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# Systemic autoinflammatory diseases in pediatric population

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## ABSTRACT

**Background:** Systemic autoinflammatory diseases (SAID) are monogenic and polygenic inherited conditions characterized by dysregulation of the innate immune system.

**Objective:** We aimed to characterize the clinical features of patients with SAID.

**Methods:** This study was a retrospective chart review on the clinical and genetic features of the pediatric population with SAID observed from 1998 to 2020 in our center.

**Results:** A total of 54 patients were evaluated: 18 with periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; 16 with Behçet disease; 13 with systemic juvenile idiopathic arthritis; 4 with syndrome of undifferentiated recurrent fever; 1 with cryopyrin associated periodic syndrome; 1 with chronic nonbacterial osteomyelitis; and 1 with Muckle-Wells syndrome.

**Conclusion:** The analysis of clinical features of our patients are similar to other studies.

Our goal was to aware the medical community to early recognize and treat SAID to improve quality of life of pediatric patients.

**Keywords:** Behçet disease; Child; Clinical symptoms; Genetic testing; Systemic Juvenile idiopathic arthritis; Treatment

## INTRODUCTION

The autoinflammation concept was first postulated in 1999 [1]. The discovery of the inflammasome and the related genes on systemic autoinflammatory diseases (SAID) has led to a better knowledge on its pathophysiology [2, 3].

The commonest periodic fever syndromes include periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA), familial mediterranean fever (FMF), tumor necrosis factor (TNF)-receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency/hyperimmunoglobulinemia D (IgD) with periodic fever syndrome, the cryopyrin associated periodic syndromes (CAPS) (familial cold induced autoinflammatory syndrome [FCAS], Muckle-Wells syndrome [MWS], and chronic infantile neurologic, cutaneous and articular syndrome [CINCA]) [4].

**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Conceptualization: Maria Marques, Inês Cunha, Carla Zilhão. Formal analysis: Maria Marques, Inês Cunha, Carla Zilhão. Investigation: Maria Marques, Inês Cunha, Sérgio Alves, Carla Zilhão, Margarida Guedes. Methodology: Maria Marques, Inês Cunha, Carla Zilhão. Project administration: Maria Marques, Inês Cunha, Sérgio Alves, Carla Zilhão. Writing - original draft: Maria Marques, Inês Cunha. Writing - review & editing: Maria Marques, Inês Cunha, Sérgio Alves, Carla Zilhão, Margarida Guedes.

SAID could be monogenic, digenic and in some cases the genetically inherited pattern is more complex [5]. The latter include Behçet disease (BD), systemic juvenile idiopathic arthritis (sJIA), chronic nonbacterial osteomyelitis (CNO), sarcoidosis, amongst others [4]. Some pediatric patients presenting with unexplained fever, serositis, skin rash, arthralgia, myalgia, and other symptoms commonly found in autoinflammatory disorders, may not fit a specific diagnosis, either because of a nonspecific clinical phenotype or an inconclusive genetic test. Those cases are currently designated as systemic undifferentiated recurring fever syndrome (SURF) [4].

In this study, we aimed to characterize the clinical, analytical, and genetic features from patient with SAID as long as the available treatments and prognosis.

**MATERIALS AND METHODS**

This study consists of a retrospective review of medical records from children evaluated at the Pediatric Rheumatology Unit of Centro Materno Infantil do Norte, Portugal, between 1998 and 2020. These included patients (aged from 0 to 18 years) with CINCA, MWS, PFAPA, CNO, sJIA, BD and SURF.

All monogenic SAID patients were diagnosed by the presence of characteristic clinical features, genetic confirmation and clinical response to conventional/biologic treatments [6]. Patients with PFAPA were diagnosed according to the PFAPA and Pediatric Rheumatology International Trials Organization (PRINTO) diagnostic criteria [7], sJIA patients were diagnosed according to the International League of Associations for Rheumatology criteria [8] and patients with BD were diagnosed following the International classification criteria for BD in pediatric age [9-12].

Data regarding clinical and analytical results were collected and considerations regarding reports from other series of pediatric patients were made. Single cases were analyzed independently. Results were expressed in percentage as median and interquartile range.

The study protocol was approved by the ethical committee from Centro Hospital Universitário do Porto (IRB number: 28019).

**RESULTS**

From 1998 to 2020 a total of 54 patients were evaluated at our Pediatric Rheumatology Unit with clinical criteria or confirmed diagnosis of SAID.

**Table 1** displays general characterization of observed SAID.

The most frequent diagnosis was PFAPA, followed by BD and sJIA. Four cases of SURF will be explored individually in the proper section, as well as MWS, CINCA, and CNO.

**Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome**

In our center, a total of 18 patients diagnosed with PFAPA were followed and their main clinical features are described in **Table 2**.

**Table 1.** General characterization of systemic autoinflammatory diseases observed

Variable	PFAPA	MWS	CINCA	CNO	SURF	sJIA	Behçet
No. (%)	18 (33.3)	1 (1.9)	1 (1.9)	1 (1.9)	4 (7.4)	13 (24.1)	16 (29.6)
Sex							
Male	10 (55.5)	0 (0)	1 (100)	0 (0)	3 (75.0)	9 (69.2)	2 (12.5)
Female	8 (44.4)	1 (100)	0 (0)	1 (100)	1 (25.0)	4 (30.8)	14 (87.5)
Median IDD	1.50 Years (range, 0.65–4.22 years)	3 Months	13 Months	7 Weeks	Not yet classified	2 Weeks* (range, 1–4 weeks)	36 Months (range, 10.5–99 months)

PFAPA, periodic fever with aphthous stomatitis pharyngitis and adenitis; MWS, Muckle-Wells syndrome; sJIA, systemic juvenile idiopathic arthritis; CINCA, chronic infantile neurological, cutaneous, and articular; CNO, chronic nonbacterial osteomyelitis; SURF, systemic undifferentiated recurring fever syndrome; IDD, interval between onset of the disease and diagnosis.

\*Three patients without information.

In our series, 2 patients (11.1%) had positive family history of recurrent tonsillitis. Overall patients' disease started at a median age of 2.5 and the median interval between disease's onset and the diagnosis was 1.5 years. All patients had fever and the majority also had aphthous stomatitis, pharyngitis and enlarged cervical lymph nodes. In respect to general symptoms, the presence of abdominal pain, arthralgia and headache were also often reported. In our patients, inflammatory markers: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA) were elevated in crisis in 77.8%, 55.5%, and 61.1% of patients, respectively. Outside crises there were normalization of

**Table 2.** Main demographic features and clinical manifestations in patients with PFAPA (n = 18)

Variable	Value
Sex, male:female	55.5:44.4
Age of first symptoms (yr), median (IQR)	2.5 (1–5)
Family history of PFAPA	11.1
Fever	100
Aphthous stomatitis	61.0
Pharyngitis	83.3
Enlarged cervical lymph nodes	83.3
Gastrointestinal symptoms	
Abdominal pain	38.8
Diarrhea	11.1
Vomiting	11.1
Musculoskeletal signs/symptoms	
Arthralgia	22.2
Bone alteration	0
Oligoarthritis	0
Myalgia	16.7
Skin and lymphatic system	
Maculopapular rash	0
Migratory rash	0
Urticarial rash	0
Generalized enlargement of LN	0
Cervical LN enlargement	88.9
Periorbital oedema	0
Other symptoms	
Aseptic peritonitis	0
Chest pain	0
Conjunctivitis	5.5
Fatigue	22.2
Headache (any time)	33.3
Neurosensory hearing loss	0
Papilledema	0
Pericarditis	0
Pleurisy	0

Values are presented as percentage unless otherwise indicated.

PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; IQR, interquartile range; LN, lymph nodes.

SAA, CRP, and ESR in all patients. Concerning to treatment all patients were treated with corticosteroids on demand with resolution of symptoms. In some patients, adjunctive therapy with colchicine (5.5%), montelukast (11.1%), vitamin D (44.4%), and tonsillectomy (11.1%) were also tried with variable results. In 8 patients, resolution of symptoms was observed 5 years after the diagnosis.

### **Cryopyrin associated periodic syndromes**

#### *Muckle-Wells syndrome*

A 19-month-old girl presented with recurrent episodes of fever, arthralgia, myalgia, wrists, and cervical spine arthritis, urticarial lesions and irritability for a week, since 15 months old. Inflammatory markers (CRP, ESR, SAA, and leukocyte count) were elevated. Between flares there were no symptoms and inflammatory markers were normal. Genetic study identified a heterozygotic *NLRP3* gene mutation C.1909A>T (p. Met637Leu) in the child and also in her father (asymptomatic).

Initial treatment with prednisolone (1 mg/kg/day) controlled clinical manifestations, but she flared after prednisolone withdrawal, so IL-1 antagonist (Anakinra) (1 mg/kg/day) was initiated with good response after the first dose (absence of crisis, resolution of fever and decrease of inflammatory markers). An on-demand IL-1 antagonist (Anakinra) approach was initiated with no more recorded flares since the first dose.

The patient is regularly monitored to exclude disease complications such as hearing loss and amyloidosis.

#### *Chronic infantile neurologic, cutaneous and articular syndrome*

A 3-month-old boy presented persistent urticarial rash and generalized lymphadenopathies, followed by recurrent episodes of prolonged fever (1.5 months duration) and irritability since the first month of age. Complementary evaluation also identified a nodule in the epiphyseal cartilage of the knee, papillary edema, and mild development delay, with normal auditory brainstem response. Extensive investigation allowed exclusion of infection, malignancy, and immune system diseases with laboratory findings revealing elevation of inflammatory markers: ESR 55 mm/hr, CRP 81 mg/L, and SAA 15,6 mg/dL ( $N < 0,64$  mg/dL). He first started treatment with prednisolone and methotrexate and around the age of 13 months genetic study allowed the identification of a new *NLRP3* mutation C.1887A>T (p.Glu629Asp). At the age of 15 months, he started treatment with an IL-1 antagonist (Anakinra) (1 mg/kg/day) with subsequent clinical and progressive analytical improvement, including of SAA. In the following years, daily administration of Anakinra presented a problem concerning therapeutic compliance; furthermore, flares of the disease were observed during infections with persistent SAA elevation between flares (above 5 mg/dL), raising concern on the possibility of long-term amyloidosis. At the age of 8, he switched to an anti-IL1  $\beta$  (Canakinumab), 2 mg/kg every 8 weeks, with progressive adjustment of doses down to 4 mg/kg every 4 weeks, with remission of symptoms and SAA normalization.

### **Chronic nonbacterial osteomyelitis**

An 8-year-old girl with a 6-week history of right ankle and left wrist insidious pain, with nocturnal worsening, with fever, local swelling, warmth, and redness in the week before admission. Plain radiograph and magnetic resonance imaging revealed metaphyseal lytic lesions in the left radius and right tibia. Bloodwork revealed elevated CRP (190 mg/L) and ESR (51 mm/hr). CNO was suspected but, since it constitutes an exclusion diagnosis, treatment with clindamycin

was initiated. After initial worsening, treatment with anti-inflammatory dose of ibuprofen was initiated with remarkable improvement. Bone biopsy histology revealed nonspecific osteomyelitis findings, and blood and bone biopsy microbiological culture were negative. Antibiotic treatment was withdrawn and she completed 6 months of ibuprofen therapy with considerable radiographic improvement. She is currently in remission with no undercurrent treatment.

### **Syndrome of undifferentiated recurrent fever**

We hereby describe 4 SURF cases.

#### *SURF1*

A 17-year-old boy presented recurrent episodes (3–4/yr) of tonsillitis, fever, aphthous lesions, myalgia, abdominal pain, and headaches, that lasted 3–5 days, since the age of 5 years old. When he turned 14 years old frequency of episodes increased (approximately 1 per month).

Laboratory studies revealed elevation of inflammatory markers with persistent increased SAA between flares. Treatment with prednisolone 0.5 mg/kg on the first day aborted fever but other symptoms persisted and lasted for 24–48 hours.

Furthermore, he developed persistent asthenia with incapacitating myalgia and headache. After colchicine treatment failure, anti-IL-1 (Anakinra) 100 mg/day was started with pain and fatigue improvement and SAA normalization. Genetic testing showed a heterozygotic variant on *SLC29A3* gene c.419C>T (p.Thr140Met).

#### *SURF2*

A 12-year-old male presented episodes of fever, abdominal pain, arthralgia, myalgia, erythema nodosum, and maculopapular painful lesions together with aphthous stomatitis and pharyngitis with 48 hours duration. Episodes recurred every 2 months since the age of 10 years. The laboratory study showed elevation of inflammatory markers (ESR, CRP, SAA, and leukocytosis) and an increased IgD level (23.8 mg/dL), with normalization between crises. Also, urinary mevalonic acid was normal. Cutaneous biopsy revealed nonspecific inflammatory infiltrate suggesting chronic dermatitis. Genetic study for the SAID Genetic Screening Panel – Next generation sequencing (NGS) was negative. During the follow-up aphthous stomatitis was the prominent symptom, accompanied by fever and painful cutaneous lesions. Therefore, HLA typing was performed revealing positivity for HLA-B51 and HLA-B15. The patient was treated with colchicine and prednisolone on demand with good response.

#### *SURF3*

A 15-year-old boy presented, since the age of 5, recurrent and self-limited episodes of fever (max. 41°C), abdominal pain, diarrhea, arthralgia, myalgia, pharyngitis and, in 2 episodes, urticarial rash and upper lip angioedema. During crises, elevation of inflammatory markers (CRP, ESR, SAA, and leukocytosis) were observed, with a return to normal range between crises. Genetic study with SAID Genetic Screening Panel - NGS was not able to identify pathogenic mutations and additional MEFV and TNFRSF1A sequencing did not detect any duplication/deletion. The patient had a good clinical response to colchicine, with total resolution of flares within one year. Colchicine treatment was stopped without any symptom recurrence and the patient is asymptomatic for the past 2 years.

#### *SURF4*

A 9-year-old boy presented 2 episodes of prolonged fever, hypersudoresis, and unspecific

musculoskeletal complaints, with elevation of inflammatory markers at the age of 5 and 6 years old. No other symptoms were present. Conditions such as infections, autoimmune diseases, and malignancy were excluded. Otherwise, he presented general good condition in apyrexia.

Genetic study for the SAID Genetic Screening Panel – NGS was negative. He started treatment with corticosteroid 1–2 mg/kg/day until normalization of inflammatory markers with posterior weaning until suspension.

At the age of 9 (2 years after corticosteroid withdrawal) he presented another episode of prolonged fever with myalgias and elevation of inflammatory markers, together with clinical parameters of hepatitis (aspartate aminotransferase 178 U/L, alanine aminotransferase 135 U/L, with normal creatine kinase, lactate dehydrogenase, and aldolase), hyperferritinemia (1,035 ng/mL), elevation of soluble CD25 (3,022 U/mL) and hypertriglyceridemia (221 mg/dL). Positron emission tomography and myelogram were performed without remarkable findings.

Treatment with prednisolone 1–2 mg/kg/day was initiated, with clinical and analytical improvement. However, corticosteroids weaning was challenging due to recurrence of febrile episodes and persistence of SAA elevation. Therefore, treatment with anti-IL-1 (Anakinra) was initiated with a good clinical and analytical response, which allowed suspension of prednisolone, being asymptomatic to date. Additionally, sequencing of the *TNFRSF1A* gene was performed, which revealed no changes.

### **Systemic juvenile idiopathic arthritis**

A total of 13 patients were diagnosed with sJIA and the main features are described in **Table 3**.

The majority of our patients were male and approximately half reported a family history of autoimmune disease. The age of disease presentation ranged from  $\leq 2$  to 16 years, being the group of 10–16 years the most affected. At presentation, all patients had fever and arthralgia, and the majority presented arthritis, rash, and myalgias. Other less common manifestations included lymphadenopathy, organomegaly, and pericarditis.

### **Behçet disease**

A total of 16 patients were diagnosed with BD and the main clinical features are described in **Table 4**.

The majority of patients were female and had a positive family history for BD. Overall patient's disease started at a median age of 6.07 years old and the median interval between onset of the disease and the diagnosis was 2 years.

All patients presented oral aphthosis and some of them also reported genital ulceration and cutaneous involvement. Ocular involvement was reported in one-quarter of patients. Considering HLA susceptibility, 4 patients (25%) presented a positive HLA-B51/B5 result. All patients were treated with colchicine as 1st line treatment.

In patients with ocular involvement azathioprine was used in 2 patients (12,5%) and anti-TNF- $\alpha$  (Infliximab) in one (6.2%) with good outcome. Corticosteroids were used in 5 cases (31.3%) whose indications included panuveitis and severe oral or genital involvement. In our case series none of the patients had functional impairments associated to BD.

**Table 3.** Main demographic features and clinical manifestations in patients with systemic juvenile idiopathic arthritis (n = 13)

Variable	Value
Sex, male:female	69.0:31.0
Age of first symptoms (yr), median (IQR)	12.3 (2–16)
Family history of autoimmune diseases	46.2
Clinical findings at presentation	
Fever	100
Myalgias	61.50
Arthralgias	100
Rash	69.0
Lymphadenopathy	38.0
Organomegaly	30.8
Pericarditis	15.4
Arthritis	76.9
Pattern of arthritis at presentation	
None	23.1
Monoarticular	15.4
Oligoarticular	30.8
Polyarticular	30.8
Joint involvement	
Wrist	40.0
Knee	30.0
Ankle	20.0
Fingers	20.0
Elbow	30.0
Neck	10.0
Hip	20.0
Toes	20.0
Shoulder	20.0
Sacroiliac	20.0
Laboratory abnormalities	
ESR elevation	92.30
CRP	84.60
Hb	38.5% w/anemia
WBC	76.9% w/leukocytosis
Ferritin elevation	69.2
Autoimmunity study	
RF	0
ANAs	7.7
Complications	
Macrophage activation syndrome	23.1

Values are presented as percentage unless otherwise indicated.

IQR, interquartile range; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood count; RF, rheumatoid factor; ANA, antinuclear antibody.

\*Information not available.

## DISCUSSION

We herein present and discuss clinical features, genetic study, and response to conventional/biologic treatments.

Some aspects are worth to highlight, namely, the low prevalence of PFAPA in our study, which is possibly explained by low referral rate due to underdiagnosis or follow-up in other pediatric consultations. Also, most cases refer to patients diagnosed in the last 5 years, which may reflect the growing recognition of these diseases. The diagnostic criteria for PFAPA were first proposed by Marshall in 1987 [13, 14] and recently, the Eurofever Registry and PRINTO launched new classification criteria [2]. Allied with the lack of specific confirmatory

**Table 4.** Main demographic features and clinical manifestations in patients with BD (n = 16)

Variable	Value
Sex, male:female	12.5:87.5
Age of first symptoms (yr), median (IQR)	6.1 (1–15)
Family history of BD	31.3
Oral aphthosis	100
Genital aphthosis	81.2
Cutaneous manifestations	37.5
Erythema nodosum	12.5
Pseudofolliculitis	37.5
Ocular manifestations	25.0
Anterior uveitis	6.3
Arthralgia/arthritis	37.5
Gastrointestinal manifestations	18.8
Neurological manifestations	0
Vascular manifestations	0

Values are presented as percentage unless otherwise indicated.  
IQR, interquartile range; BD, Behçet disease.

laboratory or genetic tests, its presentation can be very similar to monogenic periodic fevers, therefore at the beginning the diagnosis is often presumptive. Selecting patients presenting as PFAPA but with a high risk of carrying mutations for monogenic periodic fevers can be done applying the Gaslini score [15], which is calculated considering the presence of any of the atypical clinical presentations that increase the likelihood of a genetic basis [16].

CAPS are considered a *continuum* of rare syndromes of increasing severity, including FCAS, MWS, and CINCA [2]. Its presentation may include systemic, cutaneous, musculoskeletal, and central nervous system inflammation. The genetic basis consists in a gain-of-function mutations in NLRP3 that lead to activation of the cryopyrin inflammasome [4].

MWS is characterized by recurrent systemic symptoms, ocular complains, and painful urticaria that usually begin in childhood [17, 18]. The distinctive symptom in MWS is the presence of sensorineural deafness, that can be present in 60% of cases [19]. The current knowledge supports that most patients with CAPS possess heterozygous mutations in NLRP3 [20]. Considering our patient's father, as he presented with no symptoms, it is questioned whether this could be a mutation with incomplete penetrance and of uncertain significance that results in variable manifestations.

CINCA is a rare autoinflammatory disease, typically characterized by the triad of skin rash, arthropathy, and central nervous system involvement. It represents the most severe CAPS phenotype. Autosomal dominant gain-of-function mutations in NLRP3 allow the diagnosis in 65%–70% of cases [21].

Clinical and analytical outcomes achieved in our patient were impressive considering the severity commonly associated with the disease. Early diagnosis was undoubtedly decisive, and it is possible that the implicated mutation could be associated with a better prognosis.

CNO is an autoinflammatory disorder affecting the bone. It encompasses rare genetically inherited monogenic conditions with early onset such as Majeed syndrome, deficiency of interleukin-1 receptor antagonist, and pyogenic arthritis, pyoderma gangrenosum, and acne syndrome, but also a more common “sporadic” disorder with median age of onset of 9 years [22]. Children usually present bone pain with focal swelling and warmth [22]. Clavicle, mandible



and vertebral bodies involvement are particularly distinctive [23]. Treatment with nonsteroidal anti-inflammatory drugs allows clinical remission in 60% of cases over the first year [24]. Other therapeutic options include corticosteroids, TNF- $\alpha$  inhibitors and bisphosphonates. Considering our case, we highlight the importance of early recognition of this entity, especially in the presence of multifocal insidious bone pain, in order to avoid unnecessary prolonged courses of antibiotherapy and complications such as bone deformities, fractures or growth failure.

We report 4 cases of patients in which clinical manifestations, response to SAID conventional treatment and absence of genetic diagnosis made us categorize them as SURF.

Regarding patient *SURF1*, mutations in *SLC29A3* gene can lead to H syndrome and multiple mutations have been described [25]. The most common features, apart from hyperpigmentation and hypertrichosis include flexion contractures of fingers and toes, sensorineural hearing loss, short stature, and hepatosplenomegaly followed by insulin-dependent diabetes mellitus, lymphadenopathy, and microcytic anemia [25]. Some reports also refer the presence of recurrent fever, sometimes accompanied by joint inflammation [25, 26]. Phenotypically, our patient does not present neither cutaneous nor endocrine manifestations, which are commonly associated with H syndrome and this clinical inconsistency could partially be explained by the heterozygotic variant found, that could be associated with a less severe phenotype.

Considering patient *SURF2*, although clinical picture primarily suggests a Mevalonate Kinase Deficit, despite an atypical age of presentation, genetic testing did not confirm this possibility. Clinical evolution evoked the possibility of BD, further supported by a good response to colchicine. Nevertheless, clinical criteria for BD diagnosis are not yet fulfilled.

In the patient *SURF3*, although some features were suggestive of FMF, the presence of urticaria and the absence of *MEFV* mutation were against it.

Regarding patient SURF 4, the recurrent and prolonged nature of flares was consistent with TRAPS. However genetic test, with NGS and TNFRSF1A sequencing were negative.

Recognition of SURF patients implies that the diagnosis needs to be frequently revisited, as some cases will inevitably progress and evolve into a more defined clinical entity.

sJIA is defined by specific criteria [8]. The pathogenesis of sJIA is associated with proinflammatory cytokines of the innate immune system (particularly IL-1b and IL-6) [27, 28]. Complications associated with sJIA may result from its evolution or from the treatment itself. Macrophage activation syndrome was present in 3 patients (23.1%); other isolated cases presented femoral head avascular necrosis, pulmonary hypertension, and articular damage. The use of corticosteroids (76.9%) and nonsteroidal anti-inflammatory drugs (23.1%) was complemented with methotrexate in 30.8%, mainly in those with arthritis, and as a corticosteroid sparing agent. Poor disease control and the risk for erosive polyarticular course led to the use of anti-IL6 (Tocilizumab) in 4 patients (30.8%). One of these patients presented poor response and disease progression with risk for macrophage activation syndrome which led to the switch for anti-IL1 (Anakinra).

BD is a systemic inflammatory vasculitis characterized by self-limited, unpredictable and recurrent attacks involving the oral and genital mucosa, skin, eyes and joints [10].

The real prevalence in children is unknown, though it is thought to be low [29-32]. The pathogenesis is complex, but there is a strong genetic component associated to HLA-B5 and the frequency of family cases vary between 10%–50% [33-35].

By providing data from our center we hope this report will help to expand the knowledge and awareness of these diseases, which still remain underrecognized and underdiagnosed.

The features of clinical inflammation vary according to the underlying genetic defect, but there is a wide overlap of clinical features. Molecular analysis is a great tool and accessible, however is not able to provide diagnostic confirmation in a considerable proportion of cases as the same genetic defect may present different clinical expressions. At last SAID's treatment is a permanent challenge.

## REFERENCES

1. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, Mansfield E, Gadina M, Karenko L, Pettersson T, McCarthy J, Frucht DM, Aringer M, Torosyan Y, Teppo AM, Wilson M, Karaarslan HM, Wan Y, Todd I, Wood G, Schlimgen R, Kumarajeewa TR, Cooper SM, Vella JP, Amos CI, Mulley J, Quane KA, Molloy MG, Ranki A, Powell RJ, Hitman GA, O'Shea JJ, Kastner DL. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999;97:133-44.  
[PUBMED](#) | [CROSSREF](#)
2. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, Anton J, Arostegui JI, Barron K, Ben-Cherit E, Brogan PA, Cantarini L, Ceccherini I, De Benedetti F, Dedeoglu F, Demirkaya E, Frenkel J, Goldbach-Mansky R, Gul A, Hentgen V, Hoffman H, Kallinich T, Kone-Paut I, Kuemmerle-Deschner J, Lachmann HJ, Laxer RM, Livneh A, Obici L, Ozen S, Rowczenio D, Russo R, Shinar Y, Simon A, Toplak N, Toutou I, Uziel Y, van Gijn M, Foell D, Garassino C, Kastner D, Martini A, Sormani MP, Ruperto N; Eurofever Registry and the Paediatric Rheumatology International Trials Organisation (PRINTO). Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis* 2019;78:1025-32.  
[PUBMED](#) | [CROSSREF](#)
3. Gattorno M, Federici S, Pelagatti MA, Caorsi R, Brisca G, Malattia C, Martini A. Diagnosis and management of autoinflammatory diseases in childhood. *J Clin Immunol* 2008;28 Suppl 1:S73-83.  
[PUBMED](#) | [CROSSREF](#)
4. Nigrovic PA, Lee PY, Hoffman HM. Monogenic autoinflammatory disorders: conceptual overview, phenotype, and clinical approach. *J Allergy Clin Immunol* 2020;146:925-37.  
[PUBMED](#) | [CROSSREF](#)
5. Hashkes PJ, Laxer RM, Simon A, editors. Textbook of autoinflammation [Internet]. Cham: Springer International Publishing; 2019 [cited 2020 May 4]. Available from: <http://link.springer.com/10.1007/978-3-319-98605-0>  
[CROSSREF](#)
6. Federici S, Sormani MP, Ozen S, Lachmann HJ, Amaryan G, Woo P, Koné-Paut I, Dewarrat N, Cantarini L, Insalaco A, Uziel Y, Rigante D, Quartier P, Demirkaya E, Herlin T, Meini A, Fabio G, Kallinich T, Martino S, Butbul AY, Olivieri A, Kuemmerle-Deschner J, Neven B, Simon A, Ozdogan H, Toutou I, Frenkel J, Hofer M, Martini A, Ruperto N, Gattorno M; Paediatric Rheumatology International Trials Organisation (PRINTO) and Eurofever Project. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. *Ann Rheum Dis* 2015;74:799-805.  
[PUBMED](#) | [CROSSREF](#)
7. Vanoni F, Federici S, Antón J, Barron KS, Brogan P, De Benedetti F, Dedeoglu F, Demirkaya E, Hentgen V, Kallinich T, Laxer R, Russo R, Toplak N, Uziel Y, Martini A, Ruperto N, Gattorno M, Hofer M; for Eurofever and the Paediatric Rheumatology International Trials Organisation (PRINTO). An international delphi survey for the definition of the variables for the development of new classification criteria for periodic fever aphthous stomatitis pharyngitis cervical adenitis (PFAPA). *Pediatr Rheumatol Online J* 2018;16:27.  
[PUBMED](#) | [CROSSREF](#)
8. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis:

- second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-2.  
[PUBMED](#)
9. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014;28:338-47.  
[PUBMED](#) | [CROSSREF](#)
  10. Koné-Paut I. Behçet's disease in children, an overview. *Pediatr Rheumatol Online J* 2016;14:10.  
[PUBMED](#) | [CROSSREF](#)
  11. Koné-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, Anton J, Hofer M, Chkirate B, Bouayed K, Tugal-Tutkun I, Kuemmerle-Deschner J, Agostini H, Federici S, Arnoux A, Piedvache C, Ozen S; PEDBD group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis* 2016;75:958-64.  
[PUBMED](#) | [CROSSREF](#)
  12. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;335:1078-80.  
[PUBMED](#)
  13. Matura M, Goossens A, Bordalo O, Garcia-Bravo B, Magnusson K, Wrangsjö K, Karlberg AT. Patch testing with oxidized R-(+)-limonene and its hydroperoxide fraction. *Contact Dermat* 2003;49:15-21.  
[PUBMED](#) | [CROSSREF](#)
  14. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr* 1987;110:43-6.  
[PUBMED](#) | [CROSSREF](#)
  15. Bosio I, Meini A, Cancarini P, Savoldi G, Berlucchi M, Cattalini M. PW03-002 – Calculating Gaslini diagnostic score in PFAPA. *Pediatr Rheumatol* 2013;11(Suppl 1):A228.  
[CROSSREF](#)
  16. Gattorno M, Caorsi R, Meini A, Cattalini M, Federici S, Zulian F, Cortis E, Calcagno G, Tommasini A, Consolini R, Simonini G, Pelagatti MA, Baldi M, Ceccherini I, Plebani A, Frenkel J, Sormani MP, Martini A. Differentiating PFAPA syndrome from monogenic periodic fevers. *Pediatrics* 2009;124:e721-8.  
[PUBMED](#) | [CROSSREF](#)
  17. Dodé C, Le Dù N, Cuisset L, Letourneur F, Berthelot JM, Vaudour G, Meyrier A, Watts RA, Scott DG, Nicholls A, Granel B, Frances C, Garcier F, Ederly P, Boulinguez S, Domergues JP, Delpech M, Grateau G. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet* 2002;70:1498-506.  
[PUBMED](#) | [CROSSREF](#)
  18. Glaser RL, Goldbach-Mansky R. The spectrum of monogenic autoinflammatory syndromes: understanding disease mechanisms and use of targeted therapies. *Curr Allergy Asthma Rep* 2008;8:288-98.  
[PUBMED](#) | [CROSSREF](#)
  19. Ahmadi N, Brewer CC, Zalewski C, King KA, Butman JA, Plass N, Henderson C, Goldbach-Mansky R, Kim HJ. Cryopyrin-associated periodic syndromes: otolaryngologic and audiologic manifestations. *Otolaryngol Head Neck Surg* 2011;145:295-302.  
[PUBMED](#) | [CROSSREF](#)
  20. Hoffman HM, Broderick L. Editorial: it just takes one: somatic mosaicism in autoinflammatory disease. *Arthritis Rheumatol* 2017;69:253-6.  
[PUBMED](#) | [CROSSREF](#)
  21. Finetti M, Omenetti A, Federici S, Caorsi R, Gattorno M. Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome: a review. *Orphanet J Rare Dis* 2016;11:167.  
[PUBMED](#) | [CROSSREF](#)
  22. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis. *Pediatr Rheumatol Online J* 2016;14:47.  
[PUBMED](#) | [CROSSREF](#)
  23. Menashe SJ, Aboughalia H, Zhao Y, Ngo AV, Otjen JP, Thapa MM, Iyer RS. The Many Faces of Pediatric Chronic Recurrent Multifocal Osteomyelitis (CRMO): a practical location- and case-based approach to differentiate CRMO from its mimics. *J Magn Reson Imaging* 2021;54:391-400.  
[PUBMED](#) | [CROSSREF](#)
  24. Schnabel A, Range U, Hahn G, Berner R, Hedrich CM. Treatment response and longterm outcomes in children with chronic nonbacterial osteomyelitis. *J Rheumatol* 2017;44:1058-65.  
[PUBMED](#) | [CROSSREF](#)
  25. Bloom JL, Lin C, Imundo L, Guthery S, Stepenaskie S, Galambos C, Lowichik A, Bohnsack JF. H syndrome: 5 new cases from the United States with novel features and responses to therapy. *Pediatr Rheumatol Online J* 2017;15:76.  
[PUBMED](#) | [CROSSREF](#)

26. Molho-Pessach V, Varma M, Godbole K, Kamath N, Zlotogorski A. H syndrome--four new patients from India. *Indian J Dermatol Venereol Leprol* 2014;80:579.  
[PUBMED](#) | [CROSSREF](#)
27. Lee JY, Schneider R. Systemic juvenile idiopathic arthritis. *Pediatr Clin North Am* 2018;65:691-709.  
[PUBMED](#) | [CROSSREF](#)
28. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, Ayala R, Groh B, Finkel TH, Cron RQ. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). *J Rheumatol* 2008;35:343-8.  
[PUBMED](#)
29. Karıncaoglu Y, Borlu M, Toker SC, Akman A, Onder M, Gunasti S, Usta A, Kandi B, Durusoy C, Seyhan M, Utas S, Saricaoglu H, Ozden MG, Uzun S, Tursen U, Cicek D, Donmez L, Alpsoy E. Demographic and clinical properties of juvenile-onset Behçet's disease: a controlled multicenter study. *J Am Acad Dermatol* 2008;58:579-84.  
[PUBMED](#) | [CROSSREF](#)
30. Atmaca L, Boyvat A, Yalçındağ FN, Atmaca-Sonmez P, Gurler A. Behçet disease in children. *Ocul Immunol Inflamm* 2011;19:103-7.  
[PUBMED](#) | [CROSSREF](#)
31. Zouboulis CC, Kötter I, Djawari D, Kirch W, Kohl PK, Ochsendorf FR, Keitel W, Stadler R, Wollina U, Proksch E, Söhnchen R, Weber H, Gollnick HP, Hölzle E, Fritz K, Licht T, Orfanos CE. Epidemiological features of Adamantiades-Behçet's disease in Germany and in Europe. *Yonsei Med J* 1997;38:411-22.  
[PUBMED](#) | [CROSSREF](#)
32. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, Faezi T, Ghodsi Z, Larimi R, Ashofteh F, Abdollahi BS. Behcet's disease in Iran: analysis of 6500 cases. *Int J Rheum Dis* 2010;13:367-73.  
[PUBMED](#) | [CROSSREF](#)
33. Koné-Paut I, Geisler I, Wechsler B, Ozen S, Ozdogan H, Rozenbaum M, Touitou I. Familial aggregation in Behçet's disease: high frequency in siblings and parents of pediatric probands. *J Pediatr* 1999;135:89-93.  
[PUBMED](#) | [CROSSREF](#)
34. Gül A, Inanç M, Ocal L, Aral O, Koniçe M. Familial aggregation of Behçet's disease in Turkey. *Ann Rheum Dis* 2000;59:622-5.  
[PUBMED](#) | [CROSSREF](#)
35. Krause I, Uziel Y, Guedj D, Mukamel M, Harel L, Molad Y, Weinberger A. Childhood Behçet's disease: clinical features and comparison with adult-onset disease. *Rheumatology (Oxford)* 1999;38:457-62.  
[PUBMED](#) | [CROSSREF](#)