Journal of Pediatric Sciences

Autoinflammatory diseases in children

Donato Rigante

Journal of Pediatric Sciences 2010;4:e56

How to cite this article:

Rigante D. Autoinflammatory diseases in children. Journal of Pediatric Sciences. 2010;4:e56

REVIEW ARTICLE

Autoinflammatory diseases in children

Donato Rigante

Abstract:
Autoinflammatory diseases encompass a growing number of multisystem clinical entities with genetic or acquired defects in the innate immune system. Distinct conditions can be identified in this expanding sphere: familial Mediterranean fever, mevalonate kinase deficiency, tumor necrosis factor receptor-associated periodic syndrome, cryopyrinopathies, idiopathic febrile syndromes, hereditary pyogenic disorders, pediatric granulomatous arthritides, complement dysregulation syndromes and Behçet's disease. All these multifaceted conditions display episodes of seemingly unprovoked inflammation of variable duration and different severity. The main limitation to their better knowledge is the extreme fragmentation of the diagnosed cases that are spread over different centres and countries. The discovery of new molecules involved in recognizing exogenous and endogenous danger signals that lead to inflammatory responses has allowed to understand the pathways of innate immunity and to disclose new therapeutic perspectives for children with autoinflammatory diseases.

Keywords: *autoinflammatory disease, interleukin-1, children*
Received: 05/09/2010; **Accepted:** 06/09/2010

Introduction

Autoinflammatory diseases (AID) are rare inherited and acquired errors of the innate immunity which are depicting an emerging chapter of the postgenomic medicine. Whatever their molecular mechanism, AID are caused by a dysregulation of the secretion of interleukin-1 (IL-1), a potent proinflammatory cytokine causing fever, acute phase protein oversecretion and, due to the ubiquity of its receptor, infiltration with polynuclear cells in many targeted tissues and multi-district inflammation [1].

These patients experience seemingly unprovoked recurrent fevers variably associated with systemic inflammation with a variable modality of recurrence: though clinically similar to various infectious and rheumatologic diseases, neither pathogen agents, nor specific autoantibodies can be identified [2]. The discovery of the gene responsible for *familial Mediterranean fever* was a crucial step in the understanding of AID, but the real achievement was attained with the identification of cryopyrin, a protein belonging to a multi-molecular complex into leukocytes, named "inflammasome", which mediates the activation of inflammatory caspases and controls directly the maturation of primary mediators of apoptosis and cytokines, such as IL-1. Mutations in the cryopyrin gene result in upregulated secretion of IL-1 and cause a spectrum of diseases called *cryopyrin-associated periodic syndromes* [3].

Aim of this review article is to focus on the essential clinical data of AID. A general classification of the inherited AID is proposed in the Table 1.

Donato Rigante, MD

Department of Pediatric Sciences, Università Cattolica Sacro Cuore, Rome, Italy

Corresponding Author: Donato Rigante, MD

Department of Pediatric Sciences, Università Cattolica Sacro Cuore, Largo A. Gemelli, 8 – 00168, Rome Italy
Phone: +39.06.30154290
Fax : +39.06.3383211
E-mail: drigante@rm.unicatt.it

Table 1. Classification of the autoinflammatory diseases.

Monogenic **(gene involved, protein encoded)**
Familial Mediterranean fever (*MEFV*, pyrin)
Mevalonate kinase deficiency (*MVK*, mevalonate kinase)
Tumor necrosis factor receptor-associated periodic syndrome (*TNFRSF1A*, p55 receptor of tumor necrosis factor)
Cryopyrin-associated periodic syndromes (*NLRP3*, cryopyrin)
NALP12 related recurrent fever (*NALP12*, NALP12)
Interleukin-1 receptor antagonist deficiency (*IL1RN*, interleukin-1 receptor antagonist)
PAPA syndrome (*PSTPIP1*, CD_2 antigen-binding protein 1)
Majeed syndrome (*LPIN2*, lipin 2)
Blau syndrome (*NOD2/CARD15*, NOD2/CARD15)
Hereditary angioedema (*C1NH*, C_1-esterase inhibitor)
Recurrent hydatidiform mole (*NLRP7*, NLRP7)
Polygenic
Systemic-onset juvenile idiopathic arthritis
HLA-B27 positive spondyloarthropathies
Behçet's disease
Crohn's disease
Gout and pseudogout
Castleman's disease
Type 2 diabetes

Familial Mediterranean fever

Familial Mediterranean fever (FMF, OMIM 249100) is the most common among AID and is caused by recessively inherited mutations within the *MEFV* gene (from *ME*diterranean *Fe*v*er*), which codes for pyrin (named also "marenostrin", by the Latin name of the Mediterranean sea), a protein which mainly inhibits IL-1 production by interfering with the inflammasome [4].

Almost 140.000 patients are estimated worldwide, but FMF has a peculiar ethnic distribution, as it occurs predominantly in populations living around the Mediterranean basin: Armenians (the carrier rate is 1:3), Turks, Arabs, North-Africans, Sephardic Jews and Italians. Four founder mutations in exon 10 (M694V, M680I, M694I and V726A) predominate in these patients [5].

The disease is characterized by self-limited inflammatory attacks involving serosal and synovial membranes, which start before 10 years in 80% of cases with persistent subclinical inflammation in the interfebrile periods. The attack consists of fever and serositis or acute arthritis with effusions of large joints, but patients become completely symptom-free between attacks [6]. Table 2 lists the most frequent clinical signs of FMF and their percentages in children with a confirmed FMF. Attacks of FMF occur irregularly: their frequency varies considerably from weekly bouts to once every 3 to 4 months. Each attack lasts 12 hours-3 days and can be triggered by stress, menses, exercise or infections. Attacks are typically associated with increased inflammatory markers (erythrosedimentation rate, C-reactive protein, serum amyloid-A, fibrinogen) and sometimes increased IgA and IgD [7].

Erysipeloid erythema, mostly localized along the extensor surface of the lower extremities, might appear in 20-40% of cases and is considered to be FMF-specific. Several newly described manifestations such as self-limited orchitis, vasculitis and severe protracted febrile myalgia have enriched the clinical spectrum of FMF [8]. The most serious long-term complication of FMF is amyloid deposition, primarily in the kidney, which occurred in 60% of patients in the pre-colchicine era, though a threefold higher risk of developing amyloidosis is conferred by living in Armenia, Turkey and Arab countries [9]. Several studies comparing phenotype manifestations and genotype analysis have disclosed that FMF patients homozygous for the M694V mutation have a more severe disease with an earlier onset, more frequent attacks, relevant joint involvement, require higher doses of colchicine and are more prone to develop amyloidosis [10].

Table 2. Clinical signs of acute attacks of familial Mediterranean fever and their overall percentage in the pediatric population (obtained from different unselected reports)**.**	
• Fever (lasting for an overall period of 1-4 days)	96%
• Peritonitis	91%
• Pleurisy	57%
• Arthralgias or arthritides	45%
• Erysipelas-like lesions on the skin of foot/ankle	13%
• Recurrent pericarditis	0.7-1.4%

Diagnosis of FMF remains clinical and strictly combined with ethnicity, family history and response to colchicine, since a specific laboratory test is not yet available. Several sets of criteria have been proposed through the years, though few were based on statistical evaluation studies. Table 3 defines the Tel-Hashomer diagnostic criteria, which are mostly used, and the recently reported criteria by Yalçinkaya and Özen for the diagnosis of FMF in childhood[11,12] In addition, genetic diagnosis of FMF is confirmed by the presence of two mutations in the *MEFV* gene, even if the discovery of only one mutation in patients with a haunting FMF phenotype might suggest that FMF can be viewed as a

Table 3. Tel-Hashomer criteria for the diagnosis of familial Mediterranean fever.

(diagnosis is *definite* if 2 major criteria or 1 major and 2 minor criteria are satisfied; diagnosis is *probable* if 1 major and 1 minor criterium are satisfied)

Major criteria

1. Recurrent febrile episodes associated with peritonitis, pleuritis or synovitis
2. Amyloidosis of AA-type without a predisposing disease
3. Favorable response to daily colchicine administration

Minor criteria

1. Recurrent febrile episodes
2. Erysipelas - like erythema
3. Positive history of familial Mediterranean fever in a first-degree relative

Yalçinkaya and Özen set of criteria for the diagnosis of familial Mediterranean fever in childhood.

(diagnosis is *definite* if 2 or more criteria are satisfied)

1. Fever (axillary temperature >38°C, duration of 6-72 hours, ≥3 attacks)
2. Abdominal pain (duration of 6-72 hours, ≥3 attacks)
3. Chest pain (duration of 6-72 hours, ≥3 attacks)
4. Oligoarthritis (duration of 6-72 hours, ≥3 attacks)
5. Family history of familial Mediterranean fever

dominant condition with low penetrance and variable disease expression [13].

Hippocrates introduced colchic extracts in the management of acute flares of gout, the main rheumatic disease until the late 18th century, but Stephen Goldfinger discovered colchicine as an effective drug for FMF in 1972. Colchicine has a purely prophylactic goal, in fact dose escalation during an acute attack is not effective: it reduces attack frequency and their duration in 60% of patients in a single daily dose ranging from 0.5 to 2 mg/day (the dosage is 0.25 mg/day in children aged 1-2 years, 0.5 mg/day for those aged 3-6 years and then 1 mg/day). These low daily doses required for FMF management are generally well tolerated [14]. Colchicine effectiveness exists also in the prevention of amyloidosis, though this cannot be obtained in the totality of patients. In cases of colchicine intolerance or partial efficacy, another possible therapeutic option is the IL-1 receptor antagonist anakinra (at the dose of 1 mg/kg/day) by subcutaneous injection [15].

Mevalonate kinase deficiency

Mevalonate kinase deficiency, better known as *hyper-IgD syndrome* (HIDS, OMIM 260920), is caused by mutations in the *MVK* gene, transmitted with an autosomal recessive inheritance, which codes for mevalonate kinase, the key-enzyme in cholesterol metabolic pathway, with an activity reduced to 5-10% of normal, though the enzymatic abnormality is not directly involved in the biologic process of the disease [16].

Most patients with HIDS are of Western European ancestry (particularly Danish and French), suggesting a founder gene effect in these populations. The disease usually starts in infancy or early childhood: typical flares are irregular, last for 3-7 days, have an abrupt onset and are spontaneous or induced by vaccinations, infections and menses, being staggered by asymptomatic periods of several weeks [17]. In each attack children present high fever, cephalalgia, painful cervical lymphadenopathy, splenomegaly, severe abdominal pain, diarrhoea or vomiting, arthralgias, oral or vaginal ulcers and variable rash: marked lymph node enlargement and splenomegaly help to distinguish clinically HIDS from FMF. Table 4 lists the most frequent HIDS clinical signs during acute flares. In the majority of cases all the recurring symptoms tend to decrease over time.

Table 4. Clinical signs during flares of mevalonate kinase deficiency (hyper-IgD syndrome).

• Periodic high fever (lasting 3-7 days), spontaneous or exerted by vaccinations
• Cephalalgia and irritability
• Latero-cervical lymph node enlargement
• Splenomegaly
• Arthralgia or non erosive arthritis
• Oral and genital ulcers
• Maculo-papular, nodular, urticarial, nummular or vasculitic rash
• Recurrent uveitis

In contrast to other AID, HIDS is rarely complicated by amyloidosis, which occurs in a small percentage of patients [18]. Typical of HIDS is the increased level of serum IgD (with values higher than 100 IU/ml) both during fever episodes and on basal conditions, often in association with high levels of IgA. The polyclonal elevation of serum IgD is found mostly in patients older than 3 years, but this is not specific of HIDS.

Moreover in 20% of patients there is no increase of serum IgD level. Quite suggesting is the increase in urinary excretion of mevalonic acid, which can be demonstrated during HIDS flares and is of outstanding priority for the diagnostic confirmation [19].

No evidence-based guidelines exist for treatment of HIDS and usually colchicine, corticosteroids and non-steroidal anti-inflammatory drugs are not effective. Various reports have defined the potential benefit of etanercept (0,8 mg/kg/week by subcutaneous injection), simvastatine (an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, an enzyme preceding mevalonate kinase in the cholesterol biosynthetic pathway, at the dose of 80 mg/day) and anakinra (at the dosage of 1 mg/kg/day

subcutaneously administered daily or on-demand) [20-23].

A constant increased urinary excretion of mevalonic acid can be found in children with *mevalonic aciduria* (OMIM 610377), an inborn error of cholesterol and non-sterol isoprene biosynthesis, which is caused by the absolute deficiency of mevalonate kinase and is characterized by psychomotor retardation, microcephaly, cerebellar atrophy, ataxia, cataract, retinal dystrophy, dysmorphic features, failure to thrive and periodic fever with no increase of serum IgD [24].

Tumor necrosis factor receptor-associated periodic fever syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS, OMIM 142680) is widely recognized in various ethnic groups, though it was firstly described as "familial Hibernian fever" in an Irish family with symptoms similar to FMF.

However, unlike FMF, the disease exhibits a dominant inheritance pattern and a clinical response to corticosteroids [25].

It is caused by missense mutations in the *TNFRSF1A* gene, encoding for the 55kD tumor necrosis factor receptor (TNFR): many of these mutations disrupt one of the highly conserved cysteine residues involved in extracellular disulfide bonds of the TNFR and various mechanisms might lead to the proinflammatory state of the syndrome, as decreased ligand binding, defective apoptotic signalling or TNFR trafficking defects [26].

The age of onset can be variable (from infancy to over 50 years of age) and the clinical picture is characterized by febrile episodes lasting 3-4 weeks, recurring at least 2-6 times each year, combined with abdominal pain variably associated with diarrhea, myalgia, arthralgia, ocular symptoms and skin lesions. The most frequently observed skin signs are painful serpiginous migratory erythematous plaques. Typical are centrifugal muscle edema with chronic fasciitis and the characteristic periorbital edema with painful conjunctivitis [27]. Features of TRAPS inflammatory episodes are listed in the Table 5.

The most discriminatory laboratory finding in patients with decreased receptor shedding is low serum level of the soluble TNFR (<1 ng/ml) during quiescent periods. Serum IgD levels may result elevated (but less than 100 IU/ml), nevertheless genetic testing is central to the diagnosis of TRAPS. Prognosis is determined mainly by the risk of amyloidosis, which can be observed in 15% of patients [28].

Table 5. Clinical signs during flares of tumor necrosis factor receptor-associated periodic fever syndrome.

• Periodic fever (lasting many days or even 3-4 weeks)
• Abdominal pain
• Arthromyalgia, tenosynovitis and fasciitis
• Lymph node enlargement
• Erythematous migratory rash and cellulitis-like plaques
• Periorbital edema and conjunctivitis
• Scrotal pain

Treatment with non-steroidal anti-inflammatory drugs and glucocorticoids alleviate the inflammatory symptoms, but do not affect the frequency of attacks. Anti-tumor necrosis factor therapy has been proposed due to the observation that TRAPS molecular defect is sometimes associated with an impaired TFNR shedding from cell membranes: several studies have shown that etanercept, a dimeric recombinant fusion protein consisting of two copies of the soluble extracellular ligand-binding domain of the receptor linked by the Fc fragment of IgG_1 decreases the frequency, intensity and duration of inflammatory episodes (at the dosage of 0.8 mg/kg/week by subcutaneous injection) and has been used to improve renal AA amyloidosis in patients with amyloidotic nephrotic syndrome [29]. Treatment with the IL-1 receptor antagonist anakinra, at the dose of 1 mg/kg/day by subcutaneous injection, has also shown clinical benefit in some patients [30].

Cryopyrin-associated periodic syndromes

The cryopyrin-associated periodic syndromes (CAPS)

Table 6. Summary of the general clinical signs of cryopyrin-associated periodic syndromes.

	Familial cold urticarial syndrome	*Muckle-Wells syndrome*	*CINCA syndrome*
Onset age	Infancy	Infancy-adolescence	Neonatal period
Skin manifestations	Cold-induced urticaria-like rash	Evanescent urticaria-like rash	Widespread polymorphous urticaria-like rash
Audiologic study	Normal	Sensorineural hypoacusia (for high-pitched sounds)	Sensorineural deafness
Ocular signs	Conjunctivitis	Conjunctivitis	Chronic papilledema, optic nerve atrophy, visual loss
Musculo-skeletal symptoms	Arthralgia or joint stiffness	Lifelong arthralgias, non-erosive polyarthritis	Deforming osteo-arthropathy of large joints (with premature kneecap ossification), digital clubbing
Systemic signs	Fever spikes of short duration (after cold exposure), thirst, profuse sweating (after cold exposure)	Fever, drowsiness	Recurrent fever with shivers, chronic aseptic meningitis
Dysmorphic features	-	-	Frontal bossing, saddle nose, midface hypoplasia
Long-term consequences	Fatigue, amyloidosis	Amyloidosis	Bone and joint deformities, central nervous system damage, amyloidosis

are a group of rare autosomal-dominantly inherited AID, mostly reported in the Caucasian population, with many symptoms in common, starting from infancy and often recurring on a daily basis, which encompass familial cold autoinflammatory syndrome (FCAS, OMIM 120100), Muckle-Wells syndrome as chronic infantile neurologic cutaneous articular syndrome or CINCA syndrome (OMIM 607115). system inflammatory disorder (NOMID), also known(MWS, OMIM 191900) and neonatal onset multi- These diseases share mutations of the same gene, called *NLRP3*, consisting of 9 exons and encoding for the cryopyrin protein, which is a part of the inflammasome, known to recognize a range of exogenous and endogenous stimuli. The three clinical entities belonging to this group represent a phenotypic "continuum" sharing *NLRP3* mutations as a common molecular basis. However, at least 40% of CINCA patients do not have any *NLRP3* mutation. [31]. Table 6 lists the general features of CAPS.

The first manifestations of FCAS and MWS show a significant overlap, including overwhelming fatigue, fever of several hours, variable urticaria-like rash, inflammation of eyes and joints. FCAS was first described in a young woman with a lifelong history

of urticarial eruption that occurred after 30 minutes of cold exposure and was accompanied by fever, conjunctivitis and self-limited joint stiffness. Fever, urticarial rash and arthritides are almost continuous in MWS and someway related to stress, infections and exercise [32]. CINCA syndrome is the most severe expression of *NLRP3* mutations: patients present a chronic rash at birth and develop a characteristic hypertrophic arthropathy involving both knees with premature patellar ossification. Central nervous system manifestations of CINCA syndrome include chronic aseptic meningitis, ventriculomegaly, chronic papilledema and optic nerve atrophy. Hearing loss is described in 60% of patients with MWS and in most patients with CINCA syndrome, while the potential development of renal amyloidosis has been observed in 25% of MWS patients and in 20% of CINCA ones [33].

Treatment has been quite disappointing until the impressive clinical results with IL-1 blocking agents in patients with FCAS, MWS and CINCA syndrome were published, linking these diseases to IL-1 overproduction and instituting IL-1 blockade as the treatment of choice [34]. Anakinra, the human recombinant form of IL-1 receptor antagonist, has been the first biologic designed for the selective blockade of IL-1 in CAPS. However, its short plasma half life requires a daily subcutaneous administration (at the dose of 1-3 mg/kg/day) by subcutaneous injection (only some patients with MWS might tolerate anakinra administrations at least every 2 days, remaining in ongoing remission) [35]. Two more recent IL-1 antagonists, rilonacept (a dimeric fusion protein, designed for subcutaneous administration at weekly intervals) and canakinumab (a fully human monoclonal anti-IL-1 antibody, designed for subcutaneous administration once every 8 weeks), are promising agents with a highly favourable safety profile [36,37]. No data concerning vaccinations while on IL-1 antagonists are available, though all vaccinations are recommended to be completed before biologic treatment commences.

NALP12-related recurrent fever

NALP proteins, also known as NLRPs, belonging to the NLR protein family, have rapidly gained prominence as important regulators of inflammatory responses to pathogens. NALP12-related recurrent fever is a rare genetic disease caused by *NALP12* mutations with autosomal dominant inheritance: patients suffer from recurrent bouts of fever (lasting 5-10 days) accompanied by headache, joint symptoms and skin rash triggered by cold exposure, but very few patients have been recognized [38]. There is no effective preventive treatment for attacks and biologic therapies are currently under investigation.

Idiopathic febrile syndromes

Some febrile diseases remain without a definite cause also in the pediatric age and some of these can be considered AID. In particular, **systemic-onset juvenile idiopathic arthritis** (So-JIA, OMIM 604302), corresponding to 10-20% of all forms of childhood arthritides, shows a striking similarity with CINCA syndrome and *Still's disease* and this has led to speculation over whether So-JIA should be reclassified as an autoinflammatory, rather than an autoimmune disease. Children suffering from So-JIA present with high fever spikes followed by arthritis and at least one among erythematous rash, diffuse lymph node enlargement, serositis and hepato-splenomegaly, though diagnosis derives from the exclusion of other infectious and neoplastic causes of fever. Table 7 shows the clinical definition of So-JIA according to the Edmonton 2001 revised criteria, endorsed by the International League of Associations for Rheumatology [39]. Its treatment includes non-steroidal anti-inflammatory drugs and corticosteroids, which sometimes appear ineffective. Recent in-vitro and clinical studies advocate a key-role of IL-1 as a primum movens of So-JIA and the clinical efficacy shown with anakinra (at the dose of 2 mg/kg/day) in subsets of patients resistant to conventional treatment has demonstrated the potential usefulness of IL-1 blockade in this disorder, even if very few long-term outcomes are available [40].

A rather underdiagnosed disease of the pediatric age is **PFAPA syndrome** (standing for "periodic fever /aphthous stomatitis/pharyngitis/cervical adenitis" syndrome), which is characterized by periodic fever recurring at predictable rhythms every 4-6 weeks with at least one among aphthous stomatitis, pharyngitis and/or cervical lymph node enlargement, beginning before 5 years of age, but without any evidence of upper airways infections [41]. This condition is often confused with hereditary AID, requiring that negative genotype studies are performed to confirm its diagnosis. An international registry of ascertained cases of PFAPA syndrome is

Table 7. Clinical definition of systemic-onset juvenile idiopathic arthritis (According to the Edmonton 2001 revised classification criteria by the International League of Associations for Rheumatology).

Cardinal signs	*Systemic signs*	*Exclusion criteria*
Fever (with a duration of at least 2 weeks) in association with arthritis (in one or more joints) with at least one or more systemic signs	a) non-fixed evanescent erythematous rash b) generalized lymph node enlargement c) hepatomegaly and/or splenomegaly d) serositis	- psoriasis or history of psoriasis in the patient or in a first-degree relative, - arthritis in a HLA-B27 positive male beginning over 6 years of age, -ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, acute anterior uveitis or history of one of these disorders in a first-degree relative, - rheumatoid factor positivity on at least 2 occasions at least 3 months apart

Table 8. Cardinal and systemic signs of PFAPA syndrome.

Cardinal signs	*Systemic signs*	*Exclusion criteria*
- Periodically recurring fever (with "clockwork" periodicity at intervals of about 4-6 weeks) - Child's complete wellness between febrile bouts (with normal growth) - Association with at least one systemic sign	a) aphthous stomatitis b) pharyngitis c) cervical lymph node enlargement	Signs of upper respiratory airway infection

in progress to describe the clinical presentation symptoms and evaluate the pertinence of the mostly used set of diagnostic criteria. Differential diagnosis must include primary immunodeficiency disorders such as deficiency of total immunoglobulins and its subclasses, T lymphocyte dysfunctions, infectious or haematological diseases, but also FMF, HIDS and *cyclic neutropenia* [42]. The original definition criteria of PFAPA syndrome are listed in the Table 8. Febrile bouts of PFAPA syndrome may be deleted with the administration of corticosteroids (1-2 mg/kg/dose of prednisone) on the day of fever onset

Table 9. General details of hereditary pyogenic disorders.

	Gene	*Inheritance*	*Clinical signs*
PAPA syndrome	*PSTPIP1*	Autosomal dominant	Sterile pyogenic oligoarthritis, pyoderma gangrenosum, cystic acne
Majeed syndrome	*LPIN2*	Autosomal recessive	Multifocal osteomyelitis, dyserythropoietic anemia, diffuse neutrophilic dermatosis
Interleukin-1 receptor antagonist deficiency	*IL1RN*	Autosomal recessive	Multifocal osteomyelitis, pustular skin eruption

and are mitigated for frequency by tonsillectomy [43].

Hereditary pyogenic disorders

Among hereditary pyogenic disorders (listed in the Table 9) **PAPA syndrome** (OMIM 614416) stands out for the combination of self-limited sterile pyogenic arthritides, pyoderma gangrenosum and cystic acne. This rare disease is transmitted with autosomal dominant inheritance and the involved gene, named *PTSTPIP1*, encodes the proline/serine/threonine phosphatase-interacting protein 1 (named also CD2 antigen-binding protein which has the power of inhibiting pyrin-mediated inflammatory signals [44]. There are reports describing treatment of PAPA syndrome with corticosteroids, anakinra or tumor necrosis factor blocking agents, as infliximab [45].

Another disease characterized by recurrent attacks of fever starting in infancy or early childhood with multifocal osteomyelitis, congenital dys-erythropoietic anemia and chronic dermatosis is **Majeed syndrome** (OMIM 609628), which has been reported only in Jordan. This peculiar diagnosis relies on clinical findings and molecular genetic testing of *LPIN2*, the gene involved, whilst treatment is empiric and based on non-steroidal anti-inflammatory drugs, corticosteroids and physical therapy [46].

Recently, the **deficiency of the interleukin-1 receptor antagonist** (DIRA, OMIM 612852) has been reported by Ivona Aksentijevich in 9 neonates with multifocal osteomyelitis and pustular skin eruption: DIRA appears as an autosomal recessive 1), autoinflammatory syndrome, due to homozygous mutations in the *IL1RN* gene on chromosome 2q, which stop the secretion of the IL-1 receptor antagonist, a molecule inhibiting the proinflammatory cytokines IL-1α and β in normal conditions. The absence of this physiologic antagonist causes an unopposed IL-1 activity and uncontrolled inflammatory responses, mostly localized in bone and skin [47].

The contribution of genetics is unclear for other pyogenic disorders as *SAPHO syndrome*, characterized by the combination of "synovitis, acne, pustulosis, hyperostosis and osteitis", and its pediatric variant called *CRMO syndrome* (OMIM 259680), which refers to sporadic forms of "chronic recurrent multifocal osteomyelitis" affecting long

Table 10. General details of pediatric granulomatous arthritides.

	Form	**Clinical signs**
Blau sindrome (Juvenile systemic granulomatosis)	Familial (autosomal dominant inheritance related to the *NOD2/CARD15* gene)	Recurrent granulomatous polyarthritis, uveitis, ichthyosiform rash
Early-onset sarcoidosis	Sporadic	Granulomatous inflammation of lung, lymph node and eye

bones in children without any infectious etiology [48].

Pediatric granulomatous arthritides

The general details of pediatric granulomatous arthritides are listed in Table 10: the most representative disease of the group is **Blau syndrome** (BS, OMIM 186580), also known as "juvenile systemic granulomatosis". This is a rare autosomal dominant disease related to the *NOD2/CARD15* gene localized on chromosome 16q12, which causes abnormal function of NOD2/CARD15, a member of the NOD-like receptor family of intracellular proteins, expressed in monocytes and chondrocytes. The condition is characterized by recurrent non-caseating granulomatous polyarthritis, uveitis and brown-coloured scaly rash. Treatment of BS is based on corticosteroids, immunosuppressant drugs and biologics (infliximab or anakinra) [49]. This familial form of granulomatous disease needs to be differentiated from the **early-onset sarcoidosis** (OMIM 609464), a sporadic multiorganic disease, histologically defined by non-caseating epithelioid granulomata and by the clinical triad of lung, lymph node and eye involvement [50]. Autosomal dominant missense mutations in the NACHT domain of the *NOD2/CARD15* gene, localized on chromosome 16, are the cause of BS, whilst variants in the LRR domain of the same gene have been associated with *Crohn's disease*, the granulomatous intestinal disease with a large number of extra-intestinal manifestations affecting joints, eyes and skin [51].

Complement dysregulation syndromes

The complement system has a crucial role in host defense with biologic effects such as chemotaxis, opsonization, phagocytosis of microrganisms and removal of immune complexes from the circulation. Severe illnesses, which have been recently enclosed in the chapter of AID, derive by dysregulation of complement activation. **Hereditary angioedema** (HAE, OMIM 106100) is a rare, autosomal dominant disease, caused by the deficiency of C1-esterase inhibitor and characterized by recurrent episodes of swelling, which may affect subcutaneous tissues (primarily extremities, genitalia or the face), bowel wall and the respiratory tract, potentially leading to laryngeal edema and death secondary to asphyxiation [52]. C1-esterase inhibitor is the sole plasma inhibitor of factor XII and one of the major inhibitors of kallikrein, as well as factor XI; thus in its absence the kinin-forming pathway is overstimulated. *Type 1* HAE is related to markedly suppressed protein levels as a result of abnormal secretion or intracellular degradation; *type 2* HAE is also a dominantly inherited disorder, leading to the synthesis of a dysfunctional protein. Screening plasmatic C4, (C4 is normal between swelling events in only 2% of cases) and C1-esterase inhibitor is recommended in these clinical sceneries; the C1 inhibitor level may be normal or even elevated and a functional assay is needed to assess its activity and confirm type 2 HAE [53].

The treatment of HAE has undergone rapid changes during the past years and additional drugs are likely to be approved, as recombinant human C1-esterase inhibitor concentrate for intravenous infusion. Acute episodes of circumscribed, non-pruritic and rather painful swelling, which might take grotesque proportions, must be treated with human derived C1-esterase inhibitor concentrates, especially if more than one severe episode per month occurs, but because of the significant mortality associated with HAE, careful prophylaxis is essential with antifibrinolytics (tranexamic acid) and high-dose attenuated androgens [54].

Approximately 10% of cases of **hemolytic-uremic syndrome,** characterized by nonimmune hemolytic anemia with fragmentocytes, thrombocytopenia and acute renal impairment, are classified as "**atypical**" (OMIM 235400), since they are not caused by any intestinal bacteria producing Shiga-like toxin. The mechanism underlying these atypical forms is persistent complement activation. Less than 20% of cases are familial and related to genetic abnormalities in the complement system proteins, whilst the other cases are sporadic with various triggers identified as viral infections, neoplasms, organ transplantation, drugs and pregnancy. Genetic abnormalities have been described for many complement regulators, as factor H, membrane cofactor protein, factor I, factor B, C3 and thrombomodulin, mainly characterized by reduced serum levels of complement fraction C3 and normal levels of C4, but mutations confer a predisposition rather than cause the disease. The distinction of the various forms of familial atypical haemolytic-uremic syndrome is shown in Table 11 [55].

Prognosis of atypical hemolytic-uremic syndrome is

Table 11. General details of familial atypical haemolytic-uremic syndrome.

Protein affected	*Gene*	*Complement abnormalities*	*Frequency*
Factor H	*CFH*	No binding to endotelium	20-30%
Membrane cofactor protein	*MCP*	No surface expression	10-15%
Factor HR1, R3	*CFHR1/3*	Anti-factor H antibodies	6%
Factor I	*CFI*	Low level or low cofactor activity	4-10%
Factor B	*CFB*	C3 convertase stabilization	1-2%
Complement C3	*C3*	Resistance to C3b inactivation	5-10%
Thrombomodulin	*THBD*	Reduced C3b inactivation	5%

poor with death rates as high as 25% and progression to end-stage renal disease in 50% of patients. Treatment with plasma exchange seems successful in most patients and associated with prevention of recurrences, whilst kidney transplantation is still debated as an appropriate strategy for end-stage renal disease of these patients [56].

Behçet's disease

Recent observations on Behçet's disease (BD, OMIM 109650) with its features of recurrent non-scarring muco-cutaneous lesions, enhanced inflammatory response and overexpression of proinflammatory cytokines have allowed its inclusion in the group of AID. A complex genetic background combined with

Table 12. Diagnostic criteria for Behçet's disease according to the 1990 International Study Group.

Recurrent oral ulcerations (aphthous or herpetiform ulcers recurring at least 3 times/year - observed by a physician) *plus 2 among:*
Recurrent genital ulcerations
Eye lesions (anterior or posterior uveitis, cells in vitreous on the slit-lamp examination, retinal vasculitis - observed by an ophthalmologist)
Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular nodules, acne-like lesions in the post-adolescental age with no history of corticosteroid treatment)
Positive pathergy test (*performed by puncturing the forearm skin with sterile needles)* The early reaction (a 1-2 mm elevated lesion surrounded by a reddish area) must be read by the physician, appears within 24 hours and maximizes in 48 hours

adaptive immune responses to enviromental and auto-antigens is accepted to be the hallmark of BD, which differs from the other AID due to its rare pediatric onset and to the absence of paroxysmal attacks of fever [57].

The disease has a worldwide distribution, but its prevalence is highest in Central Asia and the Far East (along the ancient "silk road"). Table 12 shows the diagnostic criteria according to the 1990 International Study Group for BD: the clinical scenery is widely heterogeneous with mucocutaneous, ocular, vascular, gastrointestinal, musculoskeletal and neurological involvement. A typical feature of BD is the positivity of pathergy test, a non-specific response of skin. Though an infectious agent might be required to trigger the responses of innate nature of BD and even if autoantigen-derived self-reactive T or B cells might be involved no definite mechanism has been yet found to explain the complex pathogenesis of this condition [58].

Conclusions

In conclusion, AID represent an expanding group of conditions heralded by recurrent bouts of systemic inflammation, which can be differentiated from auto-immunity due to the absence of antigen-specific T cells or production of autoantibodies. Recent advances in molecular genetics have helped to define AID and to elucidate the pathogenesis of these conditions. The onset of clinical manifestations is usually early, ranging from the first hours to the first decades of life and the overall delay in the diagnosis can be explained by both AID relative rarity and poor physicians' awareness of their existence.

REFERENCES

1. Goldfinger S. The inherited autoinflammatory syndrome: a decade of discovery. Trans Am Clin Climatol Assoc 2009; 120: 413-418.
2. Rigante D. Autoinflammatory syndromes behind the scenes of recurrent fevers in children. Med Sci Monit 2009; 15: RA179-187.
3. Rodrigue-Gervais IG, Saleh M. Genetics of inflammasome-associated disorders: a lesson in the guiding principals of inflammasome function. Eur J Immunol 2010; 40: 643-648.
4. Guz G, Kanbay M, Ozturk MA. Current perspectives on familial Mediterranean fever. Curr Opin Infect Dis 2009; 22: 309-315.
5. Rigante D, La Torraca I, Ansuini V, Compagnone A, Sallì A, Stabile A. The multi-face expression of familial Mediterranean fever in the child. Eur Rev Med Pharmacol Sci 2006; 10: 163-171.
6. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967; 43: 227-253.
7. Lachmann HJ, Sengul B, Yavuzşen TU, Booth DR, Booth SE, Bybee A, Gallimore JR, Soytürk M, Akar S, Tunca M, Hawkins PN. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology 2006; 45: 746-750.
8. Samuels J, Aksentijevich I, Torosyan Y, Centola M, Deng Z, Sood R, Kastner DL. Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. Medicine (Baltimore) 1998; 77: 268-297.
9. Touitou I, Sarkisian T, Medlej-Hashim M, Tunca M, Livneh A, Cattan D, Yalçinkaya F, Ozen S, Majeed H, Ozdogan H, Kastner D, Booth D, Ben-Chetrit E, Pugnère D, Michelon C, Séguret F, Gershoni-Baruch R; International Study Group for phenotype-genotype correlation in familial Mediterranean fever. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum 2007; 56: 1706-1712.
10. Soylemezoglu O, Arga M, Fidan K, Gonen S, Emeksiz HC, Hasanoglu E, Buyan N. Unresponsiveness to colchicine therapy in patients with familial Mediterranean fever homozygous for the M694V mutation. J Rheumatol 2010; 37: 182-189.
11. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-1885.
12. Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Çakar N, Düzova A, Kasapçopur O, Elhan AH, Doganay B, Ekim M, Kara N, Uncu N, Bakkaloglu A. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology 2009; 48: 395-398.
13. Marek-Yagel D, Berkun Y, Padeh S, Abu A, Reznik-Wolf H, Livneh A, Pras M, Pras E. Clinical disease among patients heterozygous for familial Mediterranean fever. Arthritis Rheum 2009; 60: 1862-1866.

14. Rigante D, La Torraca I, Avallone L, Pugliese AL, Gaspari S, Stabile A. The pharmacological basis of treatment with colchicine in children with familial Mediterranean fever. Eur Rev Med Pharmacol Sci 2006; 10: 173-178.
15. Roldan R, Ruiz AM, Miranda MD, Collantes E. Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. Joint Bone Spine 2008; 75: 504-505.
16. Frenkel J, Houten SM, Waterham HR, Wanders RJA, Rijkers GT, Kimpen JLL, Duran R, Poll-The BT, Kuis W. Mevalonate kinase deficiency and Dutch type periodic fever. Clin Exp Rheumatol 2000; 18: 525-532.
17. van der Meer JW, Vossen JM, Radl J, van Nieuwkoop JA, Meyer CJ, Lobatto S, van Furth R. Hyperimmunoglobulinaemia D and periodic fever: a new syndrome. Lancet 1984; 1: 1087-1090.
18. van der Hilst JC, Bodar EJ, Barron KS, Frenkel J, Drenth JP, van der Meer JW, Simon A; International HIDS Study Group. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine (Baltimore) 2008; 87: 301-310.
19. Ammouri W, Cuisset L, Rouaghe S, Rolland MO, Delpech M, Grateau G, Ravet N. Diagnostic value of serum immunoglobulinaemia D level in patients with a clinical suspicion of hyper IgD syndrome. Rheumatology 2007; 46: 1597-1600.
20. Takada K, Aksentijevich I, Mahadevan V, Dean JA, Kelley RI, Kastner DL. Favorable preliminary experience with etanercept in two patients with the hyperimunoglobulinemia D and periodic fever syndrome. Arthritis Rheum 2003; 48: 2645-2651.
21. Simon A, Drewe E, van der Meer JW, Powell RJ, Kelley RI, Stalenhoef AF, Drenth JP. Simvastatin treatment for inflammatory attacks of the hyperimunoglobulinaemia D and periodic fever syndrome. Clin Pharmacol Ther 2004; 75: 476-483.
22. Rigante D, Ansuini V, Bertoni B, Pugliese AL, Avallone L, Federico G, Stabile A. Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome. Rheumatol Int 2006; 27: 97-100.
23. Schneiders MS, Houten SM, Turkenburg M, Wanders RJ, Waterham HR. Manipulation of isoprenoid biosynthesis as a possible therapeutic option in mevalonate kinase deficiency. Arthritis Rheum 2006; 54: 2306-2313.
24. Simon A, Kremer HP, Wevers RA, Scheffer H, De Jong JG, van der Meer JW, Drenth JP. Mevalonate kinase deficiency: evidence for a phenotypic continuum. Neurology 2004; 62: 994-997.
25. Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghill PJ. Familial hibernian fever. QJ Med 1982; 51: 469-480.
26. Aksentijevich I, Galon J, Soares M, Mansfield E, Hull K, OH HH, Goldbach-Mansky R, Dean J, Athreya B, Reginato AJ, Henrickson M, Pons-Estel B, O'Shea JJ, Kastner DL. The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies and evidence for further genetic heterogeneity of periodic fevers. Am J Hum Genet 2001; 69: 301-314.
27. Stojanov S, McDermott MF. The tumour necrosis factor receptor-associated periodic syndrome: current concepts. Expert Rev Mol Med 2005; 7: 1-18.
28. Dinc A, Erdem H, Rowczenio D, Simsek I, Pay S, Bahce M, Lachmann H. Autosomal dominant periodic fever with AA amyloidosis: tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a Turkish family. J Nephrol 2005; 18: 626-629.
29. Jesus AA, Oliveira JB, Aksentijevich I, Fujihira E, Carneiro-Sampaio MM, Duarte AJ, Silva CA. TNF receptor-associated periodic syndrome (TRAPS): description of a novel TNFRSF1A mutation and response to etanercept. Eur J Pediatr 2008; 167: 1421-1425.
30. Simon A, Bodar EJ, van der Hilst JC, van der Meer JW, Fiselier TJ, Cuppen MP, Drenth JP. Beneficial response to interleukin 1 receptor antagonist in TRAPS. Am J Med 2004; 117: 208-210.
31. Henderson C, Goldbach-Mansky R. Monogenic autoinflammatory diseases: new insights into clinical aspects and pathogenesis. Curr Opin Rheumatol 2010; 22: 567-578.
32. Maksimovic L, Stirnemann J, Caux F, Ravet N, Rouaghe S, Cuisset L, Letellier E, Grateau G, Morin AS, Fain O. New CIAS1 mutation and anakinra efficacy in overlapping of Muckle-Wells and familial cold autoinflammatory syndromes. Rheumatology 2008; 47: 309-310.
33. Prieur AM. A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. Clin Exp Rheumatol 2001; 19: 103-106.
34. Aksentijevich I, D Putnam C, Remmers EF, Mueller JL, Le J, Kolodner RD, Moak Z, Chuang M, Austin F, Goldbach-Mansky R, Hoffman HM,

Kastner DL. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. Arthritis Rheum 2007; 56: 1273-1285.
35. Lepore L, Paloni G, Caorsi R, Alessio M, Rigante D, Ruperto N, Cattalini M, Tommasini A, Zulian F, Ventura A, Martini A, Gattorno M. Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with anakinra. J Pediatr 2010; 157: 310-315.
36. Goldbach-Mansky R, Shroff SD, Wilson M, Snyder C, Plehn S, Barham B, Pham TH, Pucino F, Wesley RA, Papadopoulos JH, Weinstein SP, Mellis SJ, Kastner DL. A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. Arthritis Rheum 2008; 58: 2432-2442.
37. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitton X, Widmer A, Patel N, Hawkins PN. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009; 360: 2416-2425.
38. Jéru I, Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, Lackmy-Port-Lis M, Grimprel E, Landman-Parker J, Hentgen V, Marlin S, McElreavey K, Sarkisian T, Grateau G, Alnemri ES, Amselem S. Mutations in NALP12 cause hereditary periodic fever syndromes. Proc Natl Acad Sci U S A 2008; 105: 1614-1619.
39. Stabile A, Avallone L, Compagnone A, Ansuini V, Bertoni B, Rigante D. Focus on juvenile idiopathic arthritis accordino to the 2001 Edmonton revised classification from the International League of Associations for Rheumatology: an Italian experience. Eur Rev Med Pharmacol Sci 2006; 10: 229-234.
40. Allantaz F, Chaussabel D, Stichweh D, Bennett L, Allman W, Mejias A, Ardura M, Chung W, Wise C, Palucka K, Ramilo O, Punaro M, Banchereau J, Pascual V. Blood leukocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade. J Exp Med 2007; 204: 2131-2144.
41. Lee WI, Yang MH, Lee KF, Chen LC, Lin SJ, Yeh KW, Huang JL. PFAPA syndrome (Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis). Clin Rheumatol 1999; 18: 207-213.
42. Tasher D, Somekh E, Dalal I. PFAPA syndrome: new clinical aspects disclosed. Arch Dis Child 2006; 91: 981-984.
43. Feder HM, Salazar JC. A clinical review of 105 patients with PFAPA (a periodic fever syndrome). Acta Paediatr 2010; 99: 178-184.
44. Tallon B, Corkill M. Peculiarities of PAPA syndrome. Rheumatology 2006; 45: 1140-1143.
45. Stichweh DS, Punaro M, Pascual V. Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome. Pediatr Dermatol 2005; 22: 262-265.
46. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, Munnich A, Lyonnet S, Majeed HA, El-Shanti H. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet 2005; 42: 551-557.
47. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, Laxer R, Tedgård U, Cowen EW, Pham TH, Booty M, Estes JD, Sandler NG, Plass N, Stone DL, Turner ML, Hill S, Butman JA, Schneider R, Babyn P, El-Shanti HI, Pope E, Barron K, Bing X, Laurence A, Lee CC, Chapelle D, Clarke GI, Ohson K, Nicholson M, Gadina M, Yang B, Korman BD, Gregersen PK, van Hagen PM, Hak AE, Huizing M, Rahman P, Douek DC, Remmers EF, Kastner DL, Goldbach-Mansky R. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 2009; 360: 2426-2437.
48. Ferguson PJ, El-Shanti HI. Autoinflammatory bone disorders. Curr Opin Rheumatol 2007; 19: 492-498.
49. Okafuji I, Nishikomori R, Kanazawa N, Kambe N, Fujisawa A, Yamazaki S, Saito M, Yoshioka T, Kawai T, Sakai H, Tanizaki H, Heike T, Miyachi Y, Nakahata T. Role of the NOD2 genotype in the clinical phenotype of Blau syndrome and early-onset sarcoidosis. Arthritis Rheum 2009; 60: 242-250.
50. Coto-Segura P, Mallo-Garcia S, Costa-Romero M, Arostegui JI, Yague J, Ramos-Polo E, Santos-Juanes J. A sporadic case of early-onset sarcoidosis resembling Blau syndrome due to the recurrent R334W missense mutation on the NOD2 gene. Br J Dermatol 2007; 157: 1257-1259.
51. Tattoli I, Travassos LH, Carneiro LA, Magalhaes JG, Girardin SE. The Nodosome: Nod1 and Nod2 control bacterial infections and inflammation. Semin Immunopathol 2007; 29: 289-301.
52. Lipsker D, Hauptmann G. Cutaneous manifestations of complement deficiencies. Lupus 2010; 19: 1096-1106.

53. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, Aygoeren-Pürsün E, Craig T, Binkley K, Hebert J, Ritchie B, Bouillet L, Betschel S, Cogar D, Dean J, Devaraj R, Hamed A, Kamra P, Keith PK, Lacuesta G, Leith E, Lyons H, Mace S, Mako B, Neurath D, Poon MC, Rivard GE, Schellenberg R, Rowan D, Rowe A, Stark D, Sur S, Tsai E, Warrington R, Waserman S, Ameratunga R, Bernstein J, Björkander J, Brosz K, Brosz J, Bygum A, Caballero T, Frank M, Fust G, Harmat G, Kanani A, Kreuz W, Levi M, Li H, Martinez-Saguer I, Moldovan D, Nagy I, Nielsen EW, Nordenfelt P, Reshef A, Rusicke E, Smith-Foltz S, Späth P, Varga L, Xiang ZY. 2010 International consensus algorhythm for the diagnosis, therapy and managemenet of hereditary angioedema. Allergy Asthma Clin Immunol 2010; 6:24.
54. Zuraw BL. Hereditary angioedema therapies: past present and future. Allergy Asthma Clin Immunol 2010; 6: 23.
55. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009; 361: 1676-1687.
56. Taylor CM, Machin S, Wigmore SJ, Goodship TH; Working Party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol 2010; 148; 37-47.
57. Kaklamani VG, Vaiopoulos G, Kaklamanis PG. Behçet's disease. Semin Arthritis Rheum 1998; 27: 197-217.
58. Direskeneli H. Autoimmunity *vs* auto-inflammation in Behcet's disease: do we oversimplify a complex disorder ? Rheumatology 2006; 45: 1461-1465.