

 *New England Society of Allergy
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**PERIODIC FEVER
SYNDROMES**

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DISCLOSURE

- During the past 12 months, neither I nor my family have any relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

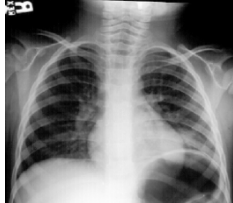


OBJECTIVES

- Describe the periodic fever (auto-inflammatory) syndromes
 - FMF
 - HIDS
 - HIDS
 - PFAPA
- Discuss pathogenesis of periodic fevers
- Learn to recognize their characteristics
- Discuss the evaluation and treatment of periodic fever syndromes

CASE PRESENTATION

- Recurrent pneumonias in an adolescent boy



FEVER

- Centrally regulated rise in body temperature in response to pathologic stimuli
- Mediated by multiple proteins (endogenous pyrogens) produced by PMN's and macrophages
- Pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF) act directly on preoptic region of anterior hypothalamus
- Exogenous pyrogens (e.g., endotoxin) stimulate leukocytes to produce these cytokines



FEVERS AT DIFFERENT SITES

BODY SITE	RANGE (MEAN) (°C)	FEVER °C (°F)
Axillary	34.7-37.3 (36.4)	37.4 (99.3)
Sublingual	35.5-37.5 (36.6)	37.6 (99.7)
Rectal	36.6-37.9 (37)	38.0 (100.4)
Ear	35.7-37.5 (36.6)	37.6 (99.7)

Arch Dis Child 2006;91:351-356

CAUSES OF UNEXPLAINED FEVERS

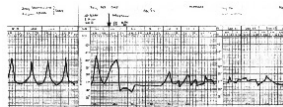
- Infectious Diseases
- Neoplastic
- Rheumatic/Inflammatory
- Miscellaneous Disorders
 - Central fevers
 - Immunodeficiencies
 - Periodic Fever Syndromes

FUO IN CHILDREN: SUMMARY OF PUBLISHED SERIES

DIAGNOSIS	PERCENTAGE
INFECTIOUS	44.6
RHEUMATOLOGIC	14.4
RESOLVED	12.6
MISCELLANEOUS	12.1
UNDIAGNOSED	10.7
NEOPLASTIC	5.6

PERIODIC FEVER SYNDROMES

- Primary dysregulation of innate immune system
- Occur through antigen-independent inflammation
 - Mediated by PMNs, macrophages, NK cells
- *DIFFER FROM FUO BY INTERMITTENT NATURE*



MANIFESTATIONS OF AUTOINFLAMMATORY DISORDERS

- Rash
 - Pustulosis (DIRA), pathergy (DIRA)
 - Erythema (FMF), Nail changes (DIRA)
- Joint swelling (FMF)
- Oral mucosal lesions (DIRA)
- Periostitis (CINCA)
- Serositis (FMF)
- Nephritis (CINCA)
- Conjunctivitis (TRAPS)
- Abdominal pain, diarrhea (HIDS)
- Meningitis, fatigue (CINCA)
- Fever (most)



Lachmann HJ et al, *N Engl J Med* 2009;360:2416.

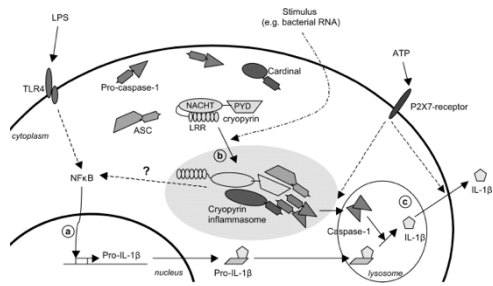
LABORATORY FINDINGS IN AUTOINFLAMMATORY DISORDERS

- Elevated acute phase reactants
- Increased risk of amyloidosis
- Elevation of level of IL-1 and of IL-1 related cytokines (IL-6, MIP-1 α , TNF- α , IL-8, IL-17)
- Infiltrating PMN's at sites of inflammation
- Immunosuppressive therapy has little or no effects
- Steroids or specific inhibitors of IL-1 beneficial

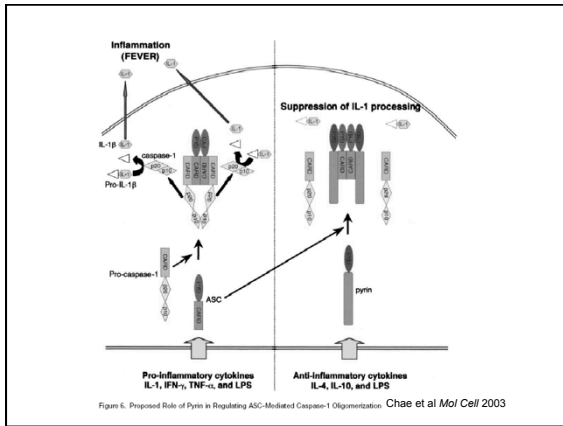


Aksentjevich I et al, An Autoinflammatory Disease with Deficiency of the IL-1-Receptor Antagonist. *N Engl J Med* 2009; 360:2426.

PROPOSED PATHOGENESIS OF PERIODIC FEVER SYNDROMES



Simon A, van der Meer J W M Am J Physiol Regul Integr Comp Physiol 2007;292:R86-R98
 AMERICAN JOURNAL OF PHYSIOLOGY
 Regulatory, Integrative and Comparative Physiology
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AUTOINFLAMMATORY DISORDERS


- Many are hereditary
 - May have typical ethnic predilection
- Many have onset during childhood
- Disorders are uncommon
 - Recent advances in diagnosis and treatment
 - Important for pediatricians to recognize the more common syndromes

AUTOINFLAMMATORY DISORDERS

- **Familial Mediterranean Fever (FMF)**
- **Hyperimmunoglobulin D Syndrome (HIDS)**
- **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)**
- **Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome (PFAPA)**


PFAPA SYNDROME

- No mutation identified
- Sporadic
- No ethnic predisposition
- Usual onset between ages 2-5 years
- Slight male predominance
- Most cases resolve within 5-7 years

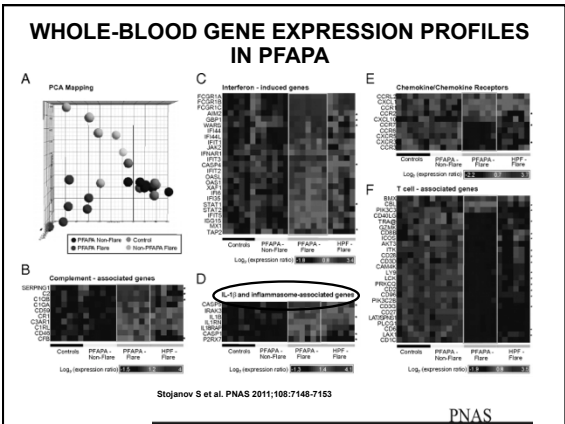


PFAPA CRITERIA

- **INCLUSION**
 - ≥ 3 documented fevers
 - Last no more than 5 days
 - Occur at 3-6 week intervals
 - Pharyngitis, aphthous ulcers or tender cervical lymph nodes
 - Well between episodes
- **EXCLUSION**
 - Neutropenia
 - Inflammation between fevers
 - Family History



J Pediatr 1999;135:15



CLINICAL FEATURES OF PFAPA

- Brief prodrome
- Temperature suddenly increases to 39°C-41°C
- Typically responds poorly to anti-pyretics
- Fever lasts 3-4 days



SYMPTOMS IN PFAPA (N=54)

<i>Pharyngitis</i>	96%
<i>Abdominal pain</i>	65%
<i>Cervical adenopathy</i>	61%
<i>Chills</i>	61%
<i>Headache</i>	46%
<i>Aphthous stomatitis</i>	39%
<i>Nausea/vomiting</i>	35%
<i>Rhinorrhea</i>	33%
<i>Cough</i>	28%
<i>Myalgia</i>	22%
<i>Diarrhea</i>	13%
<i>Rash</i>	4%
<i>Classic cluster</i>	28%

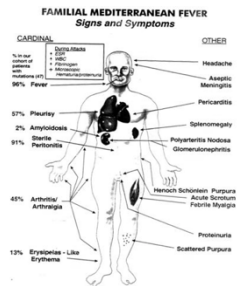
Arch Dis Child 2006;91:981-984

TREATMENT OF PFAPA

- Cimetidine effective in ~ 40%
 - 20-40 mg/kg daily
- Prednisone
 - Single dose at start of prodrome shortens fever course in 90%
 - Often decrease interval between fevers
- Tonsillectomy effective in ~90%
- Anti-IL-1 therapy effective in large majority

(J Pediatr 2007, PNAS 2011)

FAMILIAL MEDITERRANEAN FEVER



FMF-Clinical

- Febrile episodes last 1-4 days
- Typically T > 38.5° C
- Fever accompanied by
 - Serositis
 - Peritonitis
 - Pleuritis
 - Pericarditis
 - Rash
 - Large joint arthritis



FMF

- Attacks remit spontaneously
- Patient well between episodes
 - Increased risk of Polyarteritis nodosa, HSP, other inflammatory disorders
- Chronic disease causes amyloidosis in 1-5%
- Daily treatment with colchicine prevents attacks and prevents amyloidosis

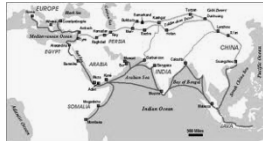
FMF

- Most common auto-inflammatory syndrome

POPOULATION	GENE FREQUENCY
<i>Ashkenazi Jewish</i>	<i>1 in 5</i>
<i>Armenian</i>	<i>1 in 7</i>
<i>Sephardic Jewish</i>	<i>1 in 10</i>
<i>Turkish</i>	<i>1 in 15</i>
<i>Arabic</i>	<i>1 in 50</i>

FMF

- Onset before age 10 in 80%
- Dominant activating mutation in MEFV (chromosome 16p)
 - Encodes *pyrin*, down-regulator of IL-1
 - Over 100 known mutations



HYPERIMMUNOGLOBULIN D SYNDROME (HIDS)

- Rare autosomal recessive
- 60% of patients are Dutch or French
- Mutations of the mevalonate kinase (MVK) gene on chromosome 12
 - Decreased MVK leads to periodic fever
 - Mutation less severe than in mevalonic aciduria
- IgD levels are elevated
 - Increases release of TNF from monocytes

HIDS

- Early onset (usually before 6 months old)
- Fever, abdominal pain, vomiting, diarrhea
 - May mimic acute abdomen
- Rapid onset of high fever ($\geq 39^{\circ}$ C)
 - Lasts 4-7 days
 - Recurs irregularly every 4-8 weeks
- Amyloidosis rare complication

HIDS Treatment


- No uniformly successful treatment
- Colchicine ineffective
- NSAIDs or pulse steroids may help
- Investigational therapy
 - Statins
 - Montelukast
 - Anti TNF agents (etanercept, adalimumab)
 - IL-1 antagonists (anakinra, canakinumab)

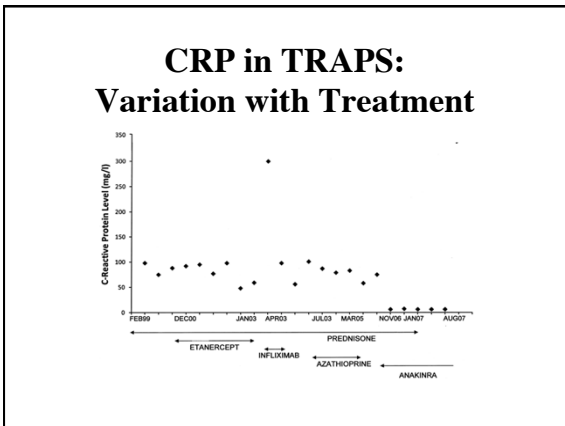
Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

- Autosomal dominant
- Originally called Hibernian fever
 - Most cases described in Irish, Scottish kindreds
- Mutation of TNFRSF1A gene on chromosome 12p
 - 80 known mutations
 - Low serum concentration of TNF receptor

TRAPS

- Begins in early childhood (3-5 years)
- Fever and
 - Abdominal pain
 - Deep myalgias
 - Migratory rash
 - Conjunctivitis (hallmark)





AUTOINFLAMMATORY DISORDERS

CONDITION	AGE AT ONSET	FEVER DURATION AND FREQUENCY	KEY CLINICAL FEATURES	GENETICS	ETHNICITY	THERAPY
FMF	< 10 years (80%)	1-3 days/4-8 weeks	Fever, Peritonitis, Rash, Arthritis, Amyloidosis	AR/MEFV on chromosome 16p	Armenian, Arab, Turkish, Italian, Greek, Jewish	Colchicine
DIRA	Neonate	None	Pustulosis, Joint swelling, Periostitis, Inflammation	IL-1 receptor antagonist on chromosome 2q	Lebanese, Dutch, Canadian, Puerto Rican	Anakinra
HIDS	6 months	4-7 days/4-6 weeks	Fever, Abdominal pain, Diarrhea	AR/IMVK	Dutch, French	NSAIDS, Steroids, Anti IL-1
TRAPS	3 years	Days-weeks/irregular	Fever, Abdominal and Muscle pain, Conjunctivitis	AD/TNFRS1A	Irish, Scottish	Steroids, Anti TNF
CAPS	Neonate and up	3-5 days	Fever, Rash, Periostitis	CIAS1 / NALP3 on chromosome 1q	All ethnicities	Anti-IL-1

Targeted Questions for Periodic Fever Evaluations

- Prodrome and first symptoms of episode
- How temperature is being taken and recorded
- Associated symptoms (e.g., mouth ulcers, etc)
- Peak of fever
- Duration of fever
- Similarity of symptoms and course of each episode
- Interval between febrile episodes
- Appearance of new symptoms
- *IS THE CHILD COMPLETELY NORMAL BETWEEN EPISODES?*

INVESTIGATION FOR PERIODIC FEVERS

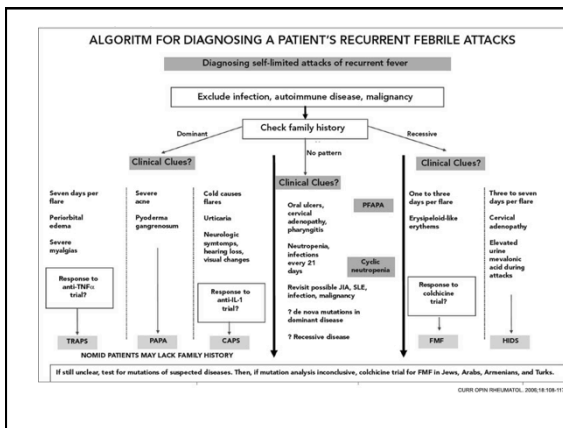
- Establishment of timeline (fever diary)
- Careful and precise history
- Confirm normal growth and development; assess growth charts
- Cautionary warnings about new symptoms and fever and the perils of doctor shopping

MIMICS OF PERIODIC FEVER SYNDROMES

- **Chronic Diseases**
 - JRA, IBD
 - Cyclic neutropenia
 - Vasculitis (PAN, Takayasu arteritis)
 - Malignancies (neuroblastoma, lymphoma)
- **Infectious Diseases**
 - Relapsing fever (*Borrelia hermsii*)
 - Sequential viruses, CMV, EBV
 - Atypical KD

LABORATORY EVALUATION OF SUSPECTED PERIODIC FEVER

CBC	Blood Culture
ESR, CRP	Urine analysis, culture
Serum Chemistries	Uric Acid/LDH
Liver Function Tests	Immune studies, HIV testing
CXR	? Genetic testing

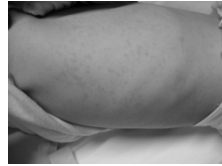


THE GROWING FAMILY OF AUTOINFLAMMATORY DISORDERS

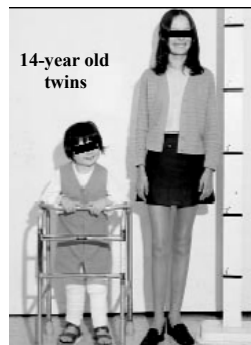
- Deficiency of IL-1 receptor antagonist (DIRA)
- Gout
- Celiac disease
- Type I Diabetes mellitus
- Crohn's disease
- Cervical mycoplasma and infertility
- Periodontal disease
- ? Systemic Onset Juvenile Idiopathic Arthritis

SYSTEMIC JRA

- Arthritis
- Fever
- Rash
- Lymphadenopathy
- Organomegaly
- Serositis



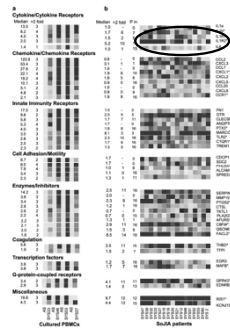
Systemic onset Juvenile Idiopathic Arthritis



14-year old twins
<http://www.rheumtext.com/content/0323024041/supfiles/chapters/Chapter85.pdf>

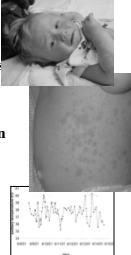
SoJIA: IMMUNOLOGY

- Increased numbers of circulating polymorphonuclear cells and monocytes
- Expansion of immature myelomonocytoid precursors (CD33+, CD 34+)
- Prominent role of proinflammatory cytokines IL-1, IL-6, IL-18
 - Spontaneous fluctuations in IL-6 levels correlating with fever pattern



Fall N, et al. *Arthritis Rheum* 2007;56:3793

**SYSTEMIC JIA:
AUTOIMMUNITY vs. AUTOINFLAMMATORY**

<p>AUTOIMMUNITY</p> <ul style="list-style-type: none">• Lymphocytes– Autoantibodies– Autoreactive T-cells– MHC associations– +/- Inflammation– Amyloid uncommon– Female predominance		<p>AUTOINFLAMMATORY</p> <ul style="list-style-type: none">• PMN'S, monocytes– No autoantibodies– No autoreactive T-cells– No MHC association– Prominent inflammation– Amyloid common– No gender bias
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CASE: DENOUEMENT

- *Therapeutic trial of anticytokine therapy*
- *Pneumonias resolved, respiratory symptoms improved*

– BUT genetic testing for periodic fever syndromes negative!

CONCLUSION

The spectrum of autoinflammatory disorders, and the implications of heterozygous mutations, continue to expand.



SIR WILLIAM OSLER:

“The key to a long life is acquiring a chronic disease and taking good care of it.”
