Febrile syndromes in childhood

Fever - characteristics

- fever = T>38.5ºC

  - ***Protracted***:
    - >5 days
  - ***FUO*** (pUO):
    - >2-3 weeks
  - ***Recurrent / periodic fever***

Really febrile?

- Objectivisation of fever:
  - Measurment technique
  - Fever:
    - Duration
    - Height
    - Dynamics (fever chart)

Associated features

- Clinical symptoms
  - During fever
  - During afebrile interval
- Laboratory
  - During fever
  - During afebrile interval

FUO

- **Infection**
  - Anatomical pre-disposition
    - Congenital anomalies
  - Functional pre-disposition
    - Immune deficiencies
      - Inherited
      - Acquired
  - Unusual / agressive pathogens
    - leishmaniasis, brucelosis, endocarditis

FUO

- **Systemic malignancies**
  - ALL
  - Neuroblastoma
  - Lymphomas
  - Hemophagocytic lymphohistiocytosis (HLH)

- **ALL -** FBC
  - **!** surprisingly „normal“ WBC + high ESR/CRP
  - **!** **profound** anemia (normocytic)
  - **!** Normal/low PLT
  - **!** CS administration dangerous
  - Initial BM aspirate may be normal...
  - Non-specific features: ↑ LDH, uric acid, ferritin
- **Neuroblastoma**:
  - Age group
  - Screening: abd US, bone scan, urine catecholamines
- General:
  - bone pain x mild or no objective joint findings

FUO

- **Systemic inflammatory diseases**
- **Autoinflammatory diseases**

Systemic diseases

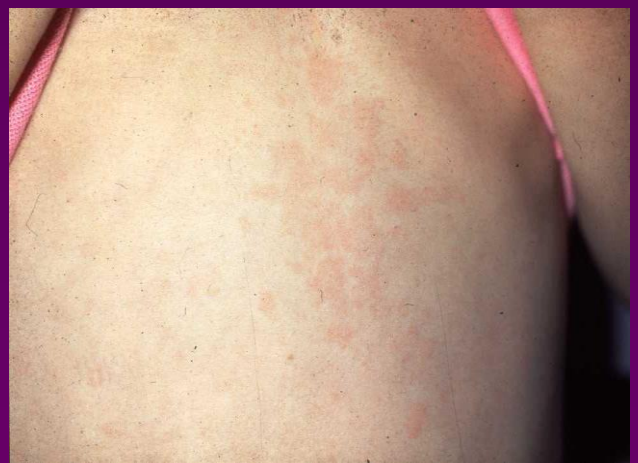
- „Non-rheumatological“
  - IBD
- „Rheumatological“
  - Still´s disease
  - Systemic vasculitis
  - SLE

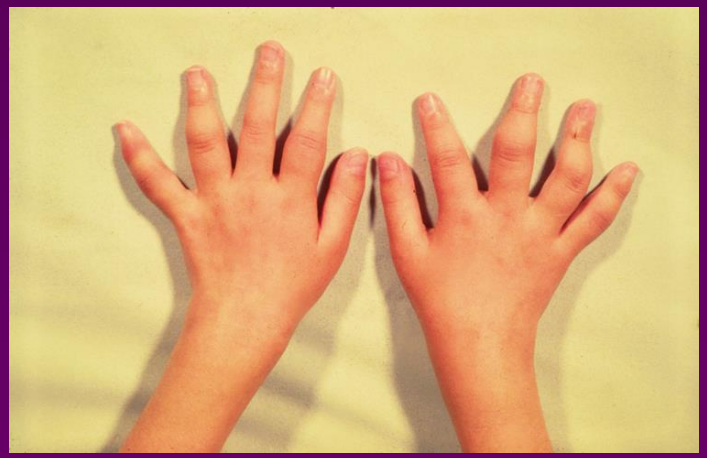
S-JIA – Still´s disease

- **Arthritis +** fever or fever prior to arthritis

+ at least 1 of:

  - Evanescent **rash**
  - Generalized **LNpathy**
  - **Hepatosplenomegaly**
  - **Serositis**





sJIA - complication

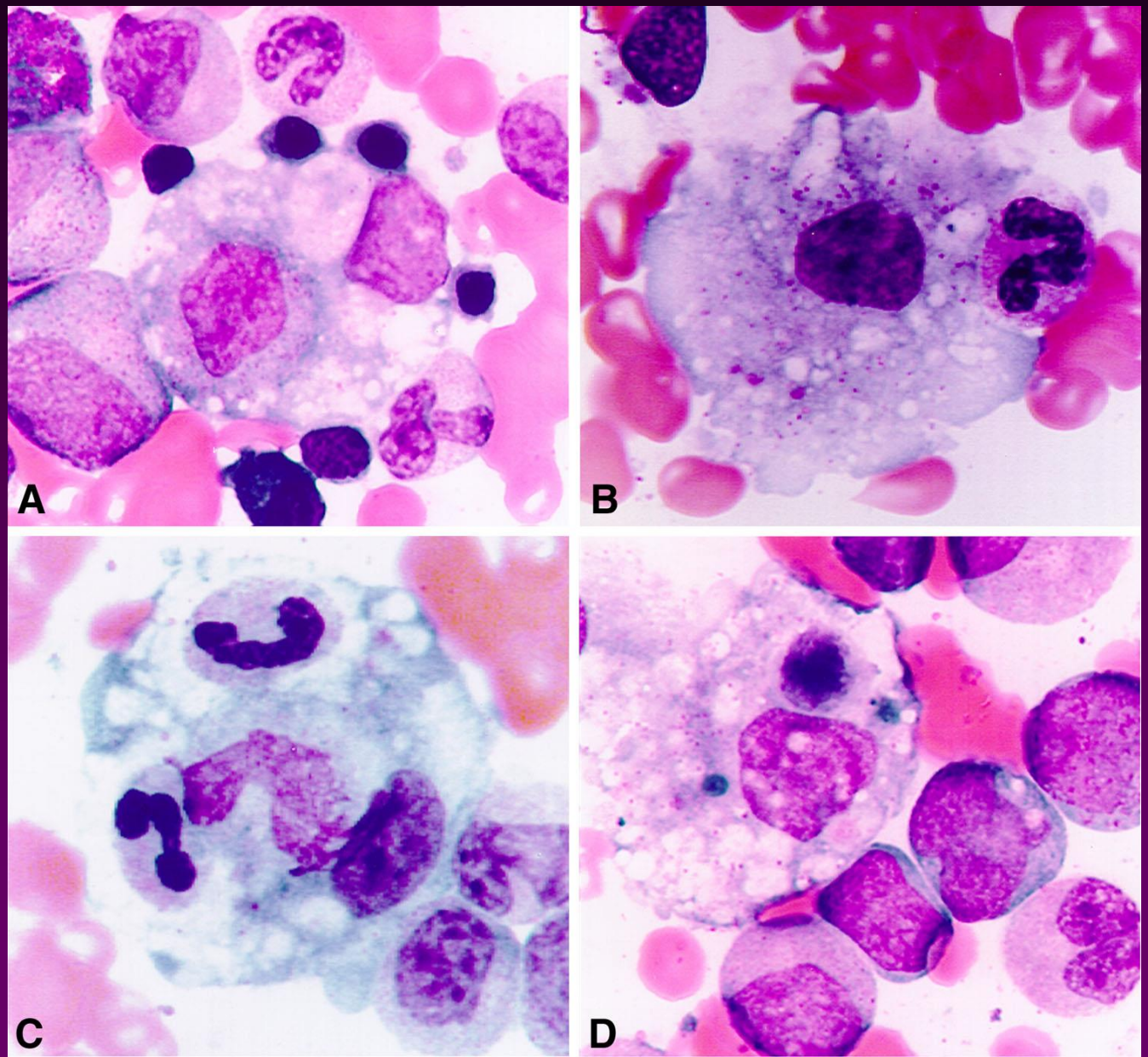
- **MAS: M**acrophage **A**ctivation **S**yndrome
  - Life-threatening
  - Excesive proliferation ans activation of T-cells and macrophages
  - Cytokine storm
- Reactive (secondary) lymphohistiocytosis
- In up to 7% sJIA (=10% JIA)
- KDDL: 8x sJIA, 1x systemic leishmaniasis

- **Main cause of death in paed rheum**

Clinical findings

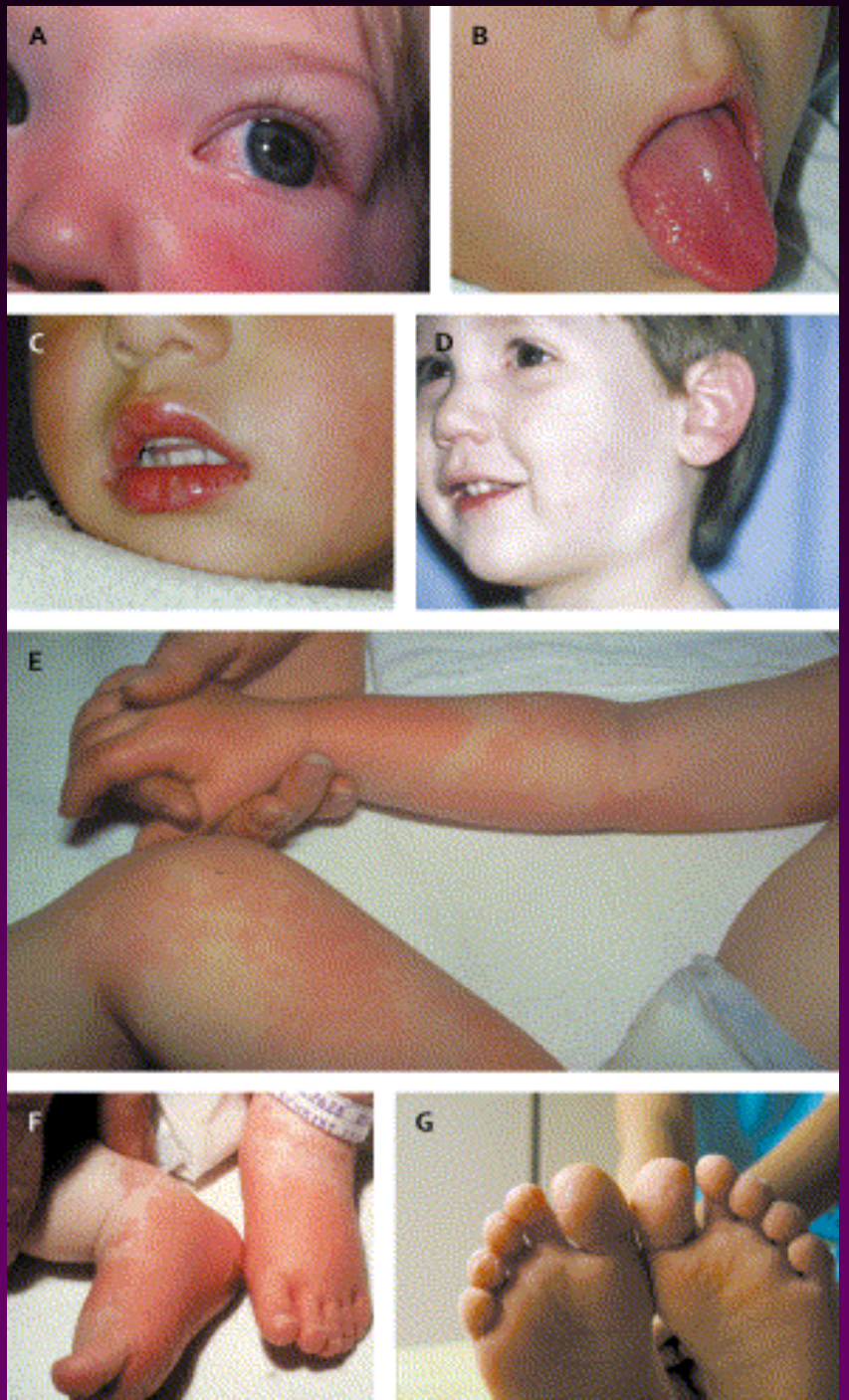
- **Change in fever pattern**
- General deterioration, petechie, neurological symptoms
- **Labs**
  - **Decrease of ESR** ang FBG
  - **Cytopenia** (hemophagocytosis)
  - **Hepatopathy**
  - **Coagulopathy**
  - ↑ **ferritin** (>10 000 ng/ml), IL-18, triglycerides
- Multiorgan failure

Bone marrow (HE × 1,000) Grom AA,2004



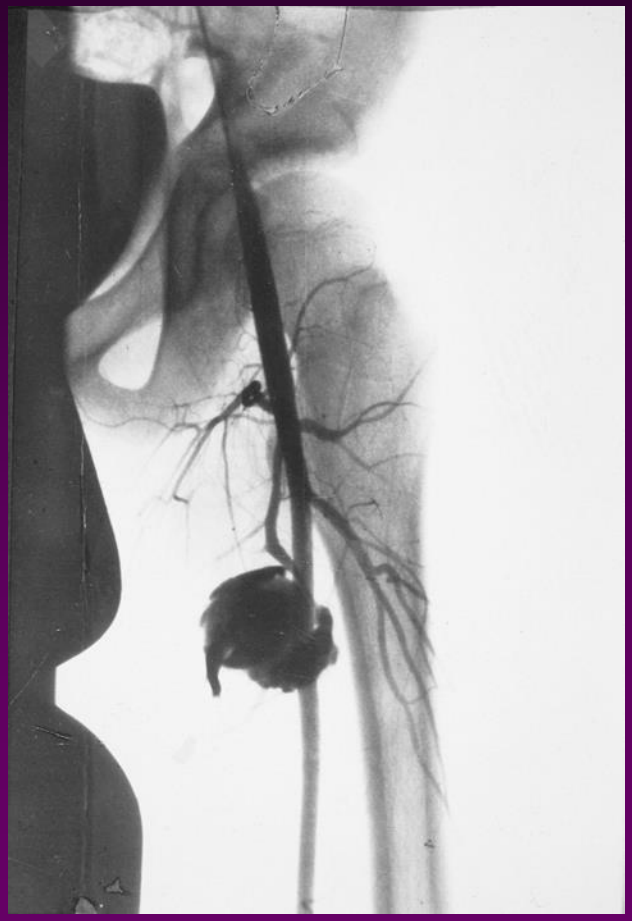
Kawasaki disease

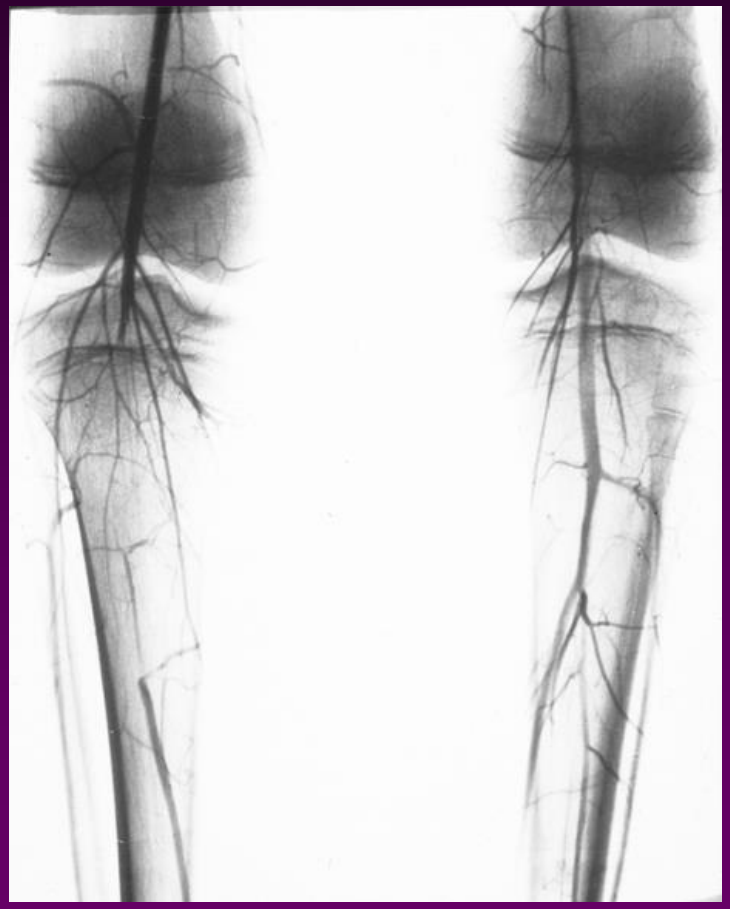
- Fever (100%)
  - > 5 days
- A: conjunctivitis (85%)
  - Bilat., bulbar, non-suppurative
- B,C: mucosal changes (90%)
  - Red cracked lips, strawberry tongue, oropharyngeal erythema
- D: Lymphadenopathy(70%)
  - Cervica, acute, non-suppurative, >1,5 cm
- E: Rash (80%)
  - Polymorphous
- F,G: Extremity changes.(70%)
  - Palm and sole erythema / induration, skin peeling



Large/medium vessel vasculitis

a





b

cPAN Ozen et al 2006

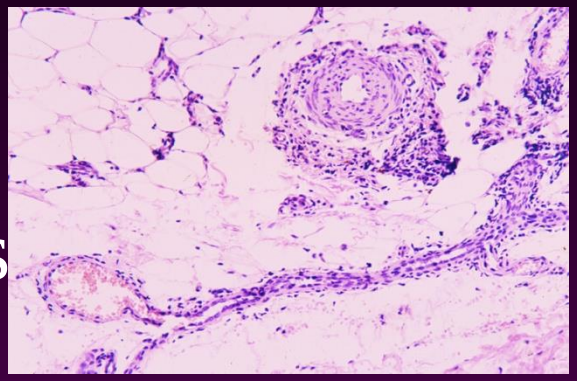
Systemic disease with

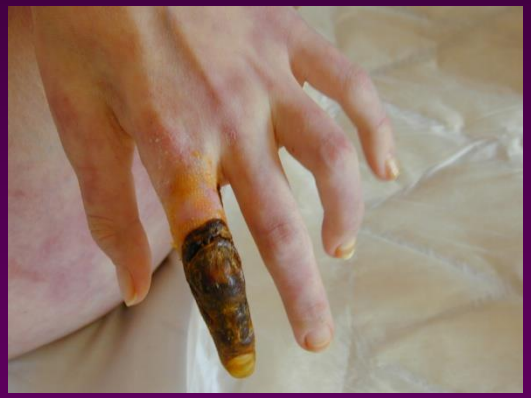
necrotizing vasculitis on biopsy

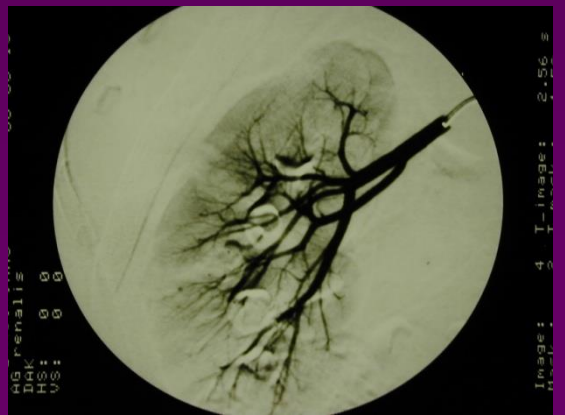
OR ***angiography changes*** + at leas

2 from:

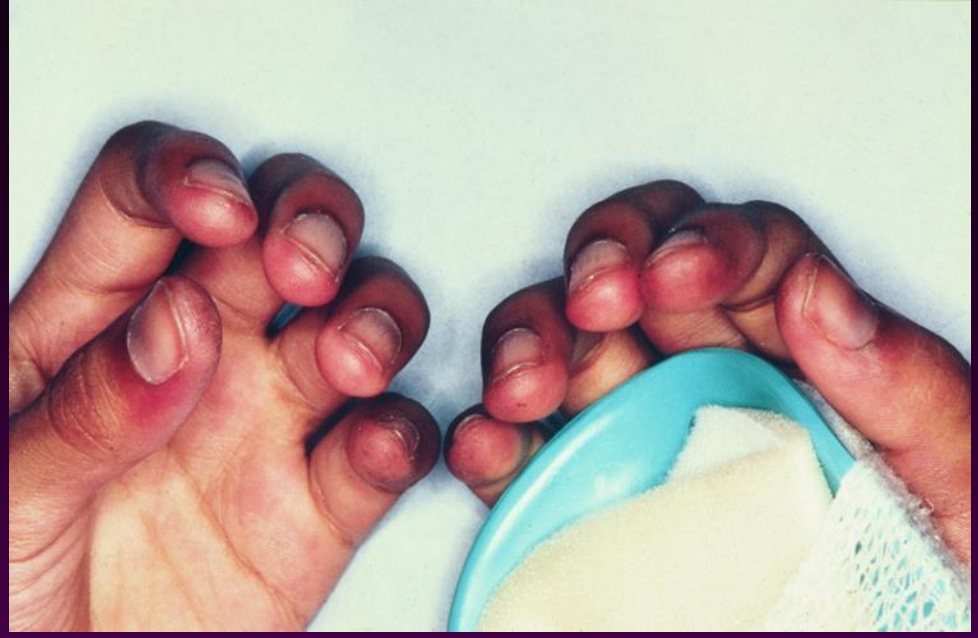
- Cutaneous findings
- Myalgia
- Systemic hypertension
- Mononeuropathy / polyneuropathy
- Renal involvement
- Testicular pain
- Vasculitis of other organs

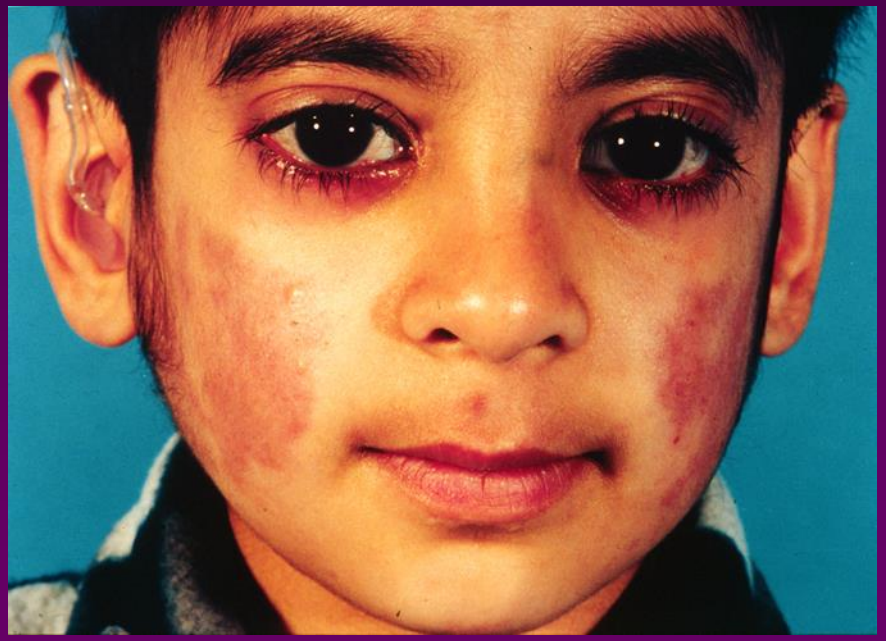


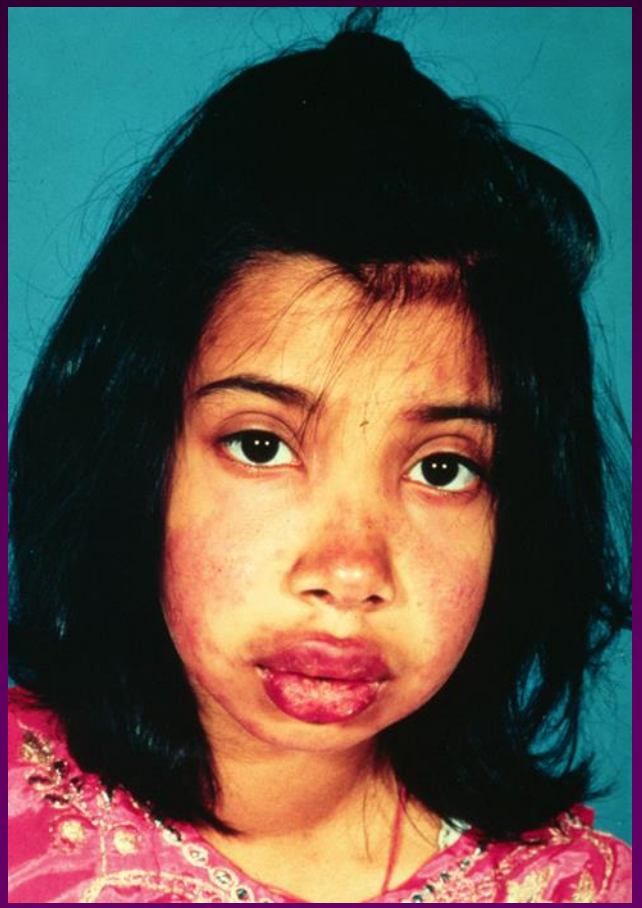




SLE

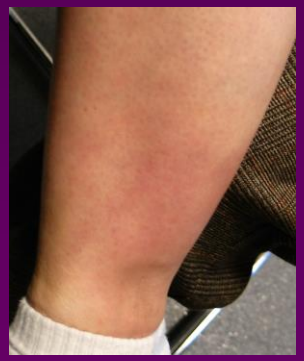


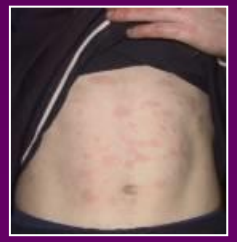
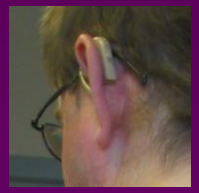
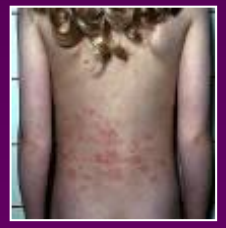


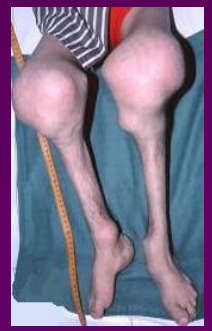


Autoinflammatory diseases

- ✓ General overview
- ✓ Monogenic fevers
  - ✓ FMF, MKD, CAPS, TRAPS
- ✓ Pustular dermatoses
- ✓ Granulomatius diseases
- ✓ Monogenic vasculitis

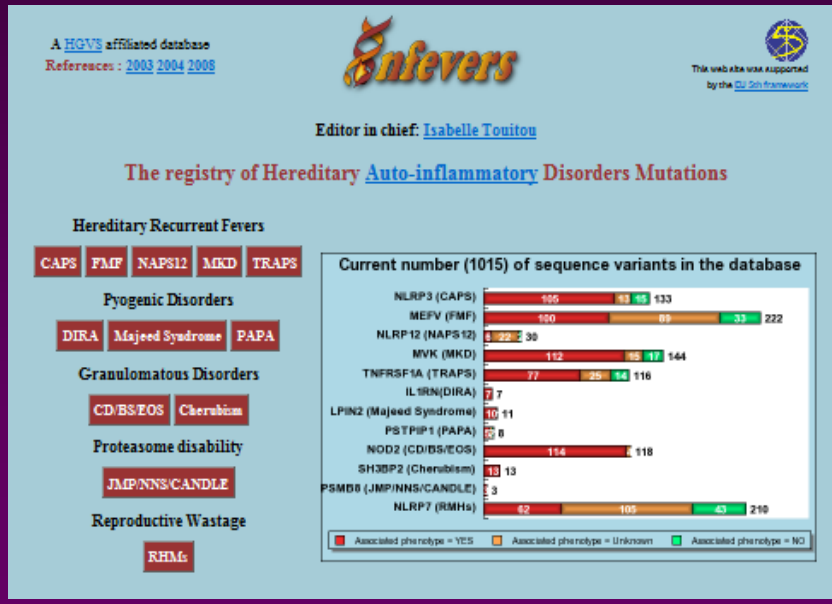




„Autoimmune“ x „**autoinflammatory**“

- Dysregulation of innate immune system
- Recurrency / periodicity
  - Local and general inflammation
  - Asymptomatic intervals
- Early onset
  - Usually before 10 years
- Individual variability



Epidemiology

Toplak et al. Pediatric Rheumatology 2010, 8:29
http://www.ped-rheum.com/content/8/1/29

PEDIATRIC RHEUMATOLOGY

SHORT REPORT Open Access

Periodic fever syndromes in Eastern and Central European countries: results of a pediatric multinational survey

Nataša Toplak[1*], Pavla Dolezalovà[2], Tamas Constantin[3], Anna Sedivà[4], Srdjan Pašić[5], Peter Čižnar[6], Beata Wolska-Kuśnierz[7], Miroslav Harjaček[8], Mariana Stefan[9], Nicolino Ruperto[10], Marco Gattorno[10†], Tadej Avčin[1†], Eastern/Central European autoinflammatory collaborating group for the Paediatric Rheumatology International Trials Organization (PRINTO) and Eurofever Project[10]

Table 1 Genetically confirmed and suspected cases of periodic fever syndromes in ECE countries and estimated number of patients per number of children 0-19 years

Periodic fever syndrome	Genetically confirmed cases	Suspected cases	Total	Estimated number per number of children 0-19 years*
FMF	11	49	60	1/465.500
MKD	14	24	38	1/771.400
TRAPS	11	16	27	1/1.080.000
CINCA	4	7	11	1/2.454.500

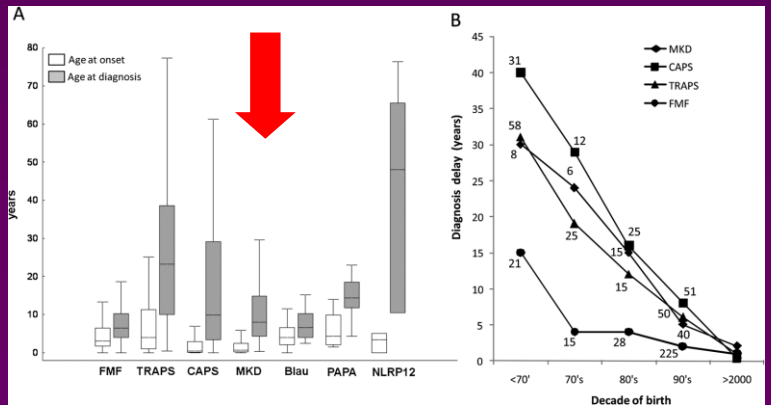
* Adult patients were excluded from calculation.
FMF- familial Mediterranean fever
MKD- mevalonate-kinase deficiency
TRAPS- tumor necrosis factor (TNF) receptor associated periodic syndrome
CINCA- chronic infantile neurological, cutaneous and articular syndrome

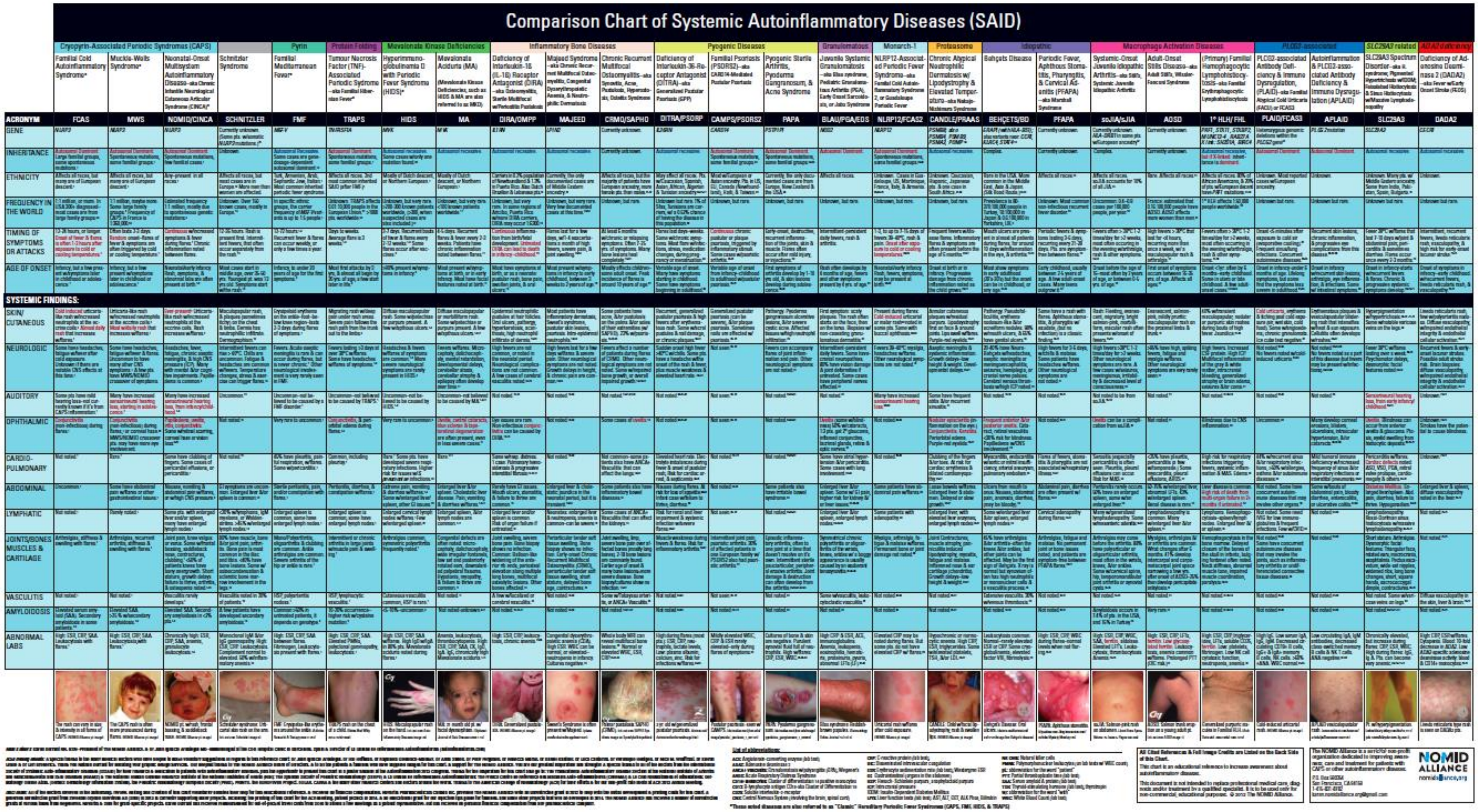
ARD Online First, published on February 29, 2012 as 10.1136/annrheumdis-2011-200549
Clinical and epidemiological research

EXTENDED REPORT

An International registry on Autoinflammatory diseases: the Eurofever experience

Natasa Toplak,[1] Joost Frenkel,[2] Seza Ozen,[3] Helen J Lachmann,[4] Patricia Woo,[5] Isabelle Koné-Paut,[6] Fabrizio De Benedetti,[7] Benedicte Neven,[8] Michael Hofer,[9] Pavla Dolezalova,[10] Jasmin Kümmerle-Deschner,[11] Isabelle Touitou,[12] Veronique Hentgen,[13] Anna Simon,[14] Herman Girschick,[15] Carlos Rose,[16] Carine Wouters,[17] Richard Vesely,[18] Juan Arostegui,[19] Silvia Stojanov,[20] Huri Ozgodan,[21] Alberto Martini,[22] Nicolino Ruperto,[23] Marco Gattorno[23]





http://saidsupport.org/wp-content/uploads/2014/03/periodic-fever-syndrome-diagnostic-chart.png?c88512

Most common periodic syndromes

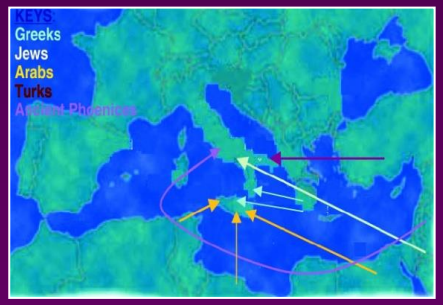
- ***Non-hereditary***
  - PFAPA
- ***Hereditary periodic fevers***
  - FMF
  - HIDS
  - TRAPS
  - CAPS

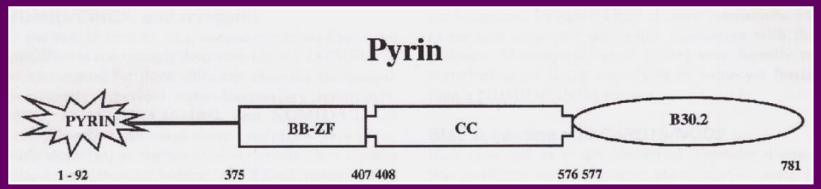
Periodic fever

- Repeat episodes of fever lasting **days to weeks**
- **Asymptomatic intervals**
- **Hereditary and idiopathic syndromes**

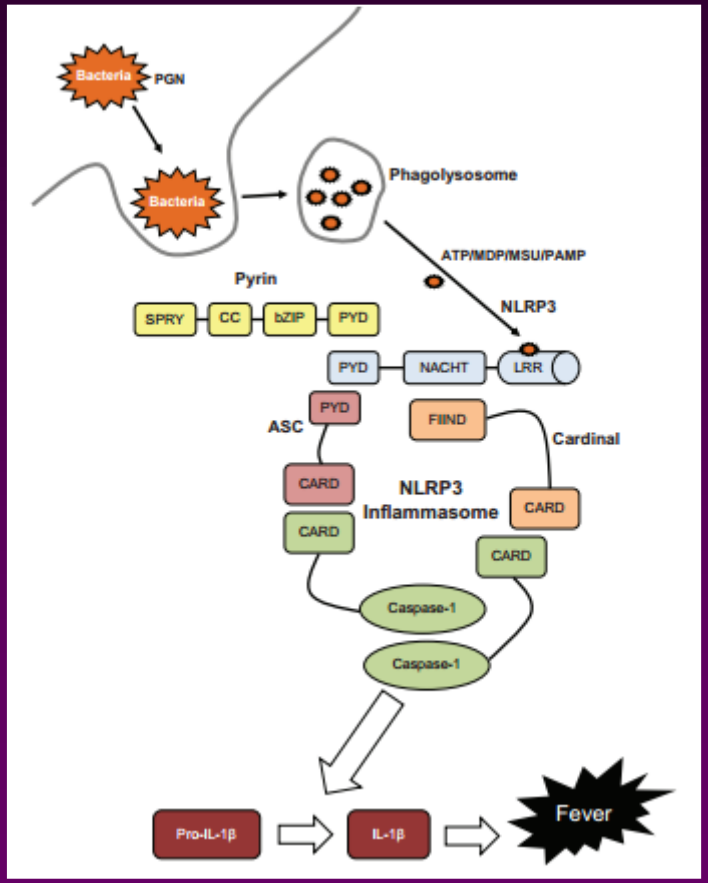
Familial Mediterranean Fever (FMF)

- AR inheritance [1]
- Ethnicity [1]
  - Jewish, Arab, Turkish, Armenian, Greek [1]
- Mutation of MEFV gene
  pyrin (marenostrin) 16CH [1]





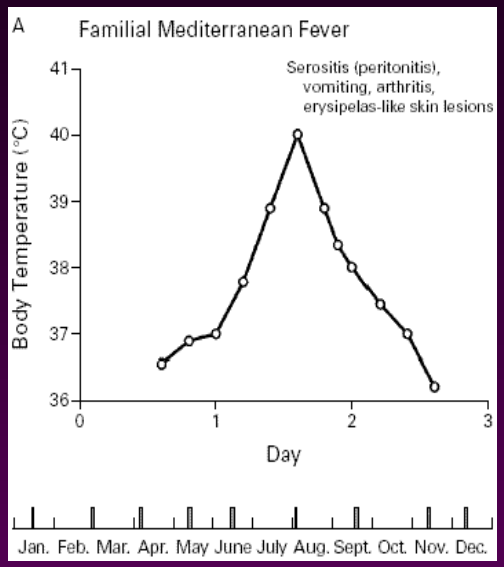
1

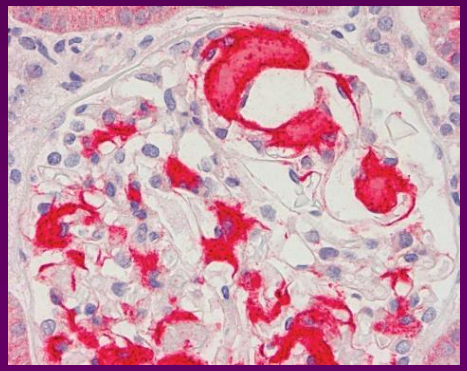


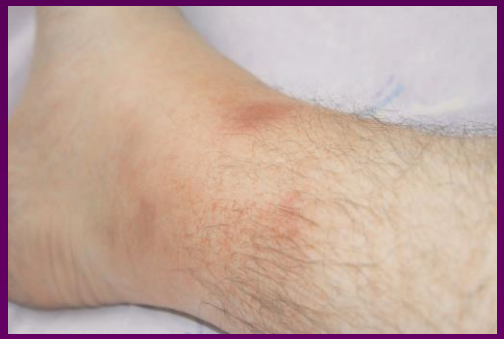
1. Hull K. Et al. The expanding spectrum of systemic autoinflammatory disorders and their rheumatic maniefstations. Curr Opin Rheumatol. 2003 Jan;15(1):61-9
2. Dickie L. Et al. Periodic fever syndrome and autoinflammatory diseases. F1000 Medicine reports 2010, 2:3

FMF

- **Most frequent PF, AR**
- MEFV gene - Pyrin/marenostrin
- **Short fever attacks** + serositis, arthritis, rash, myalgia, **AA amyloidosis**
- **Labs**: nonspecific inflammatory
- **Therapy**:
  - NSA
  - Colchicine
  - Blockade of IL-1



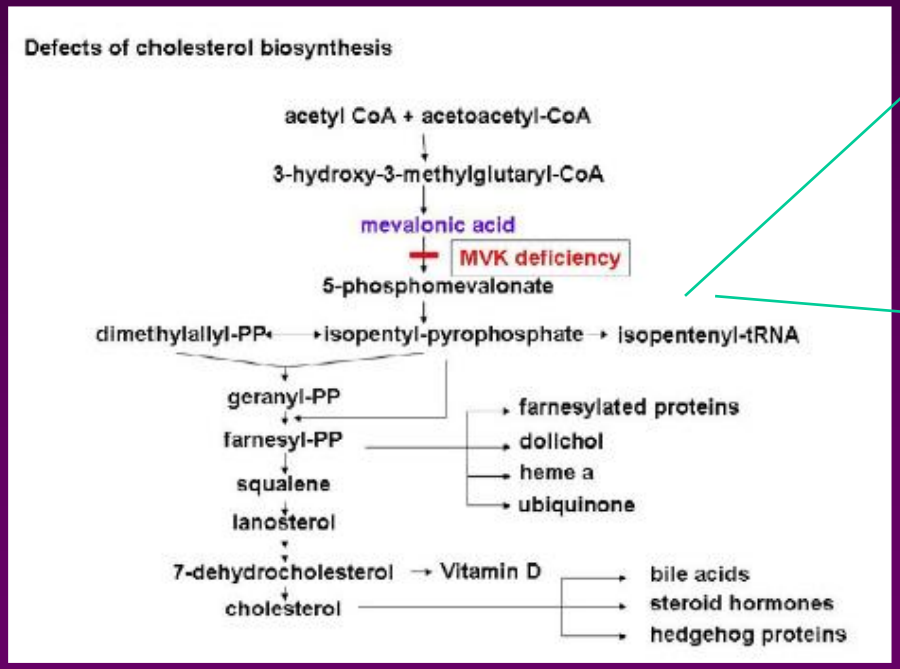


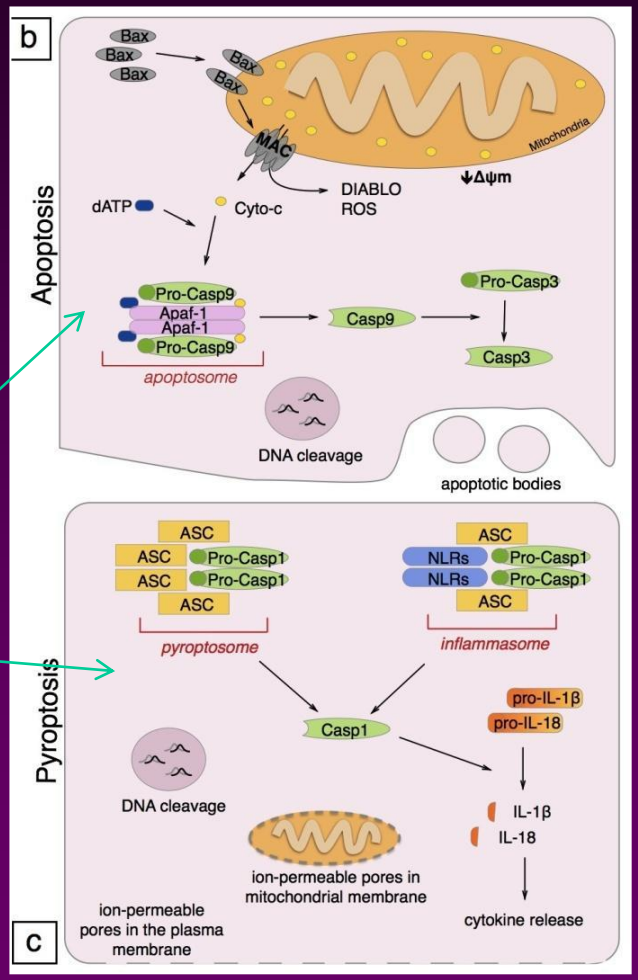


Kallinich D et al, ARD 2006
Galeazzi M et al, CER 2006

Mevalonate kinase deficiency (MKD)

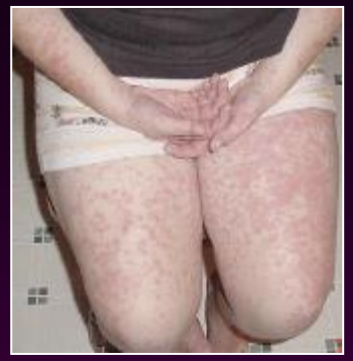
- AR
- MVK gene mutation CH12q24 [1]
  - Decreased enzymatic activity





1. Hyper-IgD syndrome/mevalonate kinase deficiency: what is new? Manders et al. Immunopathol (2015) 37: 371-376

MKD



Syndrome Hyper IgD (HIDS)

- Episodic fevers staring before age 12 months
- 4-6 days
- Lymphadenopthy, hepatosplenomegaly, abd pain, rash, arthralgias
- Triggers common (infection, vacination, stress…)

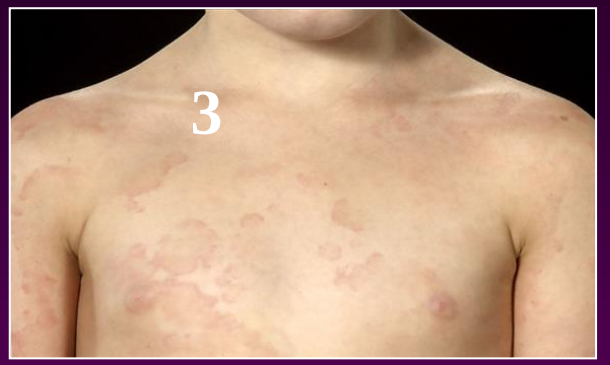
Mevalonic aciduria (MA)

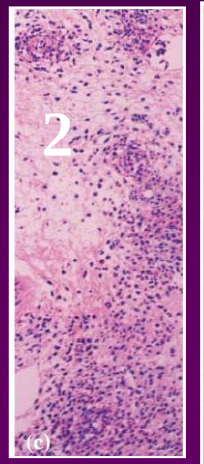
- Psychomotoric retardatio, cereberal ataxia, kraniofacial dysmorphia, blue sclerae, cataract, hypotonia, maopathy

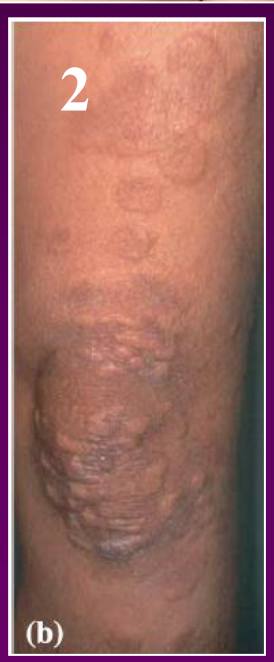
1. Hyper-IgD syndrome/mevalonate kinase deficiency: what is new? Manders et al. Immunopathol (2015) 37: 371-376
2. Mevalonate kinase deficiencies: from mevalonic aciduria to hyperimmunoglobulinemia D syndrome Haas et col. Orphanet Journal of Rare diseases 2006, I:13
3. https://en.wikipedia.org/wiki/Mevalonate_kinase_deficiency

MKD - Hyper IgD Syndrome (HIDS)

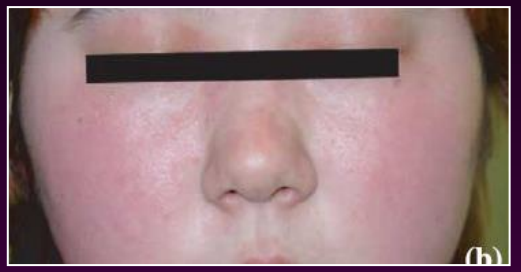
- **Labs**:
  - nonspecific + IgD, IgA, MVA in urine
- **Therapy**:
  - CS, NSAID
  - **Anakinra**
  - **(Etanercept, tocilizumab)**
- **Prognosis**: problematic

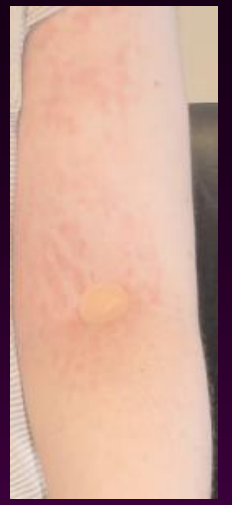




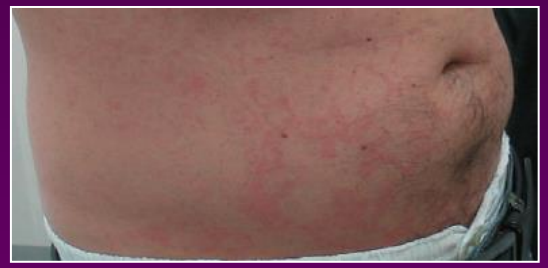


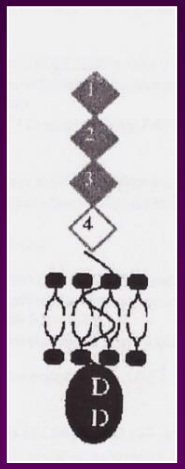
TNF-Receptor Associated Periodic Syndrome TRAPS

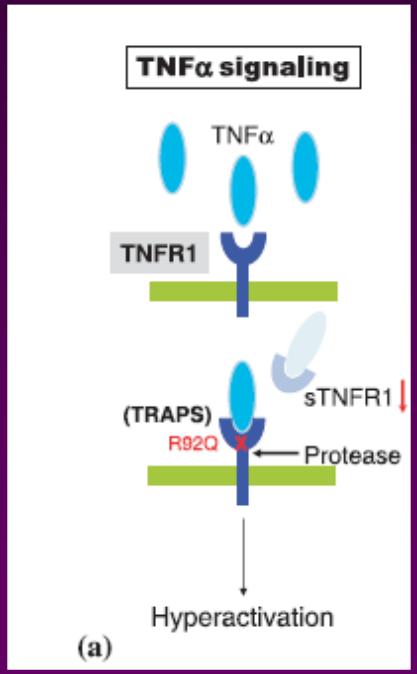




- **TNFRSA1 gene mutation**
  - Structural protein change, accumulation of abnormal protein – IL-1 activation
- **Presentation**:
  - Protracted fever for weeks, 2-6x per year
  - **myalgia**, **ocular symptoms,** abd pain, pleuritis, rash, arthralgia
  - AD inheritance
- **Labs**:
  - Nonspecific, ↓ TNFR1
- **Therapy**:
  - CS during attack
  - Cytokine blockade (etanercept, anakinra)
- **Prognosis**: risk of AA-amyoidosis (25%)





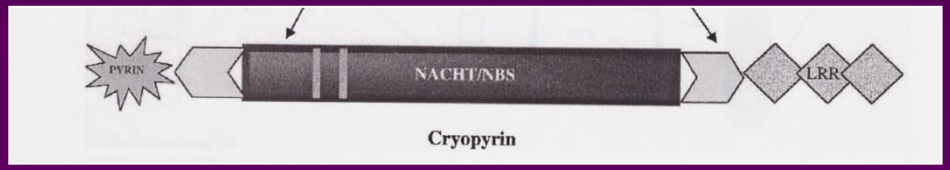


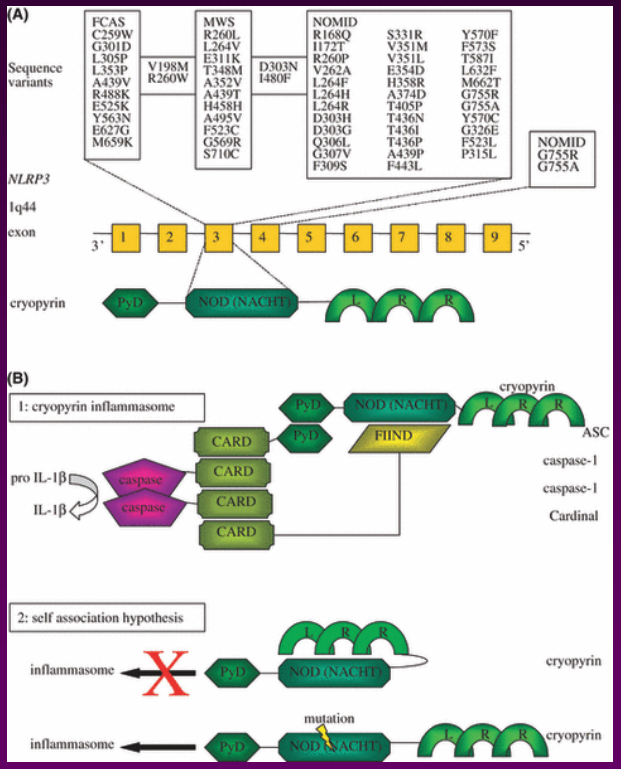
Kallinich D et al, ARD 2006

Cryopyrin associated periodic syndromes CAPS

- AD
- NLRP3 gene mutation coding cryopyrin
- Regulates IL-1 production

1



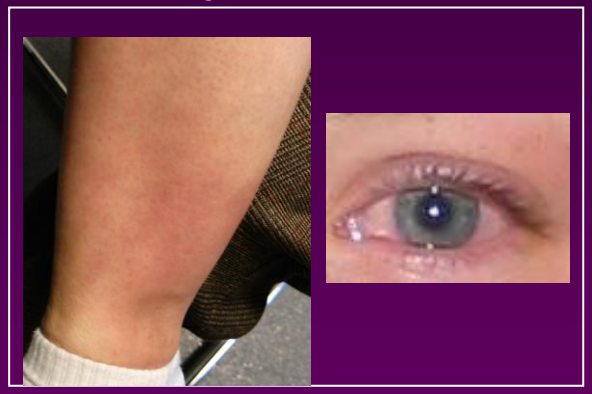


1. Hull K. Et al. The expanding spectrum of systemic autoinflammatory disorders and their rheumatic maniefstations .urr Opin Rheumatol. 2003 Jan;15(1):61-9
2. Lachmann H. Clinical immunology review series: An approach to the patient with a periodic fever syndrome. Clin Exp Immuno.l 2011 Sep; 165 (3): 301-309

CAPS - cryopyrinopathies

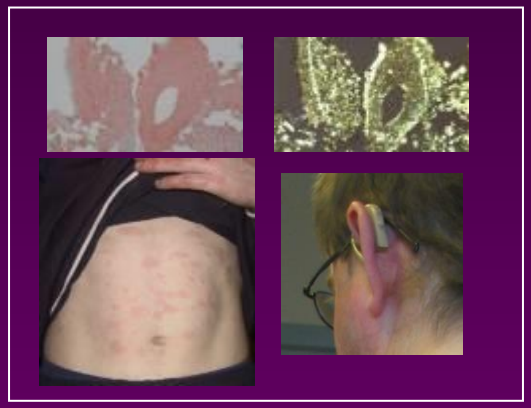
Familiar cold urtica (FCAS)

- Cold induced
  - Rash
  - Arthralgia
  - Conjunctivitis



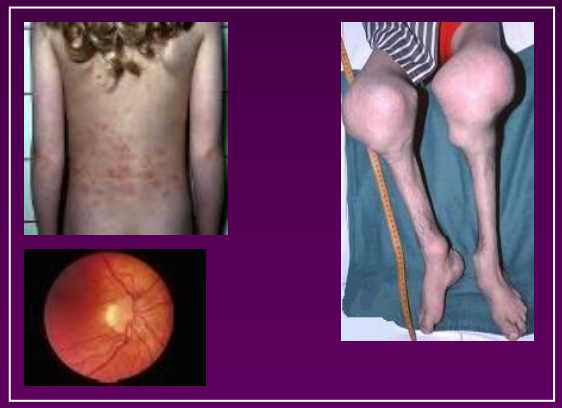
Muckle–Wells syndrome (MWS)

- Rash
- Deafness
- AA amyloidosis (25%)



NOMID/CINCA

- Sporadic
- Chronic meningitis
- Deafness
- PM retardation, bklindness
- Destructive arthropathy



MILD

SEVERE

- **Therapy:** Blockade of IL-1 (anakinra, canakinumab)

Lachman H et al, 2010

AD familiar fevers ADPF

- **F**amilial **C**old **A**utoinflammatory **S**yndrome = **(FCAS)**
  - ***AD, onset before 1 yr***
  - Cold induces non-itchy ***maculopapulous*** rash, in 93% with fever; conjunctivitis (84%), arthralgia (96%)

ADPF

- **Muckle-Wells syndrome (MWS)**
  - Not cold-induced
  - often + progressive senzorineural deafness

- missense ***mutation in CIAS1 gene*** on ch 1, **protein with pyrin domain**

CINCA/NOMID:

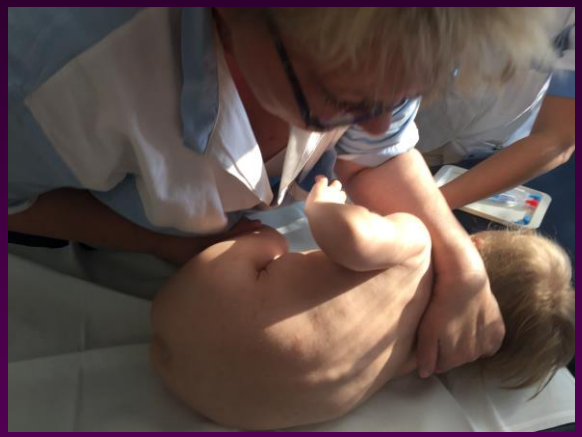
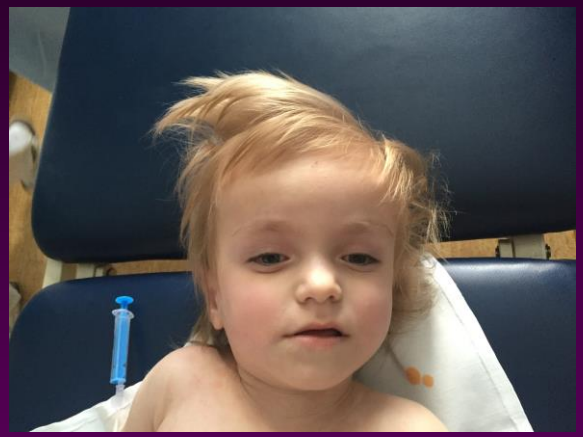
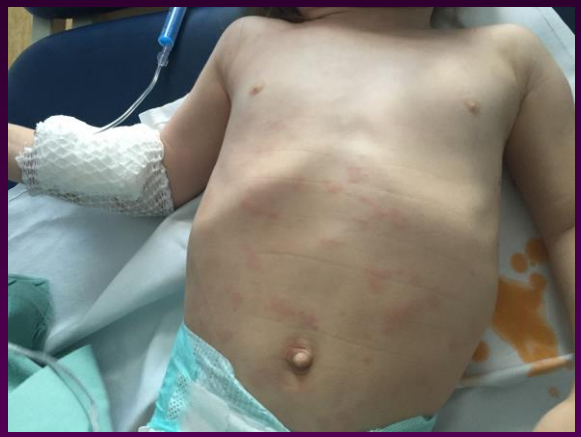
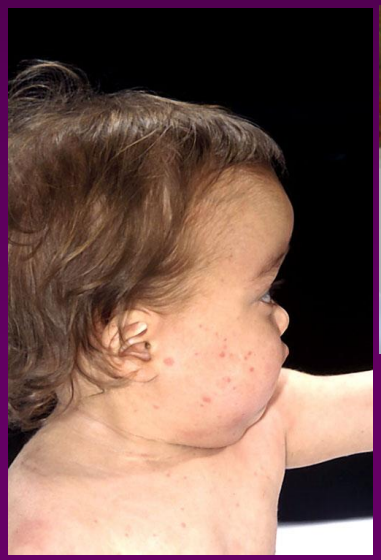
- **C**hronic **I**nfantile **N**eurological **C**utaneous and **A**rticular syndrome

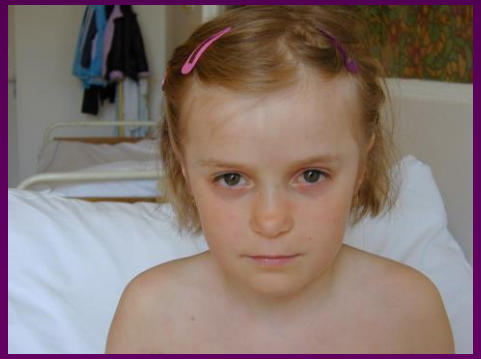
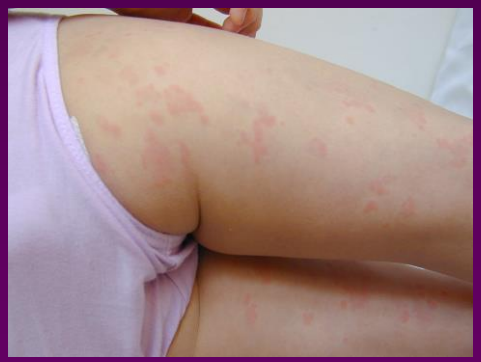
- **N**eonatal **O**nset **M**ulti**I**nflammatory **D**isease

CINCA

- Specific phenotype:
  - Stunted growth
  - Saddfle nose, prominent front
  - Variable CNS disease
  - arthropathy

CINCA / NOMID

Therapy: **IL-1 blockade lifelong**

P ERIODIC

F EVER

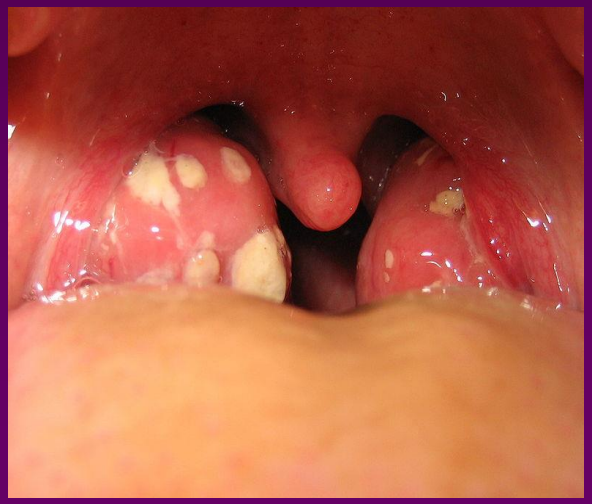
A PHTOUS STOMATITIS

P HARYNGITIS

A DENITIS CERVICAL

Clinical picture

- A thriving, healthy-looking toddler reffered for recurrent unexplained short fever episodes
- History of recurrent antibiotic exposure for tonsillitis and high CRP
- Absence of positive throat cultures and other microbiology
- Antibiotics make no difference

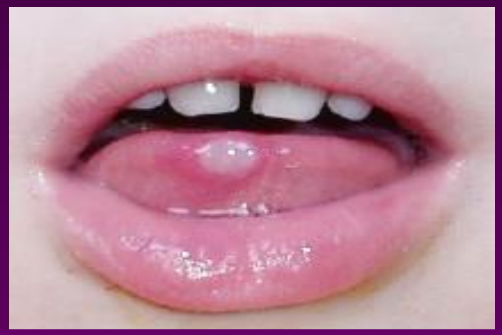


- Regular episodes similar one to another
- Individually unique combination of features
- Absence of usual URTI symptoms (running nose, cough)
- Striking rapid response to single-dose corticosteroid
- Remission after TE

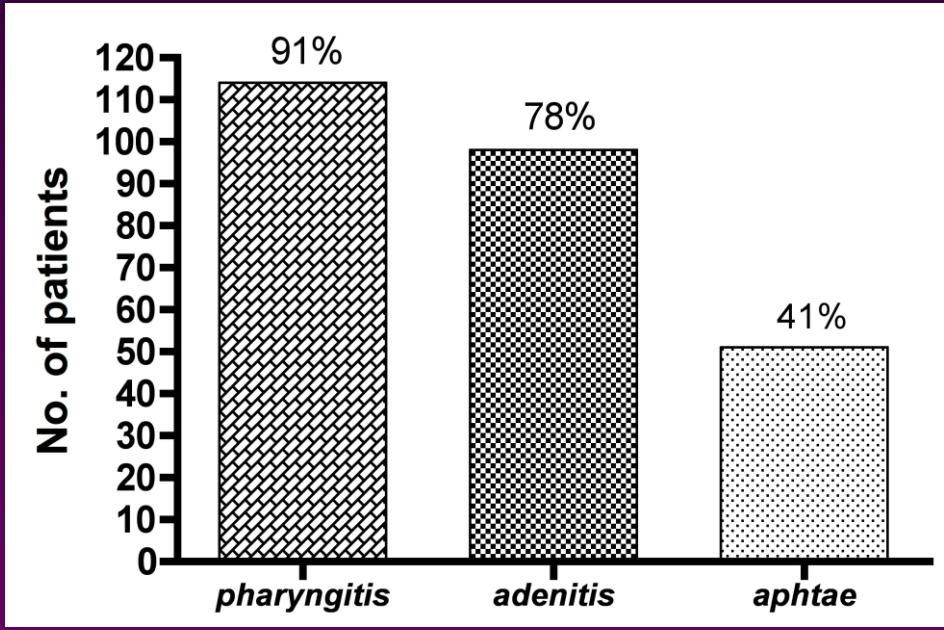
PFAPA Diagnostic criteria

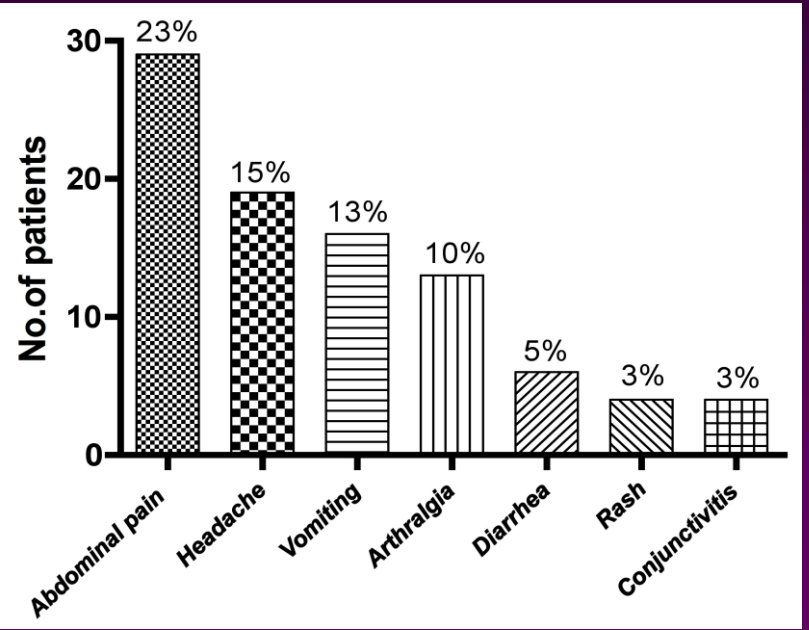
Marshall et al 1989, Thomas KT et al 1999, Hofer M, Gattorno M et al, 2008

- Regularly recurring fevers with an early age of onset (<5 years of age)
- Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs:
  - aphthous stomatitis
  - cervical lymphadenitis
  - pharyngitis
- Exclusion of cyclic neutropenia
- Completely asymptomatic interval between episodes
- Normal growth and development
- (Exclusion of monogenic periodic fevers mainly in patients with GI symptoms and rash)



Clinical symptoms





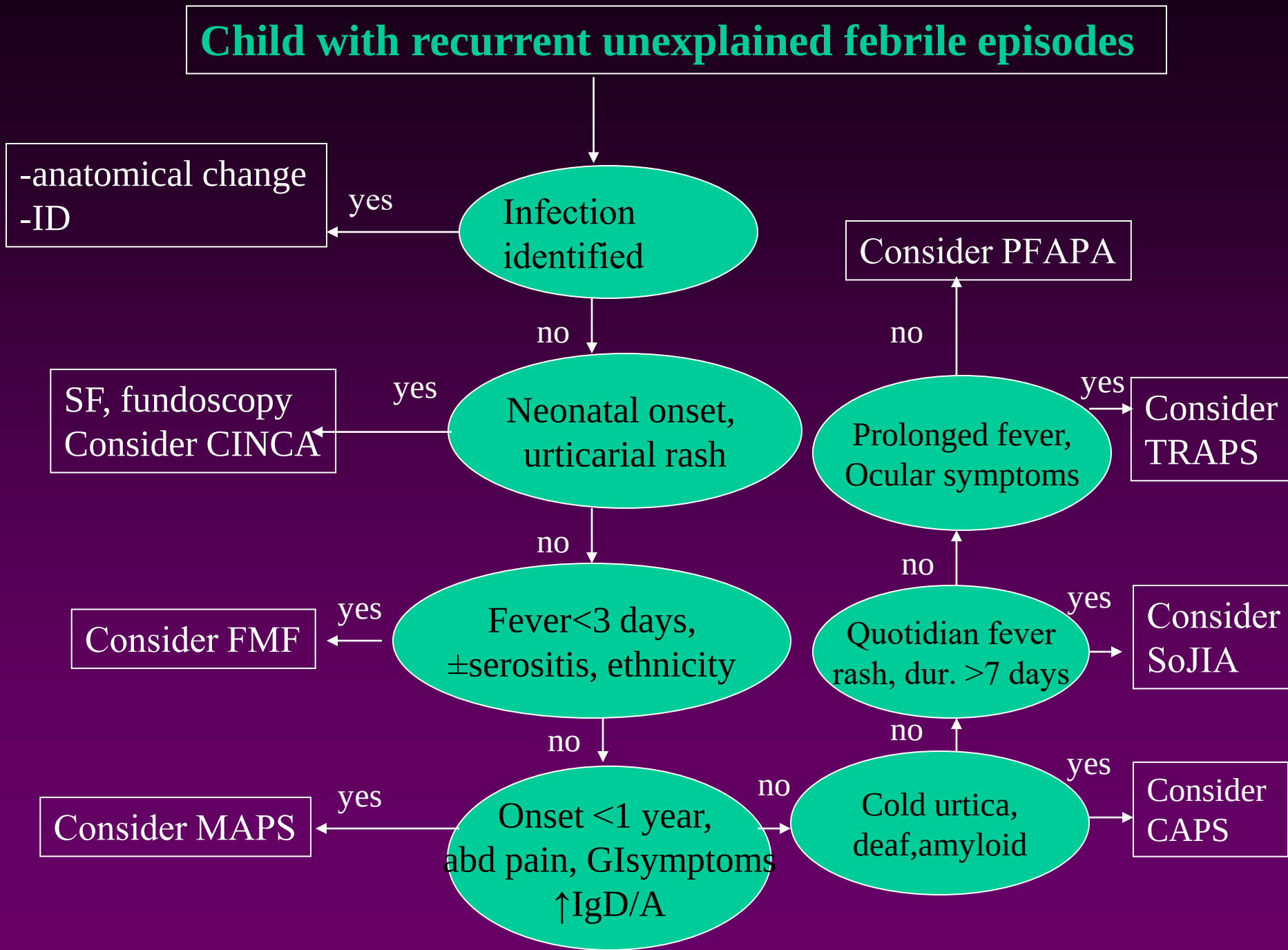
Król P, 2013

Therapeutic algorithms

1. **Watch-and-wait**
   - No specific treatment, symptomatic therapy during febrile attack, avoidance of antibiotics
2. **Prednisone**
   - Single dose 1mg/kg up to 24-48 hours from onset
3. **Second-line treatments**
   - Cimetidin, Colchicin
   - Tonsillectomy

Conclusion

- PFAPA syndrome appears to be the most common periodic fever in Caucasians
- Significant morbidity, psychosocial and monetary impact
- Excellent prognosis
- Early identification and adequate management impact grossly patient/family quality of life
- Patient and primary care physicians education necessary


Child with recurrent unexplained febrile episodes
Infection identified
yes
-anatomical change
-ID
no
Neonatal onset, urticarial rash
yes
SF, fundoscopy
Consider CINCA
no
Fever<3 days, ±serositis, ethnicity
yes
Consider FMF
no
Onset <1 year, abd pain, GIsymptoms ↑IgD/A
yes
Consider MAPS
no
Cold urtica, deaf,amyloid
yes
Consider CAPS
no
Quotidian fever rash, dur. >7 days
yes
Consider SoJIA
no
Prolonged fever, Ocular symptoms
yes
Consider TRAPS
no
Consider PFAPA

Pustular dermatoses

- PAPA
- DIRA
- DITRA
- CAPMS
- SAPHO
- PASH
- PAPASH

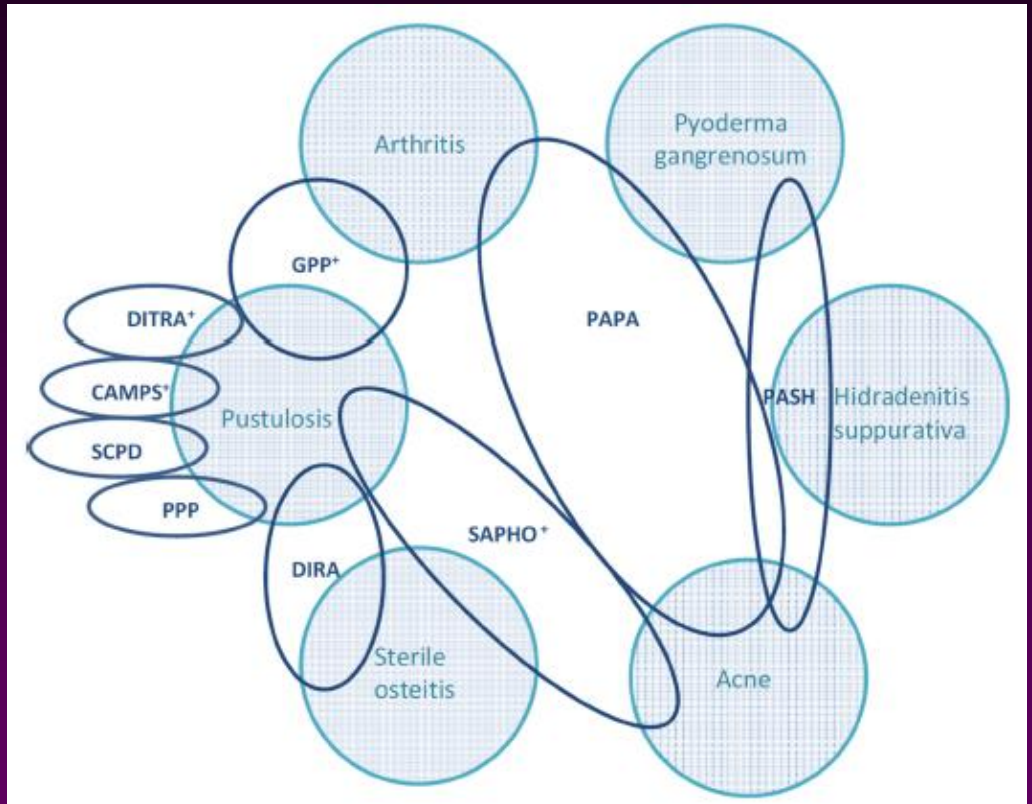


Figure 1. Overlapping clinical features of pustular dermatoses
CARD 14-mediated pustular psoriasis (CAMPS); deficiency of IL-1 receptor antagonist (DIRA); deficiency of the IL-36 receptor antagonist (DITRA); generalized pustular psoriasis (GPP); pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA); pyoderma, acne and suppurative hidradenitis (PASH); palmoplantar pustulosis (PPP); synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO); subcorneal pustular dermatosis (SCPD).

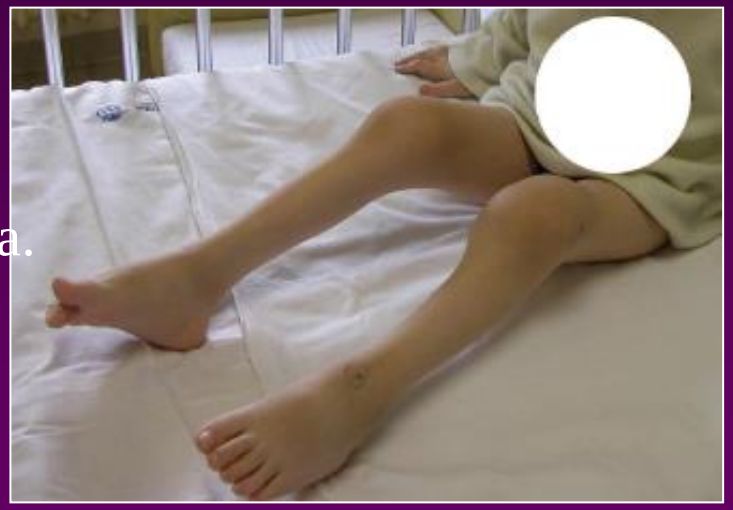
Nalk H et. Al. Autoinflammatory pustuar neutrophilic dise

PAPA syndrome

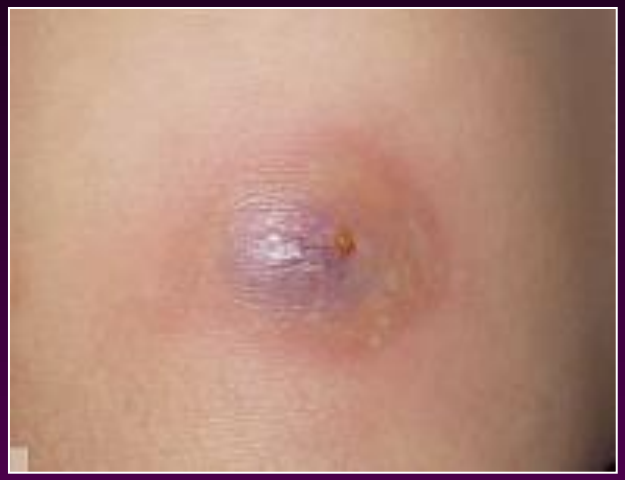
- Sterile destructive arthritis
- Cystic acne
- Pyoderma gangrenosum [1]

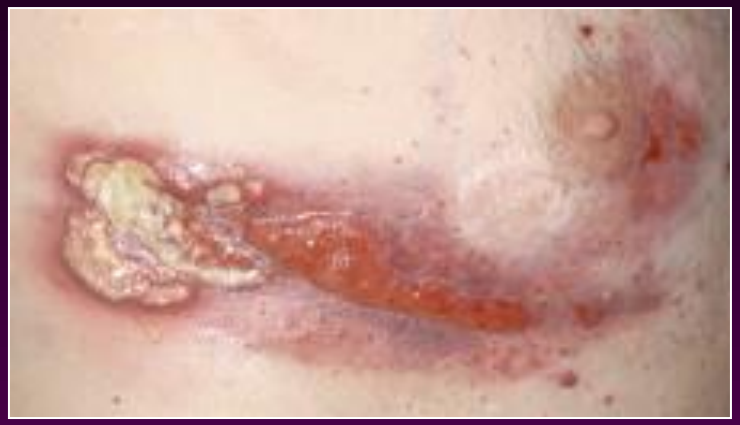
- + Recurrent otitis media, lymphadenopathy, splenomegaly, thrombocytopenia, hypergamaglobulinaemia. hemolytic anemia, T lymphocytosis

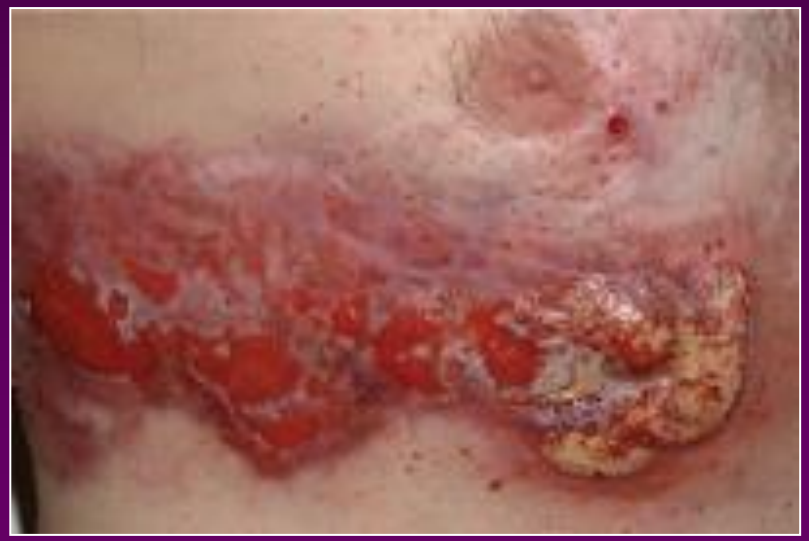
- Therapy – antiTNF[1]

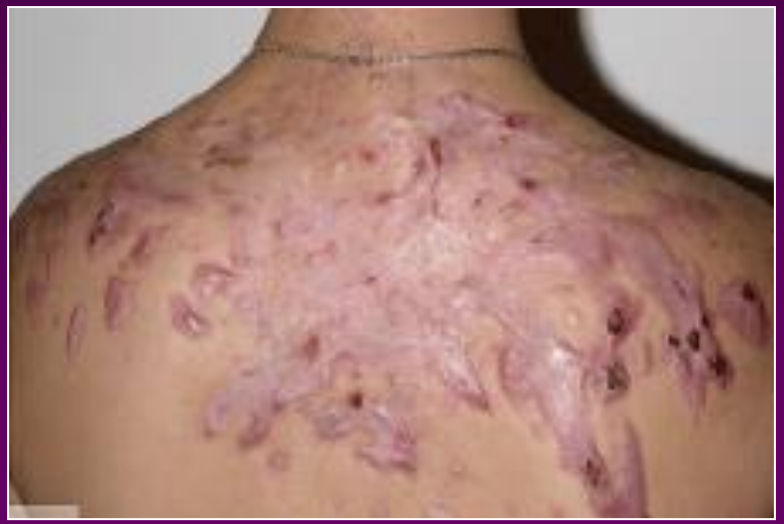


1. Nalk H et. Al. Autoinflammatory pustuar neutrophilic diseases. Dermatol Clin 2013 July; 31(3):405-425
2. Federici S. Et al. The autoinflammatory diseases. Swiss Med Wkly. 2012; 142:w13602





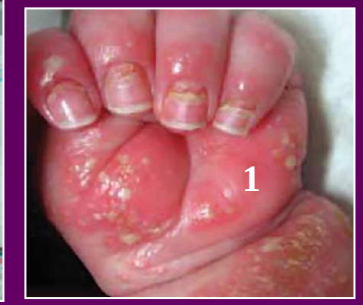


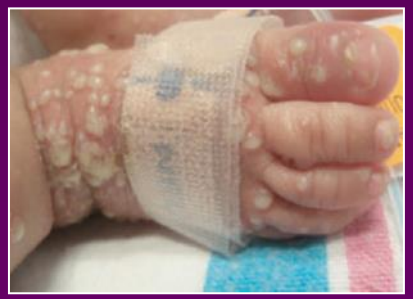


Nguyen T. Et al. Autoinflammatrion: From monogenic syndromes to common skin diseases. J Am Acad Dermatol 2013;68:834-53

DIRA (Deficiency of IL1RAntagonist)

- Episodic multifocal aseptic osteomyelitis, periostitis, pustular dermatitis
- Early onset (by 2 mo)
- No fevers
- ...lung infiltrates, thrombotic episodes, vasculitis
- Therapy – IL-1 blockade [2]



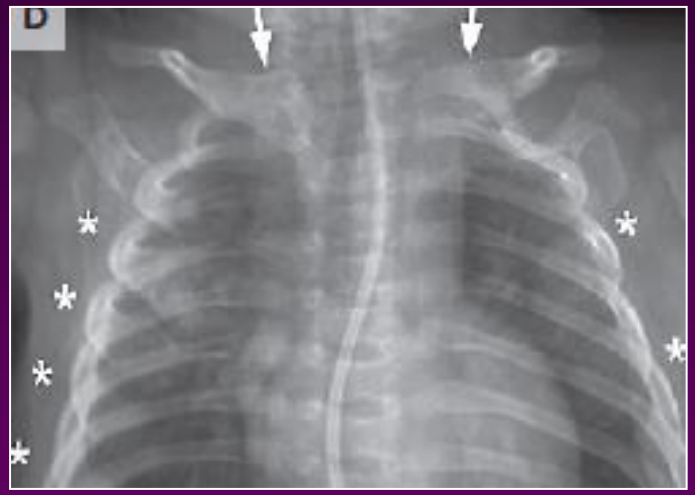


1. Minkis K. Et al. Interleukin 1 receptor antagonist deficiency presening as infantile pustulosis mimicking infantile pustular psoriasis. Arch Dermatol. 2012 June; 148(6):747-752
2. Schnellbacher CH. Et al. Deficiency of interleukin-1 receptor antagonist responsive to anakinra. Pediatr Dermatol. 2013n November; 30(6)

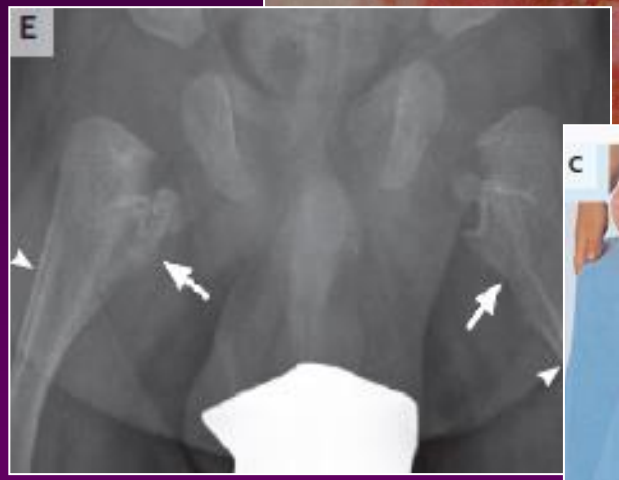
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

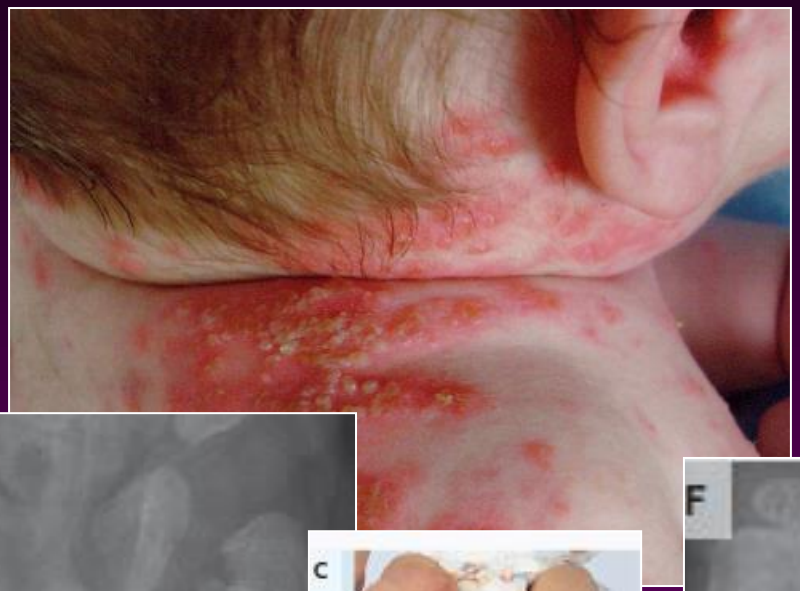
An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist

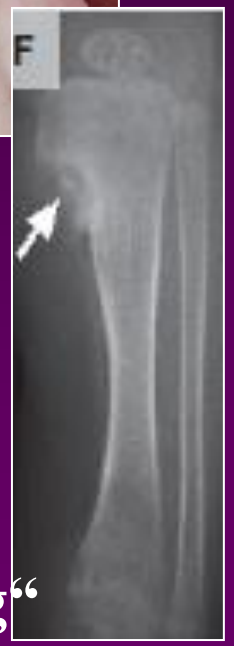


„widening“



„periosteal elevation“



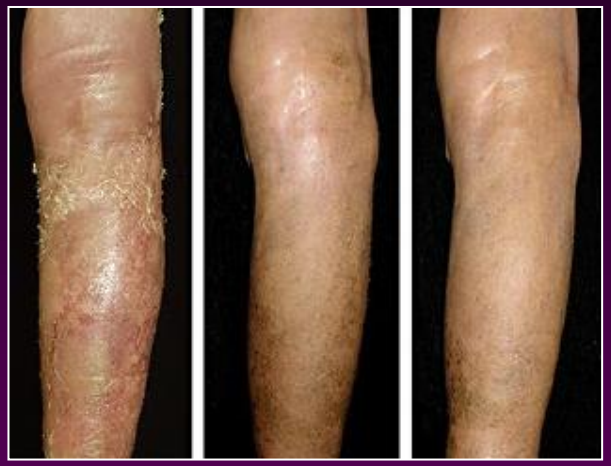


„ballooning“

Aksentijevich I. et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist

DITRA (Deficiency of IL36r antagonist)

- AR
- Generalised pustular psoriasis
- Fever, malaise, weight loss
- No other organ involvement

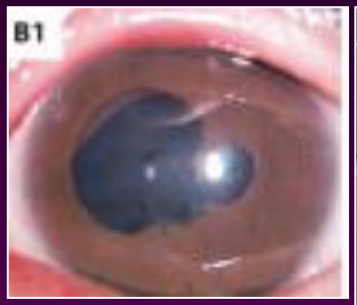


- Therapy – IL-1 blockade

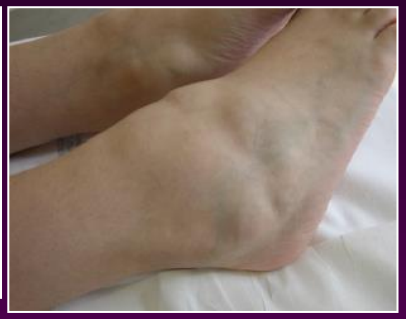
1. Touitou et al. The expanding spectrum of rare monogenic autoinflammatory diseases. Orphanet Journal of Rare Diseases 2013. 8:162
2. Tominaga CH. Et al.A case of ald age-onset generalized pustular psoriasis with a deficiency of IL-36RN (DITRA) treated by granulocyte and monocyte apheresis. Case rep dermatol 2015;7:29-35

Blau syndrom/early onset sarcoidosis

- AD
  - NOD2 gene (CARD15) mutation CH16
  - Hyperactivation of NFkB [1]
- Polyarthritis
- Uveitis granulomatous
- Rash



[2]



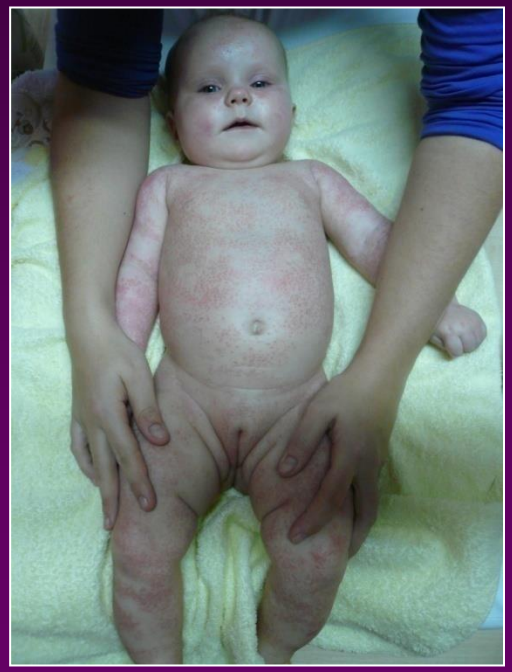
[3]

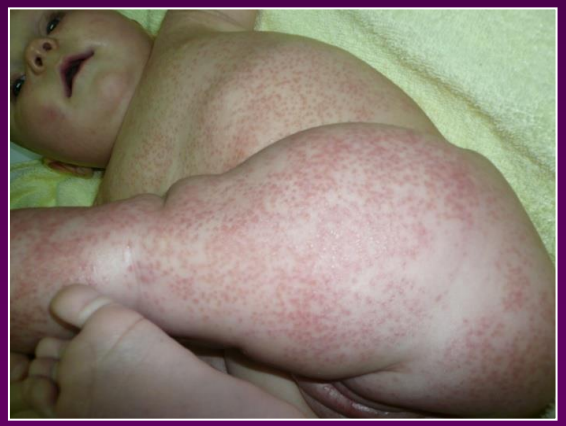
- Variety of other organ involvement – less frequent in children

1. Dávila-Seijo P. Et al. Autoinflammatory syndromes for the dermatologist. Clinics in Dermatology (2014): 32, 488-501
2. Sanchez G et al. Monogenic autoinflammatory diseases: disorders of amplified danger sensing and cytokine dysregulation. Rheum Clin North Am. 2013 November; 39(4):701-734
3. Kanazawa N et al. Autoinflammatory syndromes with a dermatological perspective. J Dermatol 2007 Sep; 34 (9): 601-618

Blau syndrome / EOS

- Skin:
  - lichenoid papules [1]
  - Histology: nekaseifikující granulomy v dermis, panikulitida [1]



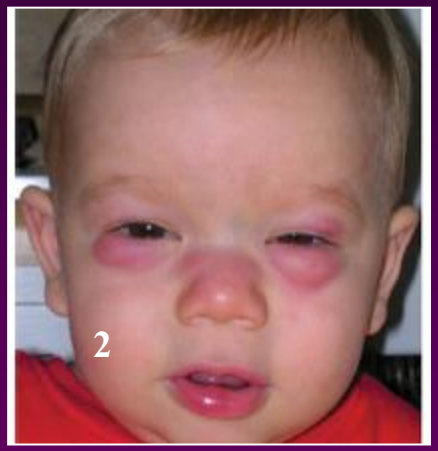


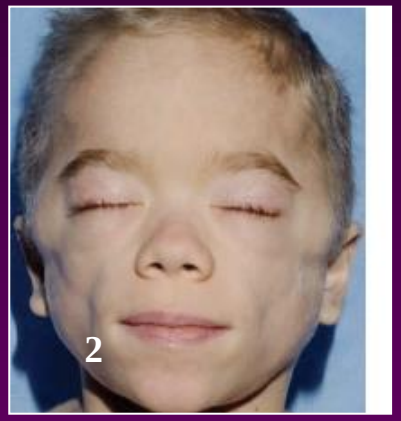
KAZUISTIKA

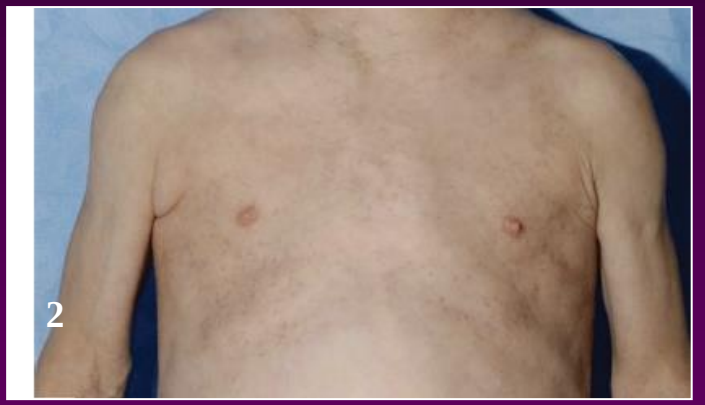
- Generalizovaný exantém od 3 měsíců ve sledování dermatologa (lichenoidní varianta juvenilního xanthogranulomu)
- Později pouze hyperpigmentovaná ložiska
- Od 2 let progredující hybná porucha a kloubní kontraktury
- Diagnóza stanovena až ve 3,5 letech !!!!

Dávila-Seijo P. Et al. Autoinflammatory syndromes for the dermatologist. Clinics in Dermatology (2014): 32, 488-501

CANDLE (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature syndrome)





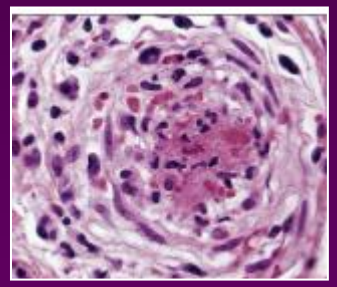


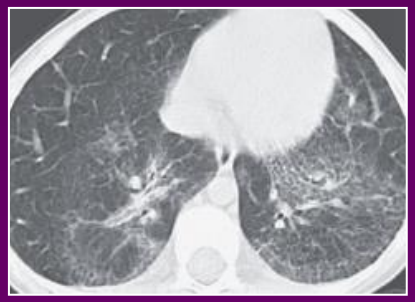
1. Dávila-Seijo P. Et al. Autoinflammatory syndromes for the dermatologist. Clinics in Dermatology (2014): 32, 488-501
2. Nguyen T. Et al. Autoinflammatrion: From monogenic syndromes to common skin diseases. J Am Acad Dermatol 2013;68:834-53

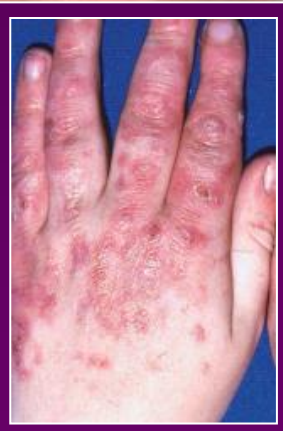
SAVI(STING Associated Vasculopathy with onset in Infancy)

- AD
- Mutation of TMEM73/STING gene
  - Coding for stimulator of interferon genes = interferonopathy[1]
  - Early manifestation
- Cutaneous
- Vasculitic - polyarteritis

- Lung interstitial disease
- Myositis







1. Liu Y. Et al. Activated STING in a vascular and pulmonary synrome. N Engl J Med 371;6