Anakinra or IL-1Ra
- IL-1R

Inflammation; Fever, rash, pain
Control of inflammation: CAPS

- Anakinra
- Rilonacept
Canakinumab induced a complete clinical and biochemical response in all cases.

Immediately pre first treatment

C-reactive protein (CRP) mg/L

Days from infusion

24 hours post treatment
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Multidisciplinary care

Medical team
- Pediatric Rheumatologist
- Pediatrician
- Other pediatric specialists
- Adolescent medicine
- Transition: adult rheumatologist

Aims
- Disease remission
- Functional integrity
- Psycho-social support
- School support
- Professional integration

Specialised nurse
- Education for therapy and disease
- Counseling for patients and families
- Hotline

Physiotherapist
- Physical activity
- Psychologist
- Social worker
Juvenile Inflammatory Rheumatism (JIR) cohort

Large prospective longitudinal cohort to follow patients chronic inflammatory rheumatisms

1. Evaluate the safety of treatments over the long-term
2. Evaluate efficacy and treatment changes
3. Evaluate specific aspects (uveitis, vaccinations, TMJ, US)

Cohort developed in collaboration with

- French and Belgian Pediatric Rheumatologists
- European Cohort (Pharmachild)
- Adult Rheumatologists (SCQM)
Take home messages

• Eye involvement is common in CAPS patients
• Unspecific symptoms may delay the diagnosis
• Importance of early recognition of CAPS
• Confirmation of the diagnosis by a specialist
• Importance of early treatment for better outcome
• Care by CAPS specialist in collaboration with GP and different specialists, inclusive ophthalmologist
• Long-term follow-up through registries