Periodic fever syndromes

Principal investigator
Paul Dancey, MD, FRCP, Janeway Children’s Hospital, Memorial University, St. John’s NL A1B 3V6; tel.: 709-777-4766; fax: 709-777-4343; paul.dancey@easternhealth.ca

Co-investigators
Susanne Benseler, MD, University of Toronto
Marco Gattorno, MD, “G. Gaslini” Scientific Institute for Children, Genoa, Italy
Anne Junker, MD, University of British Columbia
Ronald Laxer, MD, University of Toronto
Paivi Miettunen, MD, University of Calgary
Lesley Turner, MD, Memorial University

Background
Periodic fever syndromes represent a group of rare, inflammatory disorders, which have their onset in childhood and are associated with significant lifelong morbidity, and at times, increased mortality. The majority of affected children have recurrent, self-limited inflammatory episodes with unprovoked fever. Rarely an affected child can have a more chronic disease course that will wax and wane. In addition to the fever, the severe inflammatory state during an attack causes signs and symptoms in one or more organ systems (Table 1).1 Disease manifestations can include skin rashes, oral ulcers, uveitis or conjunctivitis, arthritis, myalgias, neurological effects, and serositis (peritonitis, pericarditis, pleuritis).1,2 While many of these features resolve with each event, the long-term complications can be significant, including deafness, blindness, developmental delay, destructive arthritis, amyloidosis with renal failure, and at times, death. The term “autoinflammatory” has been used to describe these conditions, as patients have high levels of inflammatory markers during attacks, yet they lack the high titer auto-antibodies and antigen specific T-cells seen in inflammatory autoimmune diseases.1,3 Due to the rarity of these syndromes and the subsequent lack of awareness in the medical community, patients will often have seen several physicians before the correct diagnosis is made, resulting in patient morbidity, increased cost to health care, loss of time from school for the children and work absences for the parents.

The periodic fever syndromes can be recognised by their characteristic clinical features, and in some cases by a specific genetic mutation (Table 1).3 It is important to note, however, that a subgroup of patients meeting a clinical and laboratory definition of a periodic fever syndrome will not have a confirmed genetic mutation, and are thus diagnosed as “periodic fever syndrome – undefined”. This group of patients can also be at risk for cumulative organ damage.
Most importantly, recent discoveries in pathophysiology of these diseases, including genetic abnormalities, have resulted in development of effective treatments that can ameliorate the symptoms and at times prevent or reverse cumulative organ damage, such as renal amyloidosis, hearing loss, or arthritis.1-6 The early recognition of the disease is an essential step in achieving this goal.

The rationale of this CPSP study will be to document the regional incidence, patterns of presentation, and the associated burden of illness of this rare form of disease. Ultimately, we hope to improve the well-being of patients and reduce their overall morbidity.

**Methods**

Through the established methodology of the CPSP, over 2,500 paediatricians and paediatric subspecialists will be actively surveyed for new cases of periodic fever syndromes.

**Objectives**

1) Estimate the incidence of periodic fever syndromes in the Canadian paediatric population.
2) Describe the presentation, demographics, and outcome of these rare diseases.
3) Raise the awareness of these rare conditions amongst the medical community.
4) Facilitate earlier diagnosis and initiation of effective therapies.

**Case definition**

Report any patient less than 18 years of age presenting with a newly diagnosed periodic fever syndrome (autoinflammatory syndrome) meeting the criteria outlined below.

**Inclusion criteria**

Patients must have one of the following diagnoses (see Appendix 1 for specific details; characteristic features are outlined in Table 1):

1. Familial Mediterranean fever (FMF)
2. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
3. Hyperimmunoglobulin D syndrome (HIDS)
4. Cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID)
5. Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA)
6. Periodic fever syndrome – undefined

**Exclusion criteria**

1. Detailed clinical assessment and investigations compatible with infections, malignancy, or the classical inflammatory or autoimmune rheumatic diseases (e.g., systemic lupus erythematosus, systemic juvenile idiopathic arthritis, inflammatory bowel disease).
2. Febrile attacks with regular periodicity and low neutrophils counts, suggestive of cyclic neutropenia.
Periodic fever syndromes (continued)

Duration
September 2011 to August 2014

Expected number of cases
Approximately 50 to 100 cases per year

Ethical approval
Human Investigations Committee at Memorial University, Newfoundland and Labrador

Analysis and publication
An annual interim analysis of the collected data will be done. Annual and final reports will be published in the CPSP Results and circulated to all participants. Dissemination of completed study results will be submitted for publication to appropriate peer-reviewed journals and presented at national and international scientific meetings.

References
### Table 1: Characteristic features of the periodic fever syndromes

<table>
<thead>
<tr>
<th>Features</th>
<th>FMF</th>
<th>TRAPS</th>
<th>HIDS</th>
<th>Cryopyrin-associated periodic syndromes</th>
<th>FCAS</th>
<th>MWS</th>
<th>NOMID</th>
<th>PFAPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>&lt; 20 yrs</td>
<td>&lt; 20 yrs</td>
<td>&lt; 1 yr</td>
<td>Usually &lt; 1 yr; sometimes later in life</td>
<td>&lt; 1 yr</td>
<td></td>
<td></td>
<td>&lt; 5 yrs</td>
</tr>
<tr>
<td><strong>Duration of attack</strong></td>
<td>1-3 days</td>
<td>1-4 weeks</td>
<td>2-7 days</td>
<td>1-3 days to continuous</td>
<td>Variable; continuous</td>
<td>Days</td>
<td>3-6 days</td>
<td></td>
</tr>
<tr>
<td><strong>Interval between attacks</strong></td>
<td>Weeks to months</td>
<td>Weeks to months</td>
<td>Weeks to months</td>
<td>Variable; cold-induced</td>
<td>Days</td>
<td>3-6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td>Erysipelas-like in ~40%</td>
<td>Migratory rash. May be painful; cellulitis-like.</td>
<td>Very common, 90%. Diffuse maculopapular may be purpuric.</td>
<td>Cold-induced urticarial rash</td>
<td>Urticarial rash</td>
<td>Urticarial rash</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Adenopathy</strong></td>
<td>No</td>
<td>Not typical</td>
<td>Common and may be generalized.</td>
<td>Not typical</td>
<td>Not typical</td>
<td>Not typical</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Oral ulcers</strong></td>
<td>No</td>
<td>No</td>
<td>May occur</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>Present in 95%, often as acute abdomen.</td>
<td>Common, colicky</td>
<td>Often present. Can be severe with diarrhea.</td>
<td>No</td>
<td>May occur.</td>
<td>May occur.</td>
<td>May occur.</td>
<td></td>
</tr>
<tr>
<td><strong>Joints and muscles</strong></td>
<td>Arthralgia, oligoarthritis, myalgia</td>
<td>Localized myalgia is typical. Arthralgias of large joints common, arthritis less common.</td>
<td>Symmetric oligoarthritis of large joints. Arthralgias frequent.</td>
<td>Arthralgias</td>
<td>Polyarthralgias or arthritis</td>
<td>Arthralgia, arthropathy secondary to osseous overgrowth</td>
<td>Arthralgias may occur.</td>
<td></td>
</tr>
<tr>
<td><strong>Serositis</strong></td>
<td>Peritonitis common. Unilateral pleuritis 30%, Pericarditis &lt;1%.</td>
<td>Pleuritis and peritonitis may occur.</td>
<td>No</td>
<td>No</td>
<td>Pericarditis may occur but is uncommon.</td>
<td>Not typical</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Amyloidosis</strong></td>
<td>Untreated, occurs in 60%.</td>
<td>Occurs in ~25%.</td>
<td>No</td>
<td>May occur.</td>
<td>Occurs in ~30%.</td>
<td>May occur.</td>
<td>No</td>
<td></td>
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<tr>
<td><strong>Other</strong></td>
<td>Scrotal swelling and pain</td>
<td>Periorbital edema and/or conjunctivitis is common. Headache and testicular pain may occur.</td>
<td>Conjunctivitis</td>
<td>Conjunctivitis, episcleritis, Sensorineural hearing loss.</td>
<td>Conjunctivitis, episcleritis, uveitis, papilledema. Chronic meningitis. Sensorineural hearing loss.</td>
<td>Leukocytosis during attacks</td>
<td></td>
<td></td>
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<tr>
<td><strong>Laboratory findings in addition to raised ESR or CRP during attacks</strong> (SAA = serum amyloid A)</td>
<td>Raised SSA during and sometimes between attacks. Proteinuria is very suggestive of amyloidosis.</td>
<td>Leukocytosis. IgD levels may be mildly raised. Raised ESR and CRP may persist between attacks.</td>
<td>Mild leukocytosis and raised urinary mevalonate during attacks. IgD levels often very high, but may be normal. Raised SAA during attacks.</td>
<td>Leukocytosis during attacks.</td>
<td>Leukocytosis during attacks. Raised ESR, CRP and SAA may persist between attacks.</td>
<td>Leukocytosis during attacks</td>
<td></td>
<td></td>
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<tr>
<td><strong>Inheritance pattern</strong></td>
<td>Autosomal recessive</td>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant / de novo</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>MEFV Pyrin</td>
<td>12p13 TNFRSF1A p55 TNF receptor</td>
<td>12q24 MVK Mevalonate kinase</td>
<td>1q44 NLRP3 Cryopyrin</td>
<td>1q44 NLRP3 Cryopyrin</td>
<td>1q44 NLRP3 Cryopyrin</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Periodic fever syndromes (continued)

Appendix 1: Clinical and/or genetic criteria for periodic fever syndromes

PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis)
Patients fulfilling all the following criteria:
1. Regular recurring fevers that begin at < 5 years of age.
2. Constitutional symptoms in the absence of upper respiratory infection with at least one of the following clinical signs:
   a. Aphthous stomatitis
   b. Cervical adenitis
   c. Pharyngitis
3. Exclusion of cyclic neutropenia and other known hereditary periodic fever syndromes
4. Asymptomatic between episodes
5. Normal growth and development

FMF (familial Mediterranean fever)
1. Patients with an inflammatory disease associated with two MEFV mutations.
OR
2. Patients meeting probable or definite FMF Tel Hashomer criteria as follows:
   Major criteria
   • Recurrent febrile attacks (at least three attacks with temperature ≥ 38 °C) associated with peritonitis, pleuritis and/or synovitis.
   • AA-type amyloidosis without apparent predisposing disease
   • Favourable response to colchicine prophylaxis
   Minor criteria
   • Recurrent febrile attacks (at least three attacks with temperature ≥ 38 °C).
   • Erysipelas-like erythema
   • FMF in a first-degree relative
Definite FMF = two major criteria, or one major and two minor criteria
Probable FMF = one major criterion and one minor criterion

HIDS (hyperimmunoglobulin D syndrome)
1. Patients with an inflammatory disease associated with two mutations in both alleles of MVK (mevalonate kinase) and/or residual mevalonate kinase enzyme activity below 20% of normal.
OR
2. Patients with one pathogenic mutation in MVK and strongly elevated urinary mevalonic acid during fever.

Note: Periodic fever patients with a HIDS phenotype (Table 1), but in whom genetic testing has not been done, or who are not found to have a pathogenic mutation, will be considered to have an undefined periodic fever syndrome. See criteria below.
TRAPS (tumour necrosis factor receptor-associated periodic syndrome)

Patients with an inflammatory disease associated with a pathogenic mutation of the TNFRSF1A gene.

Note: Periodic fever patients with a TRAPS phenotype (Table 1), but in whom genetic testing has not been done, or who are not found to have a pathogenic mutation, will be considered to have an undefined periodic fever syndrome. See criteria below.

CAPS (cryopyrin-associated periodic syndromes). These include FCAS (familial cold autoinflammatory syndrome), MWS (Muckle-Wells syndrome), and NOMID (neonatal-onset multisystem inflammatory disease)

Patients with an inflammatory disease associated with a pathogenic mutation of the CIAS1/NLRP3 gene.

Note: Patients with the CAPS phenotype (Table 1) may be mutation negative. For the purposes of this surveillance study, they are to be considered to have an undefined periodic fever syndrome. See criteria below.

Periodic fever syndrome (autoinflammatory disease) – undefined

1. Patients with ≥ 3 attacks of fever > 38.0°C (any method including oral, rectal, tympanic or axillary) over a period of six months, and occurring at least seven days apart. All of the following must be present:
   • Increased acute phase reactants (i.e., ESR, CRP) during, or within four days of the episodes
   • Normal clinical and laboratory features in-between the attacks
   • Not fulfilling the inclusion criteria for PFAPA, HIDS, FMF, TRAPS, CAPS

OR

2. Patient with a CAPS phenotype (Table 1), but in whom genetic testing is negative or has not been done, and fulfilling at least one of the following three scenarios:
   • Recurrent urticaria (or urticaria-like persisting rash) of early onset (< 1 year of age) with suspicion of (or proven) central nervous system involvement (e.g., recurrent headaches, irritability in infants, sterile meningitis with neutrophils) and/or hypertrophic arthropathy
   • Recurrent episodes of cold-induced fever with urticaria of early onset (< 5 years of age), with familial history suggesting autosomal-dominant inheritance
   • Recurrent episodes of urticaria (or urticaria-like persisting rash) and fulfilling at least two of the following four criteria:
     ▶ urticaria episodes associated with fever
     ▶ early onset (< 5 years of age)
     ▶ familial history suggesting autosomal dominant inheritance
     ▶ recurrent arthritis/arthralgias/myalgia