

# The Added Value of a Multidisciplinary Clinic for Systemic Autoinflammatory Diseases

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**Background:** Systemic autoinflammatory diseases (SAID) are characterized by inappropriate activation of the innate immune system and include not only monogenic periodic fever syndromes but also multifactorial conditions. As SAID are rare and represent a diagnostic challenge, a multidisciplinary approach is important to ensure successful diagnosis and adequate follow-up of these patients.

**Objective:** To describe the organization of our multidisciplinary SAID clinic and to characterize our clinical experience, highlighting the benefits of multidisciplinary team management.

**Methods:** Our SAID clinic takes place monthly and is managed by pediatric rheumatologists closely collaborating with pediatricians specialized in infectious diseases and immunodeficiencies and one medical geneticist. Patients' data are systematically incorporated in the Rheumatic Diseases Portuguese Register (Reuma.pt). Biological samples are stored in a biobank. We describe our clinical experience based on SAID patients registered into Reuma.pt/SAID between July 2011 and June 2020.

**Results:** We have registered 176 patients, with a median age of disease onset of  $3.1 \pm 4.4$  years and median age at disease diagnosis of  $4.7 \pm 4.0$  years. Most patients were diagnosed with periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA) (n=133), 20 with undefined SAID (uSAID) and 13 with monogenic SAID, including familial Mediterranean fever (FMF) (n=5), tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (n=1), cryopyrin-associated periodic disease (CAPS) (n=1), and hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) (n=2). A genetic test was performed in 31 patients (18%), and in 26% of these a mutation responsible for the phenotype was found. Thirty-four patients (19%) achieved remission.

**Conclusion:** FMF was the most common monogenic SAID and the percentage of patients with an identified causal mutation was low. A structured electronic clinical record coupled with a biobank and a multidisciplinary approach are crucial to ensure successful diagnosis and adequate follow-up of these patients.

**Keywords:** pediatrics, rheumatology, systemic autoinflammatory syndromes

## Introduction

Systemic autoinflammatory diseases (SAID) are characterized by inappropriate activation of the innate immune system, classically including periodic fever syndromes, but also autoinflammatory disorders that do not present with fever as a major manifestation. Except for periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA syndrome), SAID are rare.<sup>1-4</sup>

SAID most frequently have their onset in childhood and the differential diagnosis often represents a challenge.<sup>5</sup> The diagnosis of monogenic SAID is challenging due to genetic heterogeneity and phenotypic overlap.<sup>3,6,7</sup> Manifestations include fever, rash, serositis, arthritis, meningitis, and uveitis among others.<sup>3,6,8</sup> In other SAIDs, such as PFAPA syndrome, multiple genes might be involved and there is no single genetic cause.<sup>9</sup> Due to their extreme rarity and complexity, and because of their demanding management, achieving a specific SAID diagnosis is often very difficult.

Patients and their families can face difficulties accessing the appropriate clinical services and undergo long, stressful, and inconclusive diagnostic journeys. The use of Next Generation Sequencing (NGS) technologies has proven to be a successful strategy to answer these unmet medical needs by inducing a marked acceleration in rare disease gene discovery and effective mutation screening, thus improving genetic SAID diagnosis, prompting further clinical assessments, providing insight into biological mechanisms, and increasing therapeutic opportunities. Indeed, NGS was revolutionary for SAID diagnosis, since it allowed the simultaneous analysis of different genes and the detection of somatic mosaicism, as demonstrated in patients presenting a typical clinical phenotype, but negative for germ-line mutations. However, in some other cases, namely in the so-called undefined SAIDs (uSAID), the NGS based gene panel sequencing results can be inconclusive or even misleading. Furthermore, a proportion of uSAID are considered multifactorial diseases, and thus particularly challenging as they are inherently complex.

As multidisciplinary patient care combines expertise from different medical areas and provides the most differentiated care, it has been acknowledged as the most adequate model in the management of complex chronic disease, as are the SAID.<sup>10,11</sup>

The aim of this experience-based manuscript is to highlight the benefits of multidisciplinary team management of patients with SAID, describing the general functioning of our SAID outpatient clinic, coupled with the Rheumatic Diseases Portuguese Register (Reuma.pt)/SAID and with the institutional Biobank. It was also an opportunity to retrospectively review the demographics, clinical entities, and treatment of all patients with SAID followed at the clinic.

This study was approved by the Scientific Committee of Reuma.pt and by the Ethics Committee of Lisbon Academic Medical Center. Reuma.pt was approved by the National Data Protection Authority and by the local ethics committees of the participating centers. The study was conducted according to the Declaration of Helsinki.

## Materials and Methods

### Systemic Autoinflammatory Diseases Outpatient Clinic

Since October 2012, the Rheumatology Department of Centro Hospitalar Universitário Lisboa Norte (CHLN) has a dedicated multidisciplinary clinic for patients with SAID. The CHLN-SAID clinic takes place monthly and is managed by two pediatric rheumatologists, two pediatricians specialized in Infectious Diseases and Immunodeficiencies and one medical geneticist. It is a multidisciplinary clinic, in which these medical specialties collaborate closely, sharing the care of these patients. The whole team regularly discusses cases of suspected SAID to define the best approach to genetic diagnosis and to make treatment decisions. Focus areas recognized as crucial in the development of the CHLN-SAID clinic are depicted in [Table 1](#).

**Table 1** Focus Areas of the CHLN-SAID Clinic

Focus Area	
Principles for referral	<ul style="list-style-type: none"> <li>• Establishment of criteria for referral</li> </ul>
Infrastructure and technology	<ul style="list-style-type: none"> <li>• Dedicated physical space where SAID patient appointments occur</li> <li>• Electronic medical records used in this clinic: Reuma.pt/SAID allows the standardized collection of data for future research</li> <li>• Reuma.pt/SAID includes disease activity assessment tools</li> <li>• Quick access when requesting blood tests for diagnostic and follow-up purposes</li> </ul>
Appointments	<ul style="list-style-type: none"> <li>• Scheduled pediatric and adult SAID appointments</li> <li>• Scheduled joint pediatrics-rheumatology appointments</li> </ul>
Meetings	<ul style="list-style-type: none"> <li>• Weekly dedicated bDMARD decision clinic</li> <li>• Digital conference discussions whenever necessary</li> </ul>
Organization of human resources	<ul style="list-style-type: none"> <li>• The team is composed of two pediatric rheumatologists, two pediatricians specialized in infectious diseases and immunodeficiencies and one medical geneticist</li> </ul>

## Assessment Tools

Data from every patient with a confirmed diagnosis of SAID is registered into the Reuma.pt/SAID module. Registered patients are required to sign an informed consent. Reuma.pt was created in June 2008, and has since been an essential tool in the clinical practice of Portuguese rheumatologists, allowing the structured follow-up of patients with various systemic rheumatic diseases.<sup>12,13</sup>

The database information security was approved by the Portuguese National Commission for Data Protection and the ethics committees of the participating institutions. All identifiable data is encrypted, and an individual password is attributed to physicians, only allowing access to data related to their center.

In September 2013, a module specifically developed for SAIDs was introduced in Reuma.pt and has since been used by Portuguese rheumatologists and pediatricians.

The Reuma.pt/SAID module guides the clinical appointment as it can be used as an electronic clinical record. Data captured by this registry are specific for SAID and include: 1) clinical data, including the diagnosis, symptom onset, clinical manifestations, fever characterization, genetic testing, classification criteria, family history, comorbidities, and source of referral ([Supplementary Figures 1–4](#)); 2) disease activity assessment, specifically the auto-inflammatory diseases activity index (AIDAI) ([Supplementary Figure 5](#) and [6](#)); 3) complementary diagnostic exams, including laboratory screening with serum amyloid A ([Supplementary Figure 7](#)); 4) vaccination status and tuberculosis screening; 5) therapy and adverse events ([Supplementary Figure 8](#)). Data is collected directly from patients attending regular outpatient appointments and is captured immediately into Reuma.pt or, in selected conditions, obtained from clinical notes. Participants are not asked to attend extra visits or interviews.

With this tool we can collect detailed clinical data, using an electronic clinical record linked to a SQL server database, with input screens specifically developed for autoinflammatory diseases, integrated on Reuma.pt.<sup>12</sup>

Categorical variables are described as frequencies and percentages and continuous variables as median  $\pm$  interquartile range (IQR).

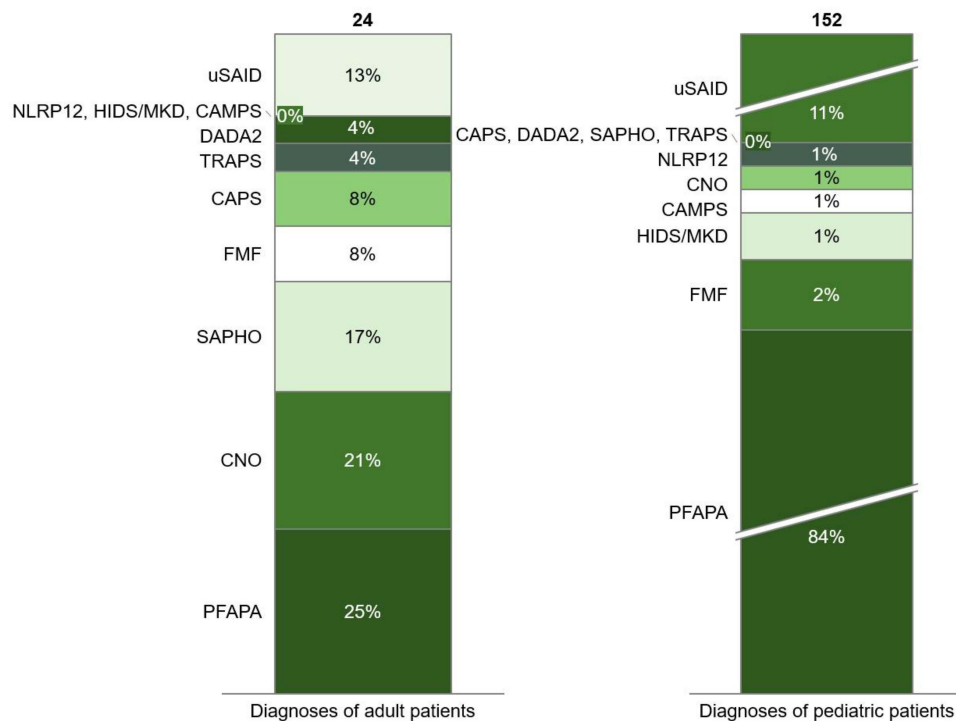
## Genetic Testing in SAID

Biological samples from all SAID patients (whole blood, serum, plasma, DNA, RNA) are stored in Biobanco-IMM, Lisbon Academic Medical Centre, since July 2013, authorized by the Ethics Committee of Lisbon Academic Medical Centre and the Portuguese commission for data protection.<sup>14</sup> Informed consent and assent are requested.

A biobank is crucial to adequately collect and preserve biological samples from SAID patients for long periods of time, so they can be used for research, or to later update the diagnosis whenever novel SAIDs are described.

The genetic characterization of these patients is provided by the analysis of one or more SAID-related genes.<sup>5,14,15</sup> This analysis is performed by a commercial laboratory with specific software either by Sanger sequencing for single genes, such as *MEFV*, *TNFRSF1A*, and *MVK* or by NGS for multigene panels associated with recurrent fever syndromes, which include the following genes: *ADAR*, *APIS3*, *ASAHI*, *CARD14*, *DDX58*, *ELANE*, *HAX1*, *IFIH1*, *IL10RA*, *IL10RB*, *IL1RN*, *IL36RN*, *LPIN2*, *MEFV*, *MVK*, *NLRC4*, *NLRP1*, *NLRP12*, *NLRP3*, *NOD2*, *OTULIN*, *PLCG2*, *PSMB8*, *PSTPIP1*, *RBCK1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *SLC29A3*, *TMEM173*, *TNFAIP3*, *TNFRSF11A*, *TNFRSF1A*, *TREX1*. This workflow allows us to detect already described as well as not yet reported genetic variants. If the identified variants are pathogenic or probably pathogenic, we propose family studies according to the underlying transmission model. This approach allows us to identify affected individuals who will profit from special assistance, and to refer carriers at risk of having affected offspring to genetic counselling. In contrast, if the variant is of uncertain significance, segregation studies are made to help clarify its clinical importance, although they cannot be used for clinical guidance.

If a diagnosis is still not established after NGS for multigene panels, especially if it will affect the therapeutic decision, we proceed to whole exome sequencing in centers with experience in SAID with dedicated bioinformatic scientists. We are currently making efforts to collaborate with international centers where somatic mutations associated with SAID are being investigated.



**Figure 1** Diagnoses of adult and pediatric patients with SAID followed at the CHLN-SAID clinic.

**Abbreviations:** uSAID, undefined systemic autoinflammatory disease; NLRP12, NLRP12-related autoinflammatory disease; HIDS/MKD, hyperimmunoglobulin D syndrome/mevalonate-kinase deficiency; CAMPS, CARD14-mediated psoriasis; DADA2, deficiency of adenosine deaminase 2; TRAPS, tumor necrosis factor receptor associated periodic syndrome; CAPS, cryopyrin associated periodic syndromes; FMF, familial Mediterranean fever; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; CNO, chronic recurrent multifocal osteomyelitis; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome.

## Results

### Clinical Characteristics

The most frequent subtype of SAID was PFAPA (n=133, 76%), followed by uSAID (n=20, 11%). [Figure 1](#) shows diagnoses found in adult and pediatric patients followed at our clinic. Consanguinity was present in 2 families, and 87 patients had a positive family history, especially Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) and PFAPA patients, with a family history of recurrent tonsillitis in all HIDS/MKD patients (n=2, 100%) and in approximately half of the PFAPA patients (n=72, 54%).

The median of the delay between disease onset and diagnosis was  $2.3 \pm 2.8$  years.

Genetic testing was performed in 32 (18%) patients, and in 9 (28%) of them a mutation was found, as shown in [Table 2](#).

Forty-seven patients were lost to follow-up (27%), 36 (20%) patients were discharged from our clinic due to sustained remission and 4 (2%) were transferred to their hometown hospital.

No deaths were reported.

[Table 2](#) details clinical characteristics for each SAID sub-type.

### Monogenic Autoinflammatory Diseases

In total, 13 (13/176, 7%) patients were diagnosed with a monogenic autoinflammatory disease, 9 (9/13, 69%) of whom had genetic results consistent with the clinical diagnosis. The median age of diagnosis was  $4.0 \pm 7.4$  years with a median time gap between symptom onset and diagnosis of  $3.9 \pm 16.5$  years. Mutations in the most relevant genes were not found in one patient (1/13; 8%), two patients (2/13; 15%) were not genetically tested, and one patient (1/13; 8%) still awaits genetic results. Clinical manifestations of these patients are reported in [Table 2](#). Although the AIDAI score<sup>16</sup> is included in the Reuma.pt/SAID module, the results are not specified due to the low number of cases it applies to.

**Table 2** Demographics, Clinical Manifestations, Diagnostic Test Findings and Treatment of the Patients Followed at the CHLN-SAID Clinic

	Monogenic Autoinflammatory Diseases							Multifactorial SAID			uSAID <sup>a</sup>
	FMF n=5	HIDS/MKD n=2	CAPS n=2	TRAPS n=1	NLRP12-rAID n=1	CAMPSn=1	DADA2 n=1	PFAPA n=133	CNO n=6	SAPHOn=4	n=20
<b>Demographics</b>											
Median age at onset, years [IQR]	12,4 [19,8]	4,6 [1,3]	3,9 [3,4]	1,1 [0]	0,7 [0]	0,1 [0]	5 [0]	2,6 [3]	12,5 [3,4]	35,8 [19,3]	3,8 [6,7]
Female (%)	2 (40)	1 (50)	2 (100)	0 (0)	0 (0)	0 (0)	1 (100)	58 (44)	1 (17)	1 (25)	8 (40)
Median time to diagnosis [IQR]	3,9 [8,1]	2,1 [1,2]	16,9 [5,4]	17,7 [0]	0,7 [0]	3,5 [0]	28 [0]	2,3 [2,6]	3,1 [3]	2,7 [2,5]	1,8 [1,7]
Time of follow-up (years)	0,7	1,7	6,3	0,6	0,6	3,1	9,6	2,5	3,5	0,0	1,5
Median number of visits [IQR]	1 [1]	3 [0]	15,5 [14,5]	3 [0]	3 [0]	2 [0]	71 [0]	4 [4]	3,5 [3,3]	1 [0]	2,5 [3,3]
Family history	2	2	0	1	0	0	0	72	1	0	9
Consanguinity	0	0	0	0	1	0	0	0	0	0	1
Ethnicity											
White	2	2	1	1	1	1	1	111	5	0	15
Black	0	0	0	0	0	0	0	2	0	0	0
Asian	0	0	1	0	0	0	0	0	0	0	1
Unknown	3	0	0	0	0	0	0	20	1	4	4
<b>Clinical manifestations</b>											
History of fever	2	2	1	1	0	0	1	133	1	0	18
Constitutional	0	0	1	0	0	0	1	7	0	0	6
Musculoskeletal	1	1	1	1	0	1	1	32	1	1	10
Arthralgia	1	0	0	1	0	1	1	12	1	0	10
Arthritis	0	0	1	0	0	1	1	0	0	1	0
Myalgia	0	1	0	0	0	0	0	21	1	0	2
Mucous membranes	0	1	0	0	0	0	0	91	1	0	3

(Continued)

Table 2 (Continued).

	Monogenic Autoinflammatory Diseases							Multifactorial SAID			uSAID <sup>a</sup>
	FMF n=5	HIDS/MKD n=2	CAPS n=2	TRAPS n=1	NLRP12-rAID n=1	CAMP5n=1	DADA2 n=1	PFAPA n=133	CNO n=6	SAPHOn=4	n=20
Cutaneous	0	1	1	0	1	1	1	4	1	1	5
Ocular	0	0	1	1	0	0	0	1	0	0	1
Ear, nose, and throat symptoms	0	2	0	0	0	0	0	119	1	0	4
Cardiorespiratory	1	0	0	0	1	0	0	1	0	0	2
Neurological	0	0	0	1	0	0	1	25	0	0	4
Reticuloendothelial system	0	1	0	1	0	1	0	89	0	0	4
Sensorineural hearing loss	0	0	0	0	0	0	0	0	0	0	1
Gastrointestinal	2	1	0	1	0	0	0	56	1	0	6
Failure to thrive	0	0	0	0	0	0	1	2	0	0	0
<b>Follow-up</b>											
Lost to follow-up	1	0	0	0	0	0	0	45	0	0	1
Remission	0	0	0	0	0	0	0	32	3	0	1
<b>Diagnostic test findings</b>											
Positive genetic testing	4/4	1/2	1/2	1/1	1/1	1/1	1/1	0/12	0/0	0/0	0/8
<b>Gene and mutations found</b>	<b>MEFV (M694V)</b>	<b>MVK (V377I and C152Y)</b>	<b>NLRP3 (E304K)</b>	<b>TNFRSF1A (p. R92Q)</b>	<b>NLRP12</b>	<b>CARD14</b>	<b>ADA2 (G47R and Y453C)</b>				
<b>Treatment</b>											
Glucocorticoids <sup>b</sup>	0	2	0	0	1	0	1	118	3	0	9
sDMARDs											
Azathioprine	0	0	0	0	0	0	0	0	0	0	2
Cyclosporine	0	0	0	0	1	0	0	0	0	0	0
Hydroxychloroquine	0	0	0	0	0	0	0	0	0	0	0
Methotrexate	0	0	1 <sup>c</sup>	0	0	0	0	0	1	0	0

bDMARDs											
Etanercept	0	0	0	1	0	0	0	0	0	0	0
Secukinumab	0	0	0	0	0	1	0	0	0	0	0
Infliximab	0	0	0	0	0	0	1	0	0	0	0
Canakinumab	0	1	1 <sup>c</sup>	0	0	0	0	0	0	0	1
Bisphosphonates	0	0	0	0	0	0	0	0	3	0	0
Colchicine	3	0	0	0	0	0	0	1	1	0	3
Tonsillectomy/ adenoidectomy	0	0	0	0	0	0	0	26	0	0	2

**Notes:** This table only shows SAIDs for which there were registered patients. <sup>a</sup>Patients with clinical manifestations consistent with SAID after exclusion of either (1) other defined inflammatory conditions (ie rheumatic diseases, inflammatory bowel diseases) or other mimicking conditions (ie hematological diseases, tumors, immune deficiencies) and (2) defined autoinflammatory diseases. <sup>b</sup>Glucocorticoids used include Prednisolone, Deflazacort and Betamethasone. <sup>c</sup>These treatments were used in the CINCA patients.

**Abbreviations:** FMF, familial Mediterranean fever; HIDS/MKD, hyperimmunoglobulin D syndrome/mevalonate-kinase deficiency; CAPS, cryopyrin associated periodic syndromes; TRAPS, tumor necrosis factor receptor associated periodic syndrome; NLRP12-rAID, NLRP12-related autoinflammatory disease; CAMPS, CARD14-mediated psoriasis; DADA2, deficiency of adenosine deaminase 2; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome; CNO, chronic non-bacterial osteomyelitis; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; uSAID, undefined systemic autoinflammatory disease; MEFV, Mediterranean fever gene; MVK, mevalonate-kinase gene; NLRP3, NOD-like receptor 3 gene; TNFRSF1A, tumor necrosis factor receptor superfamily member 1A gene; NLRP12, NOD-like receptor 12 gene; ADA2, adenosine deaminase 2 gene; CARD14, caspase recruitment domain-containing protein 14 gene; sDMARDs synthetic disease-modifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs.

The diagnosis of FMF was made in 5 patients (5/176; 3%) – 3 children and 2 adults. Four of these patients carried the Met694Val mutation of *MEFV*, in two of them (father and daughter) an autosomal dominant pattern of inheritance was present; another patient had compound heterozygosity for the *MEFV* mutation (M694V and R202Q). One patient was Turkish and the other four Portuguese. No cases of consanguinity were found.

One adult patient (1/176; 1%) presented with Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), and this patient was positive for the low-penetrance p.R92Q variant. The patient's father also had this variant and symptoms of TRAPS.

Our registry included two adult patients (2/176; 1%) diagnosed with CAPS: one patient with Familial Cold Autoinflammatory Syndrome (FCAS), and one patient with Chronic Infantile Neurological Cutaneous and Articular (CINCA). The FCAS patient had no identifiable pathogenic or likely pathogenic variant in the *NLRP3* gene, but the CINCA patient carried the *NLRP3* mutation E304K.

Two children (2/176; 1%) diagnosed with HIDS/MKD were registered. One of them had compound heterozygosity for two mutations in the *MVK* gene – V377I and C152Y. The genetic results of the second patient were still unavailable. A family history suggestive of HIDS/MKD was absent.

One adult patient (1/176; 1%) with Deficiency of Adenosine Deaminase 2 (DADA2) with two heterozygous pathogenic variants in the *ADA2* gene, namely G47R and Y453C, was included. This patient presented with painful erythematous subcutaneous nodules, asymmetric polyarthritis, livedo reticularis, digital necrosis, involvement of the central and peripheral nervous system, as well as gastrointestinal bleeding.

There was also one child (1/176; 1%) with *NLRP12*-related SAID (NLRP12-rSAID) and one (1/176; 1%) with *CARD14* mediated psoriasis (CAMPS) with heterozygosity for a variant of exon 3 on *CARD14* (c277A>G) with unknown clinical significance.

## Multifactorial SAID

PFAPA was diagnosed in 133 patients (133/176; 76%). The median age at disease onset was  $2.6 \pm 3.0$  years with 107 (80%) patients first showing symptoms before age 5. No case of consanguinity was identified, and 57 (57/133, 43%) patients reported a family history of recurrent tonsillitis. Remission occurred after a median of disease duration of  $6.8 \pm 5.1$  years. Twelve (12/133; 9%) patients were screened for genetic defects by Sanger sequencing for genes *MEFV*, *TNFRSF1A*, and *MVK*, because the phenotype did not exactly fit into a specific monogenic syndrome – no mutations were found. Apart from the typical manifestations of PFAPA, there were cases of abdominal pain (49/133; 37%), headache (25/133; 19%), myalgia (21/133; 16%), arthralgia (12/133; 9%), maculopapular rash (4/133; 3%), failure to thrive (2/133; 2%), splenomegaly (1/133; 1%) and conjunctivitis (1/133; 1%).

Six patients (6/176; 3%) with Chronic nonbacterial osteomyelitis (CNO) were registered and four adult patients (4/176; 2%) were diagnosed with Synovitis–Acne–Pustulosis–Hyperostosis–Osteitis (SAPHO) syndrome, with a median age at disease onset of  $12.5 \pm 3.4$  and  $35.8 \pm 19.3$  years, respectively.

## Undefined SAID

20 patients (20/176; 11%) – 17 children and 3 adults – were enrolled in the category of uSAID because they had clinical manifestations consistent with SAID after exclusion of either (1) other defined inflammatory conditions (ie rheumatic diseases, inflammatory bowel diseases) or other mimicking conditions (ie hematological diseases, tumors, immune deficiencies) and (2) defined autoinflammatory diseases.

Median age at which first manifestations occurred was  $3.8 \pm 6.7$  years. Eight patients (8/20; 42%) were screened for at least one autoinflammatory disease-associated gene – in most of them by Sanger sequencing of *MEFV*, *TNFRSF1A* and *MVK* and in the remainder by multigene panels –, but no mutations were found. In the past, if there was strong suspicion of a specific monogenic disease, our center first proceeded to genetic screening of *MEFV*, *TNFRSF1A* and *MVK*. Nowadays all patients are screened with a multigene panel.



## Treatment and Outcomes

For PFAPA, the most prescribed therapeutic regimen was a single dose of glucocorticoid (1mg/kg) at the beginning of a crisis. Colchicine was also prescribed to one patient due to shortening of intercritical periods and aphthae but had to be interrupted after 1 month because of gastrointestinal intolerance. Of twenty-seven PFAPA patients (27/133; 20%) who underwent tonsillectomy, twenty (20/133, 27%) achieved complete remission, three (3/133, 2%) achieved incomplete response (fever without pharyngitis) and no response was seen in four (4/133, 3%) of them.

For three of the FMF patients (3/5; 60%), the prescribed drug was colchicine 1 mg/day which led to symptom remission.

Glucocorticoids were also used in all patients with HIDS/MKD (2/2; 100%), 9 patients with uSAID (9/20; 45%), in the *NLRP12*-rSAID and DADA2 patients, as well as in 3 CNO patients (3/6; 50%). Three CNO patients (3/6; 50%) were treated with bisphosphonates.

As detailed in Table 2, five patients (5/176; 3%) were on synthetic disease-modifying anti-rheumatic drugs (sDMARDs) and five patients (5/176; 3%) were treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Three patients with CNO (3/6; 50%) and one with uSAID (1/20, 5%) also achieved sustained remission.

## Discussion

Most of our SAID cases were PFAPA. When comparing our registry to other studies, the demographic and clinical characteristics are similar, including gender distribution, age of disease onset, age at diagnosis and occurrence of abdominal pain, found in almost 70% of our patients.<sup>17</sup>

Out of 48 patients who were lost to follow-up, 45 were PFAPA cases, likely due to resolution of symptoms – expected in PFAPA<sup>18,19</sup> –, after which patients simply stopped attending visits.

Frequently, the only clinical manifestation in young infants with SAID was recurrent fever. Genetic testing was not immediately performed in these patients, since most of them have a benign clinical course and respond to prednisolone, eventually developing criteria for PFAPA. Once the diagnosis of PFAPA is established, each patient is redirected to their individual doctor.

Of the 13 patients with the diagnosis of a monogenic SAID, FMF was the most frequent one, which is in line with other studies.<sup>14,20</sup>

Regarding genetic diagnosis, one HIDS/MKD patient carried the V377I variant in the *MVK* gene, which is the most common, and it was associated with a mild phenotype and some residual MVK activity. As is the case in our patient, this variant is present in a compound heterozygous state in most HIDS/MKD patients.<sup>14,21</sup>

The TRAPS patient carried the R92Q variant in the *TNFRSF1A* gene, which is a common variant in Caucasian populations but not undoubtedly considered to be a true mutation – it could represent a low-penetrance variant, a functional polymorphism, or a susceptibility factor for inflammation, as it is associated with adult-onset and milder clinical features, as well as lower risk of amyloidosis.<sup>22,23</sup>

In the case of our patient, however, clinical manifestations suggestive of TRAPS started at 1 year of age.

Four of the monogenic SAID patients had non confirmatory genetic testing, which is expectable in up to 60% of patients with suspected SAID, despite implementation of NGS into routine diagnostic practice of SAID.<sup>24,25</sup> This is probably due to the limited number of tested genes, unknown gene mutations that may not be detected by the available molecular technology, genetic heterogeneity and/or a complex mode of inheritance.<sup>20,26</sup> Also, misdiagnosis cannot be excluded as these diseases have very similar phenotypes, which makes their clinical diagnosis difficult. It is important to continue to improve the efficiency of SAID diagnosis based on clear criteria to guide genetic screening.<sup>5,25</sup>

Regarding CAPS, it is well documented that some patients with a classical phenotype of this SAID may not have mutations in *NLRP3* gene, which can be explained by mosaicism.<sup>15,27,28</sup> Interestingly, dominant inheritance is evident in about 75% of patients with Muckle-Wells-syndrome and FCAS, whereas CINCA is usually due to *de novo* mutations and somatic mosaicism occurring during fetal growth, which may explain late onset of the disease.<sup>29–33</sup>

All mutations found in our patients are already registered as pathogenic in the Infevers database (<https://infevers.umai-montpellier.fr/web/>).<sup>34</sup>

Offering clinical expertise with a fully dedicated and multidisciplinary team is potentiated by the Reuma.pt/SAID module that guides the clinical appointment, minimizing medical error. This tool presents two simultaneous advantages: 1) it improves medical practice, and 2) it provides the center with precious, accurate and comprehensive clinical data on all patients, allowing high quality clinical and translational research.

Furthermore, our CHLN-SAID clinic enables a smooth transition from childhood to adulthood in terms of medical care, which is guaranteed by the rheumatologists of the team that continue to follow-up these patients throughout adulthood.<sup>34</sup>

The strength of this retrospective analysis is the structured data collection based on the Reuma.pt/SAID registry. Limitations of our work are the relatively short period of functioning of this clinic as well as some missing data in our registry. Another limitation is the fact that genetic testing was performed by different commercial laboratories using different gene panels, which may have underdiagnosed some genetic variants (especially when only the *MEFV*, *TNFRSF1A* and *MVK* trio was analyzed). However, we are currently working on a standardized multigene panel that will be used for all future patients followed at our clinic. Defining performance indicators and evaluating them regularly will improve the multidisciplinary team functioning.

A formalized and structured multidisciplinary clinic is vital to increase the chances of successful management of patients with SAID, and thus improve their prognosis. Maintaining this structure demands coordination, literature update, teamwork, and institutional willingness to support activities provided by a higher physician-to-patient ratio. This latter aspect has been recognized as a barrier to the development of this type of service.<sup>35,36</sup> However, establishing a multidisciplinary clinic dedicated to SAID allows to gather expertise and broaden medical knowledge. In addition, this structure helps to settle patient pathways for diagnosis and follow-up, promoting systematic monitoring and the use of treatment protocols, crucial for the management of these infrequent diseases.<sup>37</sup> This improves quality of care and opens research avenues, ultimately increasing cost-effectiveness. The goal of this paper was to share our experience with the organization of a SAID multidisciplinary clinic, coupled with an electronic registry and a biobank.

## Conclusion

In our clinic FMF was the most common monogenic condition and overall, the percentage of patients with an identified causal mutation was low.

SAID are a continuously expanding spectrum of diseases and represent a diagnostic challenge. A dedicated multidisciplinary clinic, where geneticists, pediatricians, rheumatologists, specialists in Infectious Diseases and Immunodeficiencies collaborate closely, improves diagnostic accuracy, builds clinical expertise, and allows for close monitoring of patients with these rare diseases.

The use of a structured electronic clinical record as an integrating part of our clinical activity, linked to a biobank, has been crucial for research, genetic characterization, and healthcare planning.

## Abbreviations

*ADA2*, adenosine deaminase 2 gene; AIDAI, auto-inflammatory diseases activity index; bDMARDs, biological disease-modifying antirheumatic drugs; CAMPS, CARD14 mediated psoriasis; CAPS, cryopyrin-associated periodic disease; *CARD14*, caspase recruitment domain-containing protein 14 gene; CHLN, Centro Hospitalar Universitário Lisboa Norte; CINCA, chronic infantile neurological cutaneous and articular syndrome; CNO, chronic non-bacterial osteomyelitis syndrome; DADA2, deficiency of adenosine deaminase 2 syndrome; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS/MKD, hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; IQR, interquartile range; *MEFV*, Mediterranean fever gene; *MVK*, mevalonate-kinase gene; NGS, next generation sequencing; *NLRP3*, NOD-like receptor 3 gene; *NLRP12*, NOD-like receptor 12 gene; NLRP12-rAID, NLRP12-related autoinflammatory disease; N/A, not applicable; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome; Reuma.pt, rheumatic diseases Portuguese register; SAID, systemic autoinflammatory diseases; SAPHO, synovitis–acne–pustulosis–hyperostosis–osteitis syndrome; sDMARDs synthetic disease-modifying antirheumatic drugs; *TNFRSF1A*, tumor

necrosis factor receptor superfamily member 1A gene; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; uSAID, undefined SAID.

## Disclosure

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