Hereditary Periodic Fever Syndromes

Mutations in Idiopathic Acute Recurrent Pericarditis

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References


Disclosure

I have no relevant financial relationships to disclose

Background

• Chest pain, fever, brief course, benign
• Isolated or part of a more systemic disease
• Numerous causes
  • Infectious diseases (6-8%)
    - Tuberculosis (4%)
    - Pyogenic infection (2%)
    - Fungal and parasitic infections (rare)
  • Auto-immune diseases (3-5%)
  • Cardiac surgery or myocardial infarction (5-10%)
  • Malignant diseases (5-10%)  
  • Idiopathic 70-90%

Natural History of Acute Pericarditis

<table>
<thead>
<tr>
<th>Short-term</th>
<th>Mid-term</th>
<th>Long-term</th>
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</thead>
<tbody>
<tr>
<td>Determined etiology</td>
<td>Chronic pericardial effusion</td>
<td>Recurrence 20-40%</td>
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<tr>
<td>Acute Pericarditis</td>
<td>Right Heart Failure &lt;2%</td>
<td>Constrictive Pericarditis &lt;2%</td>
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<tr>
<td>Idiopathic</td>
<td>Complete recovery</td>
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Hereditary Periodic Fever Syndromes

- **Familial Mediterranean Fever (FMF)**
  - The most prevalent periodic fever syndrome
  - Predominantly affects people from the Mediterranean basin
  - Short attacks of serositis (peritonitis, pleuritis, arthritis) & fever
  - Autosomal recessive disease
  - Treatment: colchicine

- **TNF receptor-associated periodic syndrome (TRAPS)**
  - Recurrent attacks of fever, myalgia & painful skin erythema
  - Autosomal dominant inheritance
  - Response to high doses prednisone and TNF alpha-blockers

- **Others HPFS**
  - Hyper IgD syndrome
  - Familial cold urticaria and Muckle-Wells syndrome

**Hereditary Periodic Fever Syndromes**

- Recurrences of fever lasting from a few days to a few weeks

- Symptom-free intervals of variable duration

- Diagnosis should be discussed if:
  - Attacks with a predictable course and a similar set of symptoms
  - Family history

**Idiopathic Recurrent Pericarditis (IRAP)**

- Periodic recurrences
- Symptom-free intervals
- Family history
- No auto-immune process
- Great efficacy of colchicine

**Idiopathic Recurrent Pericarditis and Hereditary Periodic Fever Syndromes - Literature data**

- Pericarditis may be the sole manifestation of FMF
  - 2 cases (Tauber T, 1995)

- Idiopathic recurrent acute pericarditis: FMF mutations... in a cohort of Caucasian patients.
  - 0/23 Italian patients with mutation (Brucato A, 2005)

- Idiopathic recurrent pericarditis refractory to colchicine treatment may reveal TRAPS syndrome
  - 4/30 (13.3%) patients with mutation (Cantarini L, 2009)
### Aims

1. To search for the presence of HPFS gene mutations in a large cohort of patients presenting with recurrent pericarditis.
2. To analyze the impact of HPFS gene mutations in patients with IRAP on:
   - Sensitivity to treatments, i.e. NSAIDs, colchicine.
   - Mid- and long-term outcome, i.e. pericarditis relapses.
   - Treatment withdrawal, i.e. steroids.

### Methods

#### Methods - 1 -

- Retrospective study: 1990 – 2010
- Pitié Salpêtrière Hospital (tertiary university)

#### Methods - 2 -

- **Epidemiologic and clinical features**
- **Inflammatory biomarkers**
  - C-reactive protein (+ if > 20mg/L)
  - Fibrinogen (+ if > 5g/L)
- **Treatment**
  - Aspirin and non steroidal anti-inflammatory drugs
  - Corticosteroids & immunosuppressants
  - Colchicine
- **Outcome: pericarditis relapse**
  - Delay, number

#### Methods – Gene Mutations of Hereditary Periodic Fever Syndrome

- Genomic DNA isolated from patients peripheral blood leucocytes
- **Mutations:**
  - MFEV gene
    - M680I, M694V, M694I, V726A, E148Q
  - TNFRSF1A gene

### Idiopathic Recurrent Pericarditis and Hereditary Periodic Fever Syndromes

- **Aims**
  - To search for the presence of HPFS gene mutations in a large cohort of patients presenting with recurrent pericarditis.
  - To analyze the impact of HPFS gene mutations in patients with IRAP on:
    - Sensitivity to treatments, i.e. NSAIDs, colchicine.
    - Mid- and long-term outcome, i.e. pericarditis relapses.
    - Treatment withdrawal, i.e. steroids.

- **Methods**
  - Retrospective study: 1990 – 2010
  - Pitié Salpêtrière Hospital (tertiary university)

- **Methods - 1 -**
  - Acute Pericarditis
    - Chest pain and fever
    - Increased inflammatory biomarkers
  - Recurrent pericarditis
  - Systematic check-up

- **Methods - 2 -**
  - Epidemiologic and clinical features
  - Inflammatory biomarkers
    - C-reactive protein (+ if > 20mg/L)
    - Fibrinogen (+ if > 5g/L)
  - Treatment
    - Aspirin and non steroidal anti-inflammatory drugs
    - Corticosteroids & immunosuppressants
    - Colchicine
  - Outcome: pericarditis relapse
    - Delay, number

- **Methods – Gene Mutations of Hereditary Periodic Fever Syndrome**
  - Genomic DNA isolated from patients peripheral blood leucocytes
  - Mutations:
    - MFEV gene
      - M680I, M694V, M694I, V726A, E148Q
    - TNFRSF1A gene
Results

Hereditary Periodic Fever Syndrome Mutations in Idiopathic Recurrent Pericarditis

- The presence of one HPFS gene mutation was found in 14/53 (26.4%) recurrent pericarditis.
  - MFEV gene mutation in 7/53 (13.2%) IRAP patients
  - TNRFS1A gene mutation in 7/53 (13.2%) IRAP patients

Hereditary Periodic Fever Syndrome Mutations in Idiopathic Recurrent Pericarditis

- HPFS gene mutation 14/53 (26.4%) in IRAP
- MFEV gene (13.2%)
  - Heterozygous M694V: 2 patients
  - Heterozygous M694I: 2 patients
  - Heterozygous E148Q: 3 patients
- TNRFS1A gene (13.2%)
  - Heterozygous R92Q: 4 patients
  - Homozygous R92Q: 1 patient
  - Heterozygous P46L: 2 patients

Epidemiologic Features

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>HPFS mutations</th>
<th>No HPFS mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, (Q1,Q3),y</td>
<td>36.5 (24,53)</td>
<td>45.5 (24,57)</td>
<td>33 (23,52.3)</td>
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<tr>
<td>Gender, M/F (%)</td>
<td>32/21 (60.4)</td>
<td>9/5 (64.3)</td>
<td>23/16 (59.0)</td>
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<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- European</td>
<td>41 (87.2)</td>
<td>11 (78.6)</td>
<td>30 (83.3)</td>
</tr>
<tr>
<td>- North Africa</td>
<td>5 (10.6)</td>
<td>2 (14.3)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>- Others</td>
<td>1 (2.1)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- NA</td>
<td>6</td>
<td></td>
<td>6</td>
</tr>
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</table>

Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
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</thead>
<tbody>
<tr>
<td>Extracardiac features</td>
<td>36 (67.9)</td>
</tr>
<tr>
<td>- Pleural effusion</td>
<td>9 (16.9)</td>
</tr>
<tr>
<td>- Arthralgia</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td>Time between 2 events, months</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>Increased inflammatory biomarkers, n (%)</td>
<td>36 (67.9)</td>
</tr>
</tbody>
</table>

HPFS: hereditary periodic fever syndrome
Treatment of Recurrent Pericarditis & HPFS Mutation

Corticosteroids withdrawal
- 5 out of 7 patients
- 3/4 with HPFS mutation
- 2/3 w/o HPFS mutation

HPFS: Hereditary Periodic Fever Syndrome

Conclusion

- Mutations of hereditary periodic fever syndromes are frequently found in patients with idiopathic recurrent pericarditis (26.4%).
- Such mutations should be searched for in patients presenting with IRAP.
- The impact of the presence of HPFS gene mutation on more specific therapeutic strategy in IRAP patients will need further studies.

Evolution of Recurrent Acute Pericarditis

Pericarditis Relapse according to HPFS Mutation

Colchicine as First-Choice Therapy for Recurrent Pericarditis

Lotrionte. Am J Cardiol. 2010

N=84 patients, fu 24 months