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Disease phenotypes in adult patients with suspected undifferentiated autoinflammatory diseases and PFAPA syndrome: Clinical and therapeutic implications

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ABSTRACT

Background: Undifferentiated autoinflammatory diseases are characterized by recurrent or persistent fever, usually combined with other inflammatory manifestations, and negative or inconclusive genetic studies for monogenic autoinflammatory disorders.
Aims: To define and characterize disease phenotypes in adult patients diagnosed in an adult reference center with undifferentiated autoinflammatory diseases, and to analyze the efficacy of the drugs used in order to provide practical diagnostic and therapeutic recommendations.
Methods: Retrospective study (2015–2022) of patients with undifferentiated autoinflammatory diseases among all patients visited in our reference center. Demographic, clinical, laboratory features and detailed therapeutic information was collected.
Results: Of the 334 patients with a suspected autoinflammatory disease, 134 (40%) patients (61% women) were initially diagnosed with undifferentiated autoinflammatory diseases. Mean age at disease onset and at diagnosis was 28.7 and 37.7 years, respectively. In 90 (67.2%) patients, symptoms started during adulthood. Forty-four (32.8%) patients met diagnostic/classification criteria for adult periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. In the remaining patients, four additional phenotypes were differentiated according to the predominant manifestations: a) Predominantly fever phenotype ($n = 18$; 13.4%); b) Predominantly abdominal/pleuritic pain phenotype ($n = 9$; 6.7%); c) Predominantly pericarditis phenotype

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(n = 18; 13.4%), and d) Complex syndrome phenotype (*n* = 45; 33.6%). Prednisone (mainly on demand), colchicine and anakinra were the drugs commonly used. Overall, complete responses were achieved with prednisone in 41.3%, colchicine in 40.2%, and anakinra in 58.3% of patients in whom they were used. By phenotypes, prednisone on demand was more effective in adult PFAPA syndrome and colchicine in patients with the abdominal/pleuritic pain pattern and PFAPA syndrome. Patients with complex syndrome achieved complete responses with prednisone (21.9%), colchicine (25.7%) and anakinra (44.4%), and were the group more often requiring additional immunosuppressive drugs.

Conclusions: The analysis of the largest single-center series of adult patients with undifferentiated autoinflammatory diseases identified and characterized different disease phenotypes and their therapeutic approaches. This study is expected to contribute to increase the awareness of physicians for an early identification of these conditions, and to provide the best known therapeutic options.

1. Introduction

Autoinflammatory diseases are a group of rare diseases characterized by episodes of recurrent or persistent fever accompanied by other systemic or organ-specific inflammatory manifestations and an increased acute phase response. Monogenic autoinflammatory conditions are caused by mutations in genes involved in inflammatory pathways producing a dysfunction of the innate immune system, in which autoantibodies or antigen-specific B or T lymphocytes do not seem to participate [1]. The discovery in 2002 of the inflammasome as a key component of the innate immune system leading to an uncontrolled production of proinflammatory cytokines, mainly interleukin (IL)-1β [2], was crucial to better understand the pathophysiology of most autoinflammatory syndromes sharing an abnormal constitutive activation of the NLRP3 inflammasome, and also responding to the pharmacological blockade of IL-1 [3]. These diseases are known as inflammasomopathies. Subsequently, new pathogenic mechanisms have been described, such as those involved in NF-κB transcription factor, ubiquitin, and interferon pathways [3–5].

Monogenic inflammasomopathies include familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), hyper-immunoglobulin (Ig)-D syndrome (HIDS), cryopyrin associated autoinflammatory syndromes (CAPS), and pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome [3,6]. Although most of them are manifested during the childhood, they can also occur in adult patients [7–10]. Compared to pediatric patients, adults with monogenic autoinflammatory diseases usually present with less severe manifestations, fewer long-term complications, and higher frequency of variants of unknown significance, non-confirmatory genotypes and post-zygotic variants [7–16].

Apart from monogenic autoinflammatory diseases, other systemic disorders with an unidentified genetic cause and mixed autoinflammatory and autoimmune backgrounds have been categorized as complex, polygenic or multifactorial autoinflammatory diseases [6,17–22]. IL-1 seems to play a prominent role in most of them, as they also respond to its specific blockade [6,17–22]. Some of these complex autoinflammatory conditions include periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome, Behçet's disease, Still's disease, Schnitzler syndrome, Crohn's disease and gout [6,17–22].

In addition to monogenic and polygenic autoinflammatory disorders, a third group has been recognized during the last years as undifferentiated autoinflammatory diseases, also named undefined [23–26] or unclassified diseases [27–29], and more recently syndromes of undifferentiated recurrent fever (SURF) in children [30,31]. They include those clinical situations presenting with recurrent or persistent fever, either alone or combined with a wide spectrum of inflammatory manifestations, in which infectious, neoplastic and autoimmune causes have been ruled out and genetic studies for monogenic autoinflammatory disorders are negative or inconclusive [7,8,23–30,32–36]. These undifferentiated syndromes have been often reported to respond to colchicine, glucocorticoids, and/or IL-1 blockers, such as anakinra [23–26,28,30–32,34–36]. Several studies have tried to identify predictors of response to colchicine or anakinra in patients with these conditions [25,30,34]. However, no previous attempts to define and characterize different phenotypes of undifferentiated autoinflammatory diseases have been conducted.

The present study aimed to identify and characterize disease phenotypes in adult patients with undifferentiated autoinflammatory diseases diagnosed in an adult reference center. Clinical and biological features, and the efficacy of the drugs used for patients in every phenotype were described and analyzed in order to provide practical recommendations for potential diagnostic and therapeutic approaches in these undifferentiated disorders.

2. Material and methods

2.1. Study design and inclusion/exclusion criteria

Among all patients referred to our adult Autoinflammatory Diseases Clinical Unit, a Catalonian, Spanish and European reference unit at the Department of Autoimmune Diseases, Hospital Clínic of Barcelona, between January 2015 and December 2022, those with a final diagnosis of an undifferentiated autoinflammatory disease were included in the study.

Patients were considered to have an undifferentiated autoinflammatory disease when they presented with recurrent or persistent fever alone and/or other concomitant systemic or single-organ manifestations during a period of at least 6 months, always having ruled out alternative diagnoses of infectious, neoplastic and autoimmune diseases. In addition, germline and post-zygotic pathogenic variants as part of confirmatory genotypes associated with monogenic autoinflammatory diseases had to be absent in a next generation sequencing (NGS) targeted gene panel of 65 genes (*ADA2*, *ADAR*, *ADGRE2*, *AP1S3*, *ARPC1B*, *CARD14*, *COPA*, *CTLA4*, *DNASE1*, *DNASE1L3*, *DNASE2*, *EGFR*, *ELANE*, *FOXP3*, *IFIH1*, *IKZF1*, *IL10*, *IL10RA*, *IL10RB*, *IL1RN*, *IL36RN*, *ISG15*, *LACC1*, *LPIN2*, *MEFV*, *MVK*, *MYD88*, *NCSTN*, *NFKB1*, *NFKBIA*, *NLRC4, NLRP1, NLRP12, NLRP3, NOD2, OTULIN, PLCG2, POMP, PSENEN, PSMA3, PSMB4, PSMB8*, *PSMB9*, *PSMG2*, *PSTPIP1*, *RBCK1*, *RELA*, *RIPK1*, *RNASEH2A, RNASEH2B, RNASEH2C*, *RNF31*, *SAMD9L*, *SAMHD1*, *SERPING1*, *TMEM173*, *TNFAIP3*, *TNFRSF11A*, *TNFRSF1A*, *TREX1*, *TRNT1*, *USP18*, *WAS*, *WDR1*, *and XIAP*).

In patients in whom genetic variants were detected, their potential pathogenic function was interpreted according to Infevers Registry, and only patients with benign or probably benign mutations, and variants of unknown significance (VUS) were included [37]. For the most frequent monogenic autoinflammatory diseases (FMF, TRAPS, CAPS, and HIDS), only those patients with VUS or non-confirmatory genotypes, not associated with the diagnosis of any of these monogenic condition based on Eurofever/PRINTO classification criteria were included [38].

Based on the predominant or clinically relevant manifestations, patients with undifferentiated autoinflammatory diseases were subsequently divided into different phenotype categories. Although PFAPA syndrome is a well-characterized pediatric disease in which previous attempts to find a genetic cause in children failed [39,40], it is still poorly recognized and not genetically investigated in adult subjects.

Because all our patients diagnosed with adult PFAPA syndrome were initially considered to have an undifferentiated autoinflammatory disease (with which can be easily confounded or misdiagnosed), this condition was separately analyzed in order to be compared with the remaining undifferentiated autoinflammatory phenotypes. Nevertheless, patients with a suspected adult PFAPA syndrome had to either fulfilled Eurofever Registry/Pediatric Rheumatology International Trials Organization (PRINTO) classification criteria [38] or Cantarini diagnostic criteria for adult-onset PFAPA syndrome [41].

Response to treatment was considered as complete, when total control of symptoms and inflammatory parameters were achieved with the used medication, and partial, when the treatment was associated with any clinical improvement (not complete) that allowed to continue taking the drug.

2.2. Data collection

Demographic, clinical, laboratory and genetic data were retrospectively obtained from electronic medical records and transferred to an anonymized database. Sex, age at disease onset and age at diagnosis (adults ≥16 years and children <16 years), family history of recurrent fever, trigger identification, disease presentation forms (periodic or persistent), duration/frequency of the attacks, and the presence of fever, asthenia, lymphadenopathy, splenomegaly, and musculoskeletal, throat, mucocutaneous, ocular, abdominal, thoracic and neurological manifestations were recorded. Collected laboratory parameters during attacks and asymptomatic periods included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and hemoglobin levels, leukocyte and platelet counts, renal function, urinalysis and presence of autoantibodies. Genetic variants considered benign, likely benign or VUS not associated with a diagnosis of a monogenic condition were also collected. Imaging tests performed during the diagnostic process and all treatments administered, the order (lines) of administration, and the response to them were analyzed.

2.3. Statistical study

Qualitative variables were expressed as absolute numbers and frequencies and compared using Fisher's exact test. The quantitative variables following a normal and non-normal distribution were presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) [percentiles 25th - 75th], and were compared using Students *t*-test or U-Mann Whitney test, respectively. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using *IBM SPSS Statistics* software packages.

2.4. Ethical considerations

This retrospective study was approved by the Research Ethics Committee of the Hospital Clínic of Barcelona (HCB/2021/1044). Patients' information was dissociated prior to analysis, all of them signed an informed consent to participate in the study, and all procedures were performed in accordance with the ethical principles expressed in the 2013 Declaration of Helsinki.

3. Results

3.1. Total number of patients diagnosed with autoinflammatory diseases

Between 2015 and 2022, 364 patients were evaluated at our Autoinflammatory Diseases Clinical Unit for suspicion of autoinflammatory diseases. Since 30 (8.3%) patients were referred with a previously performed genetic test study and already diagnosed with monogenic conditions, genetic studies of autoinflammatory genes were carried out in our unit in 334 patients. Among these 334 patients, 70 (21%) cases were diagnosed with monogenic diseases.

In 264 (79%) patients, the genetic study was negative or inconclusive. In 108 (32.4%) patients, an alternative non-autoinflammatory diagnosis was reached and included different systemic autoimmune diseases (systemic erythematosus lupus, systemic vasculitis, polymyalgia rheumatica, sarcoidosis, inflammatory bowel disease and other diseases with autoimmune features not fulfilling complete diagnostic or classification criteria), infectious diseases (citomegalovirus, Epstein-Barr virus, human herpesvirus 6 and parvovirus B19 infections, and Whipple's disease), neoplastic diseases (lymphoma and mesothelioma), and conditions such as sensorineural hearing loss, allergic urticaria, angioedema, and celiac disease, among others.

Of the remaining 156 (46.5%) patients with a negative genetic study, 22 (7%) subjects were diagnosed with adult polygenic autoinflammatory diseases, including Behçet disease ($n = 12$; 3.6%), adult-onset Still disease ($n = 7$; 2.1%), Schnitzler syndrome ($n = 3$; 0.9%), and 134 (40%) patients were categorized as having undifferentiated autoinflammatory diseases. The Fig. 1 illustrates the study flow diagram of all the patients visited and diagnosed with autoinflammatory diseases in our adult clinical unit.

3.2. Global series of patients with undifferentiated autoinflammatory diseases

3.2.1. Demographic, family history and triggers

Of the 134 patients with initially suspected undifferentiated autoinflammatory diseases, 82 (61.2%) were women and 130 (97%) had a Caucasian origin. The mean (SD) age at disease onset was 28.7 ± 19.7 years, and at diagnosis was 37.7 ± 15.3 years. In 90 (67.2%) patients, autoinflammatory symptoms started during adulthood (≥16 years). The median (IQR) time elapsed from clinical manifestations onset to disease diagnosis was of 6 (2–17) years, and patients were followed for a median (IQR) of 48 (16–108) months. Family history of first or second degree relatives with symptoms suggestive of periodic fever was detected in 26 (19.4%) patients. Triggering factors were identified in 62 (46.3%) cases, and included infections, emotional and physical stress, menstruation, vaccination and alcohol consumption.

3.2.2. Clinical, laboratory, imaging, biopsy and genetic results

A disease course with recurrent attacks occurred in 94 (70.1%) patients, and 40 (29.9%) subjects presented with persistent/prolonged course. A limited disease course not requiring any specific treatment was documented in 4 (3%) individuals. In the 94 patients with recurrent symptoms, median (IQR) duration of the attacks was 4 (3–7) days, the number of annual attacks was 12 (4–12), and 43 (45.7%) subjects presented with attacks at regular intervals.

Regarding clinical manifestations, fever was presented by 117 (87.3%) patients, with a median (IQR) maximum temperature of 39 °C (38–39.5 °C), followed by asthenia ($n = 76$; 56.7%), arthralgia ($n = 65$; 48.5%), sore throat ($n = 52$; 38.8%), lymphadenopathy ($n = 51$; 38.1%), myalgia ($n = 48$; 35.8%) and oral aphthae ($n = 38$; 28.4%). Other demographic and clinical features are included in Table 1. No patient developed secondary amyloidosis or died during the follow-up.

In the 111 and 107 patients in whom CRP and ESR levels were determined, these markers were increased during attacks in 74 (66.7%) and 52 (48.6%) of them, respectively. Leukocytosis and anemia were detected in 29 (26.1%) and 22 (19.8%) of 111 patients during attacks. A third of patients exhibited normal CRP levels during attacks. One hundred eighteen (88.1%) patients had normal acute phase reactants levels during intercritical or asymptomatic periods. Compared to intercritical periods, CRP and ESR levels, and leukocyte counts significantly increased ($p < 0.001$) and hemoglobin values decreased ($p = 0.006$) during attacks (Table 2). Sustained proteinuria (>200 mg/day) was not detected in any patient during the study period. Antinuclear antibodies without clinical relevance were identified by immunofluorescence in 28 (20.9%) patients.

Imaging studies, such as echocardiogram, abdominal ultrasound and

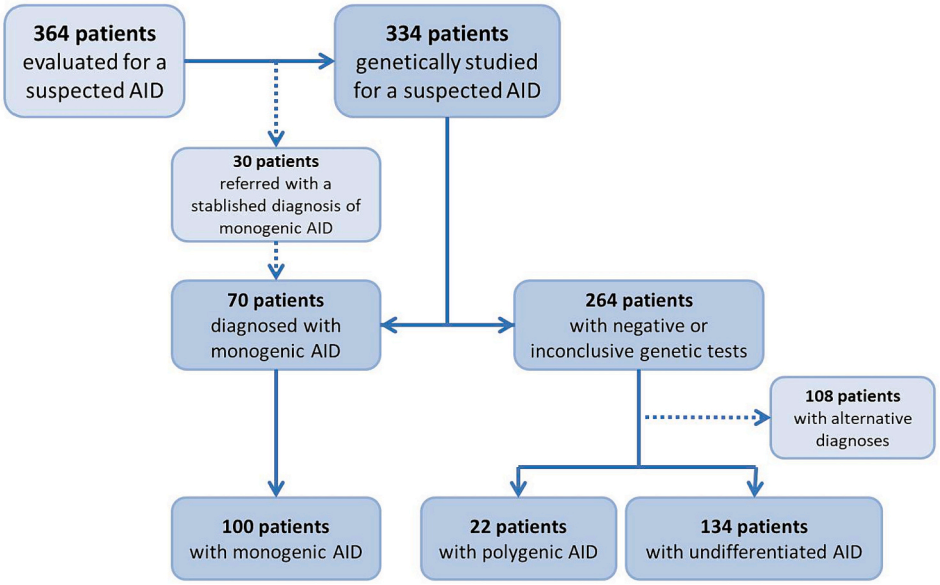

Fig. 1. Flowchart of patients with autoinflammatory diseases included in the study.

computed tomography (CT) or positron emission tomography (PET)-CT scan were performed in 25 (18.7%), 10 (7.5%), and 48 (35.8%) patients, respectively. Abnormal results of these imaging tests were evidenced in 16 (64%), 4 (40%) and 25 (52.1%) cases, respectively (Table 2). A total of 63 biopsies were performed in 39 (29.1%) patients, with abnormal but inconsistent results to achieve an alternative diagnosis in 30 (47.6%) samples (Table 2).

A genetic study of monogenic autoinflammatory diseases was performed in all patients. In 72 (53.7%) patients, 89 heterozygous variants considered benign, likely benign or VUS were found in genes associated with monogenic autoinflammatory diseases. VUS more frequently found in the genes encoding for the monogenic autoinflammatory diseases included *MEFV* ($n = 19$), *NOD2* ($n = 12$), *NLRP3* ($n = 7$), *RIPK1* ($n = 6$), *ADA2, NLRP12* and *TNFAIP3* (4 each), and *MVK*, *TNFRSF1A* and *NLRP1* genes (3 each). No patient fulfilled Eurofever/PRINTO classification criteria for FMF, TRAPS, CAPS or HIDS when considering these variants as part of a non-confirmatory genotype [38]. *NOD2* variants did not cause Blau syndrome in any patient, and variants in the *ADA2* gene were not associated with DADA2 since they were found in heterozygosity in all patients.

3.2.3. *Effectiveness of the therapeutic schemes used*

Seven (5.2%) patients presenting with recurrent inflammatory manifestations for a median (range) of 48 (16–108) months experienced a limited course of the disease without taking any specific treatment. Overall, 109 (81.3%) patients were treated with glucocorticoids (68 [50.7%] on demand and 41 [30.6%] continuous during prolonged periods), 97 (72.4%) subjects received colchicine, and anakinra was administered to 36 (26.9%) patients. Prednisone on demand was used at the beginning of the flares at medium-to-high doses (0.5 to 1 mg/Kg/day), usually during 1 to 3 days.

At the end of the study, 25 (18.7%) patients were off treatment after a median (range) asymptomatic period of 41 (15–81) months. Among patients that were still on treatment, 63 (47%) were receiving prednisone, of them 46 (34.3%) on demand, and 17 (12.7%) continuously, at a mean (SD) daily dose of 9.3 ± 6.2 mg. Sixty-five (48.5%) subjects were on colchicine, at a median (IQR) dose of 1 (1–1.5) mg/day. Among them, 25 (18.7%) were on colchicine alone, 24 (17.9%) with prednisone (18 on demand and 6 continuous), 11 (8.2%) were combining colchicine with anakinra, and 5 (3.7%) were taking colchicine with other drugs. Anti-IL-1 agents were being used in 21 (15.7%) individuals (18 on anakinra at 100 mg/day and 3 on canakinumab at 150 mg every 1–2 months, subcutaneously). Anakinra was administered on demand and continuously in 3 (2.2%) and 18 (13.4%) patients, respectively.

Overall, prednisone on demand was effective in 46/68 (67.6%) cases, and its continuous administration in 17/41 (41.5%) patients. Colchicine was of some benefit in 80/97 (85.5%) patients, by achieving complete and partial response in 39 (40.2%) and 41 (42.3%), respectively. IL-1 blockers were useful in some degree in 28/36 (77.8%) patients.

Colchicine was discontinued by 32/97 (33%) patients, 23 (71.9%) of them because of lack of efficacy and 9 (28.1%) due gastrointestinal intolerance, mainly diarrhea. Anakinra was stopped by 15/36 (41.7%) patients because lack of efficacy ($n = 11$) or injection site reactions ($n = 4$). Other immunosuppressive agents were used in 23 (17.2%) patients (Table 3). These drugs included methotrexate and other cytotoxic drugs ($n = 16$), anti-TNF agents (etanercept, infliximab, and adalimumab) ($n = 11$), tocilizumab ($n = 6$), rituximab ($n = 5$) and baricitinib ($n = 3$), of which 10 (7.5%) agents (2 anti-TNF, 2 tocilizumab, 3 rituximab and 3 baricitinib) were still being used at the end of follow-up. Treatment characteristics and response to the different drugs used are summarized in Table 3.

3.3. *Differentiating phenotypes of undifferentiated autoinflammatory diseases*

After identifying patients with adult PFAPA syndrome because they fulfilled Eurofever/PRINTO classification criteria [38] or Cantarini diagnostic criteria for adult-onset PFAPA syndrome [41], patients with undifferentiated autoinflammatory diseases were divided into four additional phenotype categories: a) *Predominantly fever phenotype*: patients with recurrent or persistent fever alone or with concomitant musculoskeletal manifestations (if present); b) *Predominantly abdominal/pleuritic pain phenotype*: patients with abdominal and/or thoracic pain due to peritoneal or pleuritic inflammation (without clinically evident pericardial involvement); c) *Predominantly pericarditis phenotype*: patients with recurrent or sustained pericarditis; and d) *Complex syndrome phenotype*: patients with fever and multiorganic involvement in whom no clear territory or manifestation was predominant over the others.

Table 1
Demographic and clinical characteristics of patients with different undifferentiated autoinflammatory disease phenotypes and adult PFAPA syndrome.

Characteristics/Phenotypes	Predominantly Fever	Predominantly abdominal/ pleuritic pain	Predominantly Pericarditis	Complex syndrome	Adult PFAPA syndrome	Total
Number of patients	18	9	18	45	44	134
Demographic						
Women/Men; n (%)	11/7 (61/39)	9/0 (100/0)	10/8 (56/44)	28/17 (62/38)	24/20 (55/45)	82/52 (61/39)
Age (years); mean (SD)	48.5 ± 14.4	57.1 ± 20.4	41.9 ± 19.5	44.5 ± 12.8	33.8 ± 11	42 ± 15.5
Caucasian ethnicity; n (%)	18 (100)	9 (100)	18 (100)	43 (95.6)	42 (95.5)	130 (97)
Family history of periodic fever; n (%)	1 (5.6)	0 (0)	4 (22.2)	9 (20)	12 (27.3)	26 (19.4)
Known attack trigger; n (%)	5 (27.8)	4 (44.4)	7 (38.9)	20 (45.4)	26 (59.1)	62 (46.3)
Follow-up time (months); median (range)	25 (18–91)	37 (20–98)	86 (25–108)	51 (20–108)	46 (16–108)	48 (16–108)
Disease presentation						
Adult onset (≥16 years); n (%)	16 (88.9)	7 (77.8)	11 (61.1)	35 (77.8)	21 (47.7)	90 (67.2)
Diagnosis at adult age; n (%)	18 (100)	9 (100)	15 (83.3)	44 (97.8)	40 (90.9)	126 (94)
Age at diagnosis (years); mean (SD)	46 ± 14.8	54 ± 21	38.1 ± 20.8	41.4 ± 13	29.7 ± 12.2	37.7 ± 15.3
Age at symptoms onset (years); mean (SD)	39 ± 17	43.7 ± 28.8	33.2 ± 21.1	31.6 ± 16.6	16.6 ± 14.6	28.7 ± 19.7
Time to diagnosis (years); median (IQR)	3 (1–7)	3 (1–19)	3 (1–7)	6 (2.5–16.5)	9.5 (3–22.5)	6 (2–17)
Course of disease; n (%)						
Recurrent	14 (77.8)	5 (55.6)	12 (66.7)	26 (57.8)	37 (84.1)	94 (70.1)
Persistent	4 (22.2)	4 (44.4)	6 (33.3)	19 (42.2)	7 (15.9)	40 (29.9)
Attacks characteristics						
Duration (days); median (IQR)	3.5 (2.5–5)	1.5 (1–2)	3 (3–5)	3 (2–7)	5.5 (3–7)	4 (3–7)
Number of attacks per year; median (IQR)	10 (4–24)	12 (9–30)	3 (2.5–10.5)	5.5 (3−12)	12 (10−12)	12 (4–12)
Clinical manifestations; n (%)						
Fever	18 (100)	3 (33.3)	12 (66.7)	42 (93.3)	42 (95.5)	117 (87.3)
*Temperature (*max *°C)*	38.8 (38–39)	38.5 (38–39)	38 (38–39)	39 (38–39)	39 (38–39.5)	39 (38–39.5)
Asthenia	16 (88.9)	4 (44.4)	6 (33.3)	23 (51.1)	27 (61.4)	76 (56.7)
Musculoskeletal	11 (61.1)	1 (11.1)	2 (11.1)	33 (73.3)	28 (63.6)	75 (56)
Arthralgia	8 (44.4)	1 (11.1)	2 (11.1)	30 (66.7)	24 (54.5)	65 (48.5)
Arthritis	3 (16.7)	0 (0)	1 (5.6)	12 (26.7)	0 (0)	16 (11.9)
Myalgia	6 (33.3)	1 (11.1)	1 (5.6)	19 (42.2)	21 (47.7)	48 (35.8)
Throat	1 (5.6)	0 (0)	2 (11.1)	11 (25)	38 (86.4)	52 (38.8)
Pharyngitis/Odynophagia	1 (5.6)	0 (0)	2 (11.1)	11 (24.4)	37 (84.1)	51 (38.1)
Tonsillitis	0 (0)	0 (0)	0 (0)	2 (4.4)	29 (65.9)	31 (23.1)
Cutaneous	0 (0)	0 (0)	0 (0)	29 (64.4)	8 (18.2)	37 (27.6)
Maculopapular rashes/plaques	0 (0)	0 (0)	0 (0)	16 (35.6)	7 (15.9)	23 (17.2)
Urticarial rashes	0 (0)	0 (0)	0 (0)	5 (11.1)	0 (0)	5 (3.7)
Mixed cutaneous lesions	0 (0)	0 (0)	0 (0)	6 (13.3)	0 (0)	6 (4.5)
Facial edema	0 (0)	0 (0)	0 (0)	7 (15.6)	2 (4.5)	9 (6.7)
Mucosal	0 (0)	0 (0)	1 (5.6)	12 (26.7)	25 (56.8)	38 (28.4)
Oral aphthae	0 (0)	0 (0)	1 (5.6)	12 (26.7)	25 (56.8)	38 (28.4)
Genital ulcers	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.3)	1 (0.7)
Ocular	0 (0)	0 (0)	1 (5.6)	13 (28.9)	2 (4.5)	16 (11.9)
Periorbital edema	0 (0)	0 (0)	0 (0)	7 (15.6)	0 (0)	7 (5.2)
Conjunctivitis	0 (0)	0 (0)	0 (0)	2 (4.4)	2 (4.5)	4 (3)
Uveitis	0 (0)	0 (0)	1 (5.6)	5 (11.1)	0 (0)	6 (4.5)
Abdominal	1 (5.6)	8 (88.9)	0 (0)	23 (51.1)	13 (29.5)	45 (33.6)
Abdominal pain	0 (0)	8 (88.9)	0 (0)	16 (35.6)	11 (25)	35 (26.1)
Diarrhea	0 (0)	2 (22.2)	0 (0)	13 (28.9)	7 (15.9)	22 (16.4)
Vomiting	1 (5.6)	4 (44.4)	0 (0)	3 (6.7)	2 (4.5)	10 (7.5)
Thoracic	0 (0)	3 (33.3)	18 (100)	8 (17.8)	1 (2.3)	30 (22.4)
Chest pain	0 (0)	1 (11.1)	15 (83.3)	7 (15.6)	1 (2.3)	24 (17.9)
Pericarditis	0 (0)	0 (0)	18 (100)	5 (11.1)	1 (2.3)	25 (18.7)
Pleuritis	0 (0)	3 (33.3)	9 (50)	4 (8.9)	0 (0)	15 (11.1)
Neurological	3 (16.7)	1 (11.1)	2 (11.1)	14 (31.1)	15 (34.1)	35 (26.1)
Headache	2 (11.1)	1 (11.1)	2 (11.1)	14 (31.1)	15 (34.1)	34 (25.4)
Sensorineural hearing loss	1 (5.6)	0 (0)	0 (0)	1 (2.2)	1 (2.3)	3 (2.2)
Lymphadenopathy	0 (0)	0 (0)	2 (11.1)	17 (37.8)	32 (72.7)	51 (38.1)
Peripheral/cervical adenitis	0 (0)	0 (0)	1 (5.6)	8 (17.8)	28 (63.6)	40 (29.9)
Generalized	0 (0)	0 (0)	1 (5.6)	9 (20)	4 (9.1)	11 (8.2)
Splenomegaly	2 (11.1)	0 (0)	0 (0)	5 (11.1)	3 (6.8)	10 (7.5)

Abbreviations: IQR = interquartile ranges [percentiles 25th - 75th]; PFAPA = Periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis; SD = Standard deviation.

Table 2
Laboratory, imaging and histopathologic data of patients with different undifferentiated autoinflammatory disease phenotypes and adult PFAPA syndrome.

Laboratory and Imaging features*	Predominantly Fever	Predominantly abdominal/ pleuritic pain	Predominantly Pericarditis	Complex syndrome	Adult PFAPA syndrome	Total**
Number of patients	18	9	18	45	44	134
CRP (mg/dL)						
Attacks	4.7 (0.9–11.5)	5.7 (0.4–18)	6 (3.9–13.3)	5.7 (1.2–14.1)	4.8 (2.8–9.5)	5.5 (2.2–12)
Intercritical periods	0.4 (0.4–0.4)	0.4 (0.4–2)	0.4 (0.4–0.4)	0.4 (0.4–0.8)	0.4 (0.4–0.4)	0.4 (0.4–0.4)
ESR (mm/1st hour)						
Attacks	64 (7–140)	15 (5–28)	57 (21–76)	33 (9–79)	20 (9–45)	25 (9–72)
Intercritical periods	10 (5–19)	5.5 (4–8)	5 (4–8)	7 (5–14)	6 (4–10)	6 (4–11)
Hemoglobin (g/L)						
Attacks	118 ± 17	108 ± 47.2	126 ± 35.3	122 ± 32	134 ± 15	124.3 ± 29.4
Intercritical periods	135.2 ± 13	135.3 ± 15.4	145.1 ± 11	134.2 ± 26.1	139.4 ± 25.2	137.7 ± 22.2
Leukocytes (cells/mm^3)						
Attacks	11,849 ± 5450	12,787 ± 10,029	12,005 ± 3996	9859 ± 7003	9681 ± 3630	10,615 ± 5789
Intercritical periods	6933 ± 2449	7788 ± 2786	7048 ± 1802	7663 ± 3399	6575 ± 1527	7115 ± 2505
Platelets (x10^9/L)						
Attacks	257.4 ± 798	285.6 ± 790	271.8 ± 624	280 ± 151	248 ± 992	267 ± 112
Intercritical periods	236.2 ± 767	293 ± 147	217.7 ± 515	244 ± 722	241 ± 529	242 ± 73
Imaging tests performed; n (%)						
Echocardiogram	1 (5.6)	4 (44.4)	17 (94.4)	3 (6.7)	0 (0)	25 (18.7)
Abnormal result; n (%)	0 (0)	0 (0)	15 (88.2)	1 (33.3)	0 (0)	16 (66.7)
CT/PET-CT scan	2 (11.1)	6 (66.7)	8 (44.4)	31 (68.9)	1 (2.3)	48 (35.8)
Abnormal result; n (%)	1 (50)#	3 (50)¦	3 (37.5)¦¦	17 (54.8)§	1 (100)~	25 (52.1)
Patients underwent any biopsy; n (%)	2 (11.1)	4 (44.4)	1 (5.6)	21 (46.7)	11 (25)	39 (29.1)
Biopsies performed; n (%)	2 (11.1)	4 (44.4)	1 (5.6)	44 (97.8)	12 (27.3)	63 (47)
Skin	0 (0)	0 (0)	0 (0)	14 (31.1)	4 (9.1)	18 (13.4)
Adenopathy	0 (0)	0 (0)	0 (0)	5 (11.1)	6 (13.6)	11 (8.2)
Gastrointestinal tract	0 (0)	1 (11.1)	1 (5.6)	9 (20)	1 (2.3)	12 (9)
Serosal	0 (0)	3 (33.3)	0 (0)	1 (2.2)	0 (0)	4 (3)
Tonsil	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (2.3)	2 (1.5)
Oral mucosa	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (0.7)
Hepatic	0 (0)	0 (0)	0 (0)	4 (8.9)	0 (0)	4 (3)
Lung	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (0.7)
Muscle	1 (5.6)	0 (0)	0 (0)	5 (11.1)	0 (0)	6 (4.5)
Renal	1 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Bone marrow aspirate	0 (0)	0 (0)	0 (0)	3 (6.7)	0 (0)	3 (2.2)
Abnormal biopsy results; n (%)	0 (0)	0 (0)	0 (0)	22 (50)¥	8 (66.7)•	30 (47.6)

Abbreviations: CRP = C-reactive protein; CT = Computed tomography; ESR = Erythrocyte sedimentation rate; PFAPA = Periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis; PET = Positron emission tomography.
CT scan with supradiaphragmatic lymphadenopathy (1 patient).
¦ PET-CT scan with pleural and pleuropericardial effusion (1 patient each), and CT scan with mesenteric panniculitis (1 patient).
¦¦ PET-CT scan with pleuropericardial effusion (1 patient) and pericardial effusion and pulmonary infiltrate (1 patient), and CT scan with pleuropericardial and peritoneal effusion (1 patient).
§ PET-CT scan with hypermetabolic involvement of supra- and/or infradiaphragmatic hypermetabolic lymphadenopathy (8 patients) with additional splenomegaly (4 patients), tonsils and cutaneous hypermetabolic lesions (1 patient each); supradiafragmatic lymphadenopathy (1 patient); adenoid hypermetabolism (1 patient); and mild large vessels hypermetabolism (1 patient). CT scan with pelvic fluid (2 patients); infradiaphragmatic lymphadenopathy (1 patient); splenomegaly (1 patient); pulmonary infiltrate (1 patient); and mesenteric panniculitis (1 patient).
~ PET-CT scan with hypermetabolic involvement of tonsils and supra- and infradiaphragmatic lymphadenopathy (1 patient).
¥ Abnormal biopsies (n = 22): Skin (n = 11): perivascular chronic dermatitis (n = 3); nodular septal panniculitis (n = 2); neutrophilic dermatosis (n = 2); leukocytoclastic vasculitis (n = 2); occlusive vasculopathy (n = 1), and urticarial dermatitis (n = 1); Lymph node biopsy (n = 5): reactive lymphadenitis (n = 5) with additional histiocytic inflammation in 2 patients; Gastrointestinal tract: non-conclusive inflammatory lesions (n = 5); Liver (n = 3): histiocytic inflammation (n = 1); autoimmune hepatitis (n = 1); and hepatic steatosis (n = 1); Muscle: non-specific inflammatory changes (n = 2); and Bone marrow aspirate: myelodysplastic changes (n = 1).
• Abnormal biopsies (n = 8): Skin: leukocytoclastic vasculitis (n = 1); Lymph node: reactive lymphadenitis (n = 6); and Tonsil: reactive follicular hyperplasia (n = 1).
*From patients with available data.
** Differences between values determined during attacks and intercritical periods were observed for CRP, ESR and leucocyte counts (p-value < 0.001) and hemoglobin levels (p-value = 0.006).

3.4. Characterizing undifferentiated autoinflammatory disease phenotypes

Clinical characteristics and acute phase reactant levels during attacks and asymptomatic periods in patients with undifferentiated autoinflammatory disease phenotypes and adult PFAPA syndrome, and all details about the main imaging test and biopsies performed (and their results), are illustrated in Tables 1 and 2, respectively. All details about the drugs used, the order (lines) of administration, and the response to them are depicted in Table 3. The most significant discriminating features are next summarized for every group.

Predominantly fever phenotype: 18 (13.4%) patients presented with fever, mostly recurrent (77.8%). Among them, 11 (61.1%) individuals also suffered musculoskeletal complaints (Table 1). During attacks, 7 of 14 (50%) patients with available data presented with elevated levels of CRP and ESR, leukocytosis and anemia, which normalized in

Table 3
Treatments used and their responses in patients with different undifferentiated autoinflammatory disease phenotypes and adult PFAPA syndrome.

Treatment characteristics / Phenotypes	Predominantly Fever	Predominantly abdominal/ pleuritic pain	Predominantly Pericarditis	Complex syndrome	Adult PFAPA syndrome	Total
Number of patients	18	9	18	45	44	134
Symptomatic treatment only; n (%)	5 (27.8)	0 (0)	0 (0)	0 (0)	2 (4.5)	7 (5.2)
Prednisone; n (%)	**10 (55.6)**	**6 (66.7)**	**14 (77.8)**	**41 (91.1)**	**38 (86.4)**	**109 (81.3)**
On demand	6 (33.3)	3 (33.3)	6 (33.3)	18 (40)	35 (79.5)	68 (50.7)
Continuous	4 (22.2)	3 (33.3)	8 (44.4)	23 (51.1)	3 (6.8)	41 (30.6)
Response						
Complete	3 (30)	3 (50)	6 (42.9)	9 (21.9)	24 (63.2)	45 (41.3)
Partial	5 (50)	3 (50)	7 (50)	26 (63.4)	11 (28.9)	52 (47.7)
None	2 (20)	0 (0)	1 (7.1)	6 (14.6)	3 (7.9)	12 (11)
At the end of follow-up	6 (33.3)	3 (33.3)	3 (16.7)	24 (53.3)	27 (61.4)	63 (47)
On demand	4 (22.2)	1 (11.1)	2 (11.1)	12 (26.7)	27 (61.4)	46 (34.3)
Continuous	2 (11.1)	2 (22.2)	1 (5.6)	12 (26.7)	0 (0)	17 (12.7)
Colchicine; n (%)	**8 (44.4)**	**9 (100)**	**18 (100)**	**35 (77.8)**	**27 (61.4)**	**97 (72.4)**
Response						
Complete	2 (25)	7 (77.8)	6 (33.3)	9 (25.7)	15 (55.6)	39 (40.2)
Partial	6 (75)	1 (11.1)	11 (61.1)	15 (42.9)	8 (29.6)	41 (42.3)
None	0 (0)	1 (11.1)	1 (5.6)	11 (31.4)	4 (14.8)	17 (17.5)
At the end of follow-up	8 (44.4)	7 (77.8)	14 (77.8)	16 (35.6)	20 (45.5)	65 (48.5)
Colchicine only	3 (16.7)	4 (44.4)	9 (50)	4 (8.9)	5 (11.4)	25 (18.7)
Anakinra; n (%)	**3 (16.7)**	**1 (11.1)**	**6 (33.3)**	**18 (40)**	**8 (18.2)**	**36 (26.9)**
Response						
Complete	2 (66.7)	1 (100)	5 (83.3)	8 (44.4)	5 (62.5)	21 (58.3)
Partial	0 (0)	0 (0)	1 (16.7)	4 (22.2)	2 (25)	7 (19.4)
None	1 (33.3)	0 (0)	0 (0)	6 (33.3)	1 (12.5)	8 (22.2)
At the end of follow-up	1 (5.6)	1 (11.1)	3 (16.7)	9 (20)*	7 (15.9)#	21 (15.7)
On demand	0 (0)	0 (0)	2 (11.1)	0 (0)	1 (2.3)	3 (2.2)
Continuous	1 (5.6)	1 (11.1)	1 (5.6)	9 (20)*	6 (13.6)#	18 (13.4)
Other immunosuppressive agents						
Number of patients treated; n (%)	1 (5.6)	0 (0)	2 (11.1)	18 (40)	2 (4.5)	23 (17.2)
Methotrexate; n **	1	0	2	11	2	16
Anti-TNF; n	0	0	0	11	0	11
Tocilizumab; n	0	0	0	6	0	6
Baricitinib; n	0	0	0	3	0	3
Rituximab; n	0	0	0	5	0	5
Patients receiving >1 drug; n (%)	0 (0)	0 (0)	0 (0)	9 (20)	0 (0)	9 (6.7)
Lines of anti-inflammatory therapies						
First prednisone / Second colchicine						
Initial prednisone	8 (44.4)	2 (22.2)	3 (16.7)	27 (60)	30 (68.2)	70 (52.2)
Additional colchicine	3 (16.7)	2 (22.2)	2 (11.1)	13 (28.9)	14 (31.8)	34 (25.4)
First colchicine / Second prednisone						
Initial colchicine	5 (27.8)	6 (66.7)	11 (61.1)	22 (48.9)	13 (29.5)	57 (42.5)
Additionalprednisone	2 (11.1)	3 (33.3)	6 (33.3)	14 (31.1)	8 (18.2)	33 (24.6)
First line combined colchicine/prednisone	0 (0)	1 (11.1)	5 (27.8)	0 (0)	0 (0)	6 (4.5)
No treatment at the end of the study						
Patients without treatment; n (%)	8 (44.4)	1 (11.1)	4 (22.2)	5 (11.1)	7 (15.9)	25 (18.7)
Period without treatment (months); median (range)	39 (23–67)	71 (–)	65 (16–66)	33 (15–77)	32 (21–81)	41 (15–81)

Abbreviations: PFAPA = Periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis; TNF = Tumor necrosis factor.
* One and # two patients were treated with canakinumab with success because of incomplete effect of anakinra.
** Methotrexate and other conventional immunosuppressive agents.

asymptomatic periods in 16 (88.9%) cases. Twelve VUS were detected in 9 (50%) patients (2 variants each in *MEFV*, *NLRP3, NOD2*, and *PLCG2* genes). PET-CT scan and biopsies were performed in 2 (11.1%) patients each (Table 2). Five (27.8%) patients had a limited course for which no specific treatment was administered. Prednisone was used in 10 (55.6%) patients with different responses (3 complete, 5 partial, and 2 no response). Colchicine was used in 8 (44.4%) subjects, 2 with complete and 6 with partial response. Anakinra was administered to 3 (16.7%) patients, 2 with complete and 1 without response. At the end of follow-up, 8 (44.4%) patients were off treatment during a median (range) of 39 (23–67) months (Table 3).

Predominantly abdominal/pleuritic pain phenotype: 9 (6.7%) patients mostly presented with abdominal ($n = 8$) or pleuritic ($n = 2$) pain. Fever was concomitantly present in 3 (33.3%) cases (Table 1). Five 5 (55.6%) patients had increased CRP levels during attacks and 2 (22.2%) during asymptomatic periods. Four VUS were found in 4 (44.4%) patients (one each in *MEFV*, *NOD2*, *ADA2*, and *PSTPIP1* genes). Echocardiogram, PET-CT scan and biopsies were performed in 4 (44.4%), 6 (66.7%) and 4 (44.4%) patients, respectively (Table 2). Prednisone was administered to 6 patients with complete and partial response in 3 cases each. Colchicine was used in the 9 patients, of whom 7 had complete, 1 partial and 1 no response. Anakinra was given to 1 patient with complete

response. One (11.1) patient could discontinue all targeted treatments during 71 months (Table 3).

Predominantly pericarditis phenotype: 18 (13.4%) patients presented with recurrent or sustained pericarditis, 9 (50%) of them with concomitant pleuritis or pleural effusion and 12 (66.7%) with fever (Table 1). CRP levels were elevated in 12 of 15 (80%) patients, and 1 (5.6%) subject maintained high CRP levels during asymptomatic periods. In 7 (38.9%) cases, 9 VUS (5 in the *MEFV* gene) were identified. Echocardiogram, PET-CT scan and biopsies were performed in 17 (94.4%), 8 (44.4%) and 1 (5.6%) patients, respectively. Among them, 15 (88.2%) echocardiograms and 3 (37.5%) PET-CT scan detected pericardial and other serosal effusions (Table 2). Prednisone was used in 14 (77.8%) patients, of whom 6 had complete, 7 partial and 1 no response. Colchicine was used in all patients, 6 with complete, 11 partial and 1 no response. Anakinra was administered to 6 patients, of whom 5 had a complete response, and 1, a partial response. Four (22.2%) patients discontinued medications during a median (range) of 65 (16–166) months (Table 3).

Complex syndrome phenotype: 45 (33.6%) individuals presented with diverse manifestations, including 42 (93.3%) with fever accompanied by musculoskeletal symptoms ($n = 33$; 73.3%), cutaneous lesions ($n = 29$; 64.4%), abdominal complaints ($n = 23$; 51.1%), ocular involvement ($n = 13$; 28.9%), and oral aphthae ($n = 12$; 26.7%), among others (Table 1). CRP levels were raised in 23/38 (60.5%) patients during attacks and in 6 (13.6%) subjects during asymptomatic periods. Twenty-eight (57.8%) patients carried 36 VUS (6 in *MEFV*, 4 in *NOD2*, 3 in *RIPK1*, and 2 each in *TNFRSF1A*, *NLRP3*, *NLRP12, TNFAIP3*, *DNASE1L3*, and *PSMG2* genes). Echocardiogram, PET-CT scan and biopsies were performed in 3 (6.7%), 31 (68.9%) and 21 (46.7%) patients, respectively. Abnormal results were identified in 1 (33.3%) echocardiogram and 17 (54.8%) PET-CT scans. Biopsies disclosing any inflammatory feature were detected in 22 (50%) of the 44 biopsied samples (detailed information in Table 2). Prednisone was given to 41 (91.1%) patients (18 on demand and 23 continuous), and 9 had a complete, 26 partial and 6 no response. Colchicine was used in 35 (77.8%) patients, 9 with complete, 15 partial and 11 no response. Anakinra was administered to 18 patients, and 8 had complete, 4 partial and 6 no response. Eighteen (40%) patients were treated with other immunosuppressive agents, and 9 (20%) of them received more than one additional immunosuppressant. Five (11.1) patients were off treatment for a median (range) of 33 (15–77) months (Table 3).

Adult PFAPA syndrome: among the 44 (32.8%) patients identified, 38 (86.4%) presented with throat complaints, 25 (56.8%) oral aphthae, 32 (72.7%) lymphadenopathy, and 28 (63.6%) cervical adenitis. Two (4.5%) patients had a limited disease without need of targeted drugs. Increased CRP levels were observed in 26/35 (74.3%) of cases, and were high during asymptomatic periods in 2 (4.5%) of them. In 24 (54.5%) cases, 28 VUS were identified (5 in *MEFV*, 4 in *NOD2*, 3 each in *NLRP3* and *RIPK1*, and 2 each in *MVK*, *TNFAIP3* and *DNASE2B* genes). PET-CT scan and biopsies were performed in 1 (2.3%) and 11 (25%) patients, respectively. Abnormal results were identified in 1 (100%) PET-CT scan and 8 (66.7%) of the 12 biopsies performed (detailed information in Table 2). Prednisone was given to 38 (86.4%) patients (35 [79.5%] on demand), 24 with complete, 11 partial and 3 without response. Colchicine was used in 27 (61.4%) subjects, 15 with complete, 8 partial and 4 with no response. Anakinra was used in 8 (18.2%) patients, 5 with complete, 2 partial and 1 with no response. At the end of the study, 7 (15.9) patients, could discontinue previous treatments during a median (range) of 32 (21–81) months (Table 3).

4. Discussion

The term "undifferentiated" describing a new group of autoinflammatory diseases was originally used in 2016 [36]. Patients with undifferentiated syndromes in centers specialized in autoinflammatory diseases account from 11% to 50% of all cases [7,27,42]. In our adult reference center, the proportion of undifferentiated diseases has increased during the last years [7], and now represents 40% of all patients consulting for a suspected autoinflammatory disease.

Undifferentiated autoinflammatory diseases have been investigated mainly in pediatric patients [23,25,26,28,33–35] since only two series have been focused on adult patients [24,36]. The Eurofever Registry analyzed 187 patients with undifferentiated autoinflammatory diseases (15% of them without a genetic study). Most patients were children with a median (IQR) age at disease onset of 4.3 (1−12) years, and only 35 (18.7%) patients with a disease onset during adulthood were included [26]. With regard to therapeutic approaches, similarly to FMF and other inflammasomopathies, patients with undifferentiated disorders seem to respond mainly to colchicine, glucocorticoids [23,25,26,28,34,35], and IL-1 blockers, such as anakinra [26,34–36].

Clinical and therapeutic characteristics of the studies on undifferentiated autoinflammatory diseases published to date are illustrated in Table 4. Comparing clinical features in our patients with those found in previous studies (expressed as the range reported by other authors after removing the two extreme values), fever is confirmed as the most common clinical manifestation in patients with undifferentiated autoinflammatory diseases (87.3% vs. 87.3–100%), followed by asthenia (56.7% vs. 50–58.8%), arthralgia (48.5% vs. 40–60.4%), arthritis (11.9% vs. 7–45.5%), myalgia (35.8% vs. 24–65.2%), pharyngitis/tonsillitis (38.8% vs. 10.2–55%), cutaneous lesions (25.4% vs. 7.5–46%), oral aphthae (28.4% vs. 27.3–32.3%), genital ulcers (0.7% vs. 1.1–3.1%), periorbital edema (5.2% vs. 4.8%), conjunctivitis (3% vs. 3–9.6%), abdominal pain (26.1% vs. 18.2–62%), diarrhea (16.4% vs. 8–16.6%), vomiting (7.5% vs. 7.5–23.5%), chest pain/pleuritis (18.7% vs. 7.5–18.2%), pericarditis (18.7% vs. 4–18.2%), headache (25.4% vs. 4.5–39.8%), sensorineural hearing loss (2.2% vs. 0–2.2%), lymphadenopathy (38.1% vs. 32–41.2%), and splenomegaly (7.5% vs. 10%) [23–26,28,30,33–36]. As observed in our study, in which 18.7% of patients were not taking any medication at the end of the study, other authors found that symptoms resolution occurred in 8.7% of patients [23]. Therefore, clinical manifestations experienced by our patients are aligned with most of the previous reported series on undifferentiated autoinflammatory diseases.

A positive effect of glucocorticoids (mainly on demand) has been reported in around 80–90% of patients in most studies about undifferentiated autoinflammatory diseases (89% in our patients), with complete responses ranging from 39.4% [26] to 76% of cases [23,34] (41.3% in our patients). Colchicine has also shown beneficial effects in 63% to 83% of patients from previous studies in which the drug was used (82.5% in our series), with complete responses ranging 14% to 65% of subjects (40.2% of our patients) [23,25,26,28,30,33,34]. In cases of inefficacy or intolerance to the previous drugs, the use of anakinra was primarily chosen in all the undifferentiated autoinflammatory diseases studies. Anakinra provided some benefit in 70% to 90% of patients (77.7% in our series), achieving complete responses in 36.4% to 54.5% of them (58.3% of our patients) [26,34–36] (Table 4).

The Eurofever Registry found specific features defining two subsets of patients with autoinflammatory diseases. Patients with cognitive impairment were younger at disease onset (median of 2.2 years) and with relatives affected more frequently (28.6%), and patients with pericarditis were older at disease onset (median of 33.8 years) and with fewer annual episodes [26]. Moreover, the presence of generalized lymphadenopathy [30] and cutaneous rash (in particular non-urticarial rash) [25] have been identified as factors associated with poorer responses to colchicine in patients with undifferentiated autoinflammatory diseases. Although a quarter of patients included in the present study had skin manifestations, no cases with a predominantly cutaneous phenotype have been included in this study. In this regard, dermatological diseases with autoinflammatory predominance, but negative genetic studies, have been described on the spectrum of psoriatic diseases, neutrophilic dermatoses, and pyoderma gangrenosum-associated autoinflammatory syndromes, among others [53,54].

Table 4
Main epidemiological, clinical and therapeutic characteristics of the studies on undifferentiated autoinflammatory diseases.

Characteristics	Chandrakasan et al. (2014) [33]	De Pauli et al. (2018) [23]	Garg et al. (2019) [35]*	Papa et al. (2020) [34]**	Demir et al. (2020) [28]	Sutera et al. (2021) [30]	Marques et al (2022) [25]	Ter Haar et al. (2019) [26]	Harrison et al. (2016) [36]	Hidaka et al. (2020) [24]	Present series
Number of patients	25	23	22	50	49	50	133	187	11	133#	134
Demographic											
Women/Men; (%)	9/16	18/5	14/8	ND	15/34	16/34	71/62	49/51	6/5	67/66	82/52
Caucasian ethnicity; n (%)	14 (56)	20 (87)	11 (50)	50 (100)	ND	50 (100)	102 (92.7)	ND	10 (90.1)	0 (0)	130 (97)
Family history of periodic fever; n (%)	0 (0)	ND	7 (32)	ND	12 (24)	4 (8)	26 (20.6)	24 (12.8)	ND	ND	26 (19.4)
Follow-up time (months)	21.5 (1–76)	ND	ND	ND	12 (12–24)	40 (12–140)	ND	ND	ND	ND	48 (16–108)
Disease presentation											
Adult onset; n (%)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	ND	0 (0)	35 (18.7)	11 (100)	ND	90 (67.2)
Age at diagnosis (years)	2.5 (0–9)	4.3 (2–9)	ND	ND	6 (3–9)	7 (2–13)	6.2 (3–11)	ND	ND	ND	37.7 ± 15.3
Age at symptoms onset (years)	1.4 (0–5)	0.8 (0.3–2)	0.6 (0–13.5)	4 (0–21)	3 (1–6)	3 (0.3–12)	2.8 (1–6)	4.3 (1–12)	43.7 (24–76)	33.4 ± 20	28.7 ± 19.7
Time to diagnosis (years)	2.5 (0.3–9)	ND	ND	ND	ND	3 (0.5–9)	2.7 (1.5–5)	ND	2.9 [1–8]	ND	6 (2–17)
Course of disease; n (%)											
Recurrent	ND	ND	ND	36 (72)	49 (100)	ND	ND	180 (96.3)	11 (100)	ND	94 (70.1)
Persistent	ND	ND	ND	14 (28)	ND	ND	ND	7 (3.7)	0 (0)	ND	40 (29.9)
Attacks characteristics											
Duration (days)	4 (3–5)	ND	ND	5.9 (4.5–7.3)	3 (2–4)	4 (3–8)	4 (3–5)	4 (3–7)	ND	ND	4 (3–7)
Number of attacks per year; n (%)	8 (4–12)	ND	ND	12 (7–24)	10 (6–12)	12 (6–25)	8 (5–10)	12 (5–14.5)	ND	ND	12 (4–12)
Clinical manifestations; n (%)										ND	
Fever	25 (100)	ND	13 (59.1)	50 (100)	49 (100)	50 (100)	127 (95.5)	187 (100)	11 (100)	133 (100)	117 (87.3)
Asthenia	ND	ND	ND	9 (50)	ND	ND	48 (36.1)	111 (58.8)	11 (100)	ND	76 (56.7)
Arthralgia	ND	ND	10 (45.5)	40 (40)	27 (55.1)	24 (48)	48 (36.1)	113 (60.4)	8 (72.7)	57 (42.9)	65 (48.5)
Arthritis	2 (8)	ND	12 (54.5)	15 (30)	4 (8.2)	3 (6)	ND	13 (7)	5 (45.5)	ND	16 (11.9)
Myalgia	ND	15 (65.2)	13 (59.1)	12 (24)	23 (46.9)	24 (48)	37 (27.8)	86 (46)	9 (81.8)	25 (18.8)	48 (35.8)
Pharyngitis/ Tonsillitis	1 (4)	13 (56.5)	12 (55)	15 (30)	5 (10.2)	19 (38)	36 (27.1)	48 (25.7)	ND	ND	52 (38.8)
Cutaneous rashes/ lesions	3 (12)	ND	ND	23 (46)	22 (44.9)	3 (6)	45 (33.8)	39 (20.9)	8 (72.7)	10 (7.5)	37 (27.6)
Oral aphthae	1 (4)	12 (52.2)	ND	15 (30)	14 (28.6)	16 (32)	43 (32.3)	54 (28.9)	3 (27.3)	ND	38 (28.4)
Genital ulcers	ND	ND	ND	1 (2)	ND	ND	4 (3.1)	2 (1.1)	1 (9.1)	ND	1 (0.7)
Periorbital edema	ND	ND	ND	2 (4)	ND	ND	ND	9 (4.8)	ND	ND	7 (5.2)
Conjunctivitis	ND	ND	ND	1 (2)	11 (22.4)	ND	12 (9.0)	18 (9.6)	ND	ND	4 (3)
Abdominal pain	1 (4)	12 (52.2)	4 (18.2)	25 (50)	31 (63.3)	31 (62)	69 (51.9)	89 (47.6)	3 (27.3)	40 (30.1)	35 (26.1)
Diarrhea	2 (8)	ND	3 (13.6)	4 (8)	5 (10.2)	12 (24)	17 (12.8)	31 (16.6)	ND	40 (30.1)	22 (16.4)
Vomiting	ND	ND	5 (22.7)	3 (6)	8 (16.3)	7 (14)	39 (29.3)	44 (23.5)	ND	ND	10 (7.5)
Chest pain	ND	0 (0)	5 (22.7)	ND	4 (8.2)	8 (16)	10 (7.5)	22 (11.8)	1 (9.1)	17(12.8)	24 (17.9)
Pericarditis	ND	ND	ND	2 (4)	1 (2)	ND	ND	11 (5.9)	2 (18.2)	ND	25 (18.7)
Pleuritis	ND	ND	ND	ND	1 (2)	ND	ND	ND	2 (18.2)	ND	15 (11.1)
Headache	1 (4)	ND	1 (4.5)	9 (18)	10 (20.4)	ND	53 (39.8)	69 (36.9)	5 (45.5)	ND	34 (25.4)
Sensorineural hearing loss	ND	ND	ND	ND	0 (0)	ND	ND	ND	ND	ND	3 (2.2)
Lymphadenopathy	1 (4)	ND	12 (54.5)	16 (32)	ND	19 (38)	35 (26.3)	77 (41.2)	ND	ND	51 (38.1)
Splenomegaly	ND	ND	ND	5 (10)	1 (2)	ND	ND	21 (11.2)	ND	ND	10 (7.5)
Response to treatment used											
Glucocorticoids (on demand)											
Complete	Variable	16/21 (76.2)	ND	22/29 (75.9)	ND	ND	ND§	41/104 (39.4)	ND	ND‡	45/109 (41.3)
Partial	ND	ND	ND	5/29 (17.2)	ND	ND	ND	44/104 (42.3)	6/10 (60)	ND	52/109 (47.7)

(*continued on next page*)

Table 4 (*continued*)

Characteristics	Chandrakasan et al. (2014) [33]	De Pauli et al. (2018) [23]	Garg et al. (2019) [35]*	Papa et al. (2020) [34]**	Demir et al. (2020) [28]	Sutera et al. (2021) [30]	Marques et al (2022) [25]	Ter Haar et al. (2019) [26]	Harrison et al. (2016) [36]	Hidaka et al. (2020) [24]	Present series
None	ND	ND	ND	2/29 (6.9)	ND	ND	ND	19/104 (18.3)	4/10 (40)	ND	12/109 (11)
Colchicine											
Complete	15/25 (60)	6/13 (46.3)	ND	6/24 (25)	12 (24.5)	31/48 (64.6)	61 (45.9)	7/49 (14.3)	ND	ND¦	39/97 (40.2)
Partial	ND	ND	ND	12/24 (50)	19 (38.8)	9/48 (18.8)	62 (46.6)	22/49 (44.9)	ND	ND	41/97 (42.3)
None	ND	ND	ND	6/24 (25)	18 (36.7)	8/48 (16.6)	10 (7.5)	20/49 (40.8)	3 (27.3)	ND	17/97 (17.5)
Anakinra											
Complete	ND	ND	8 (36.4)	6/11 (54.5)	ND	ND	ND§	5/13 (38.5)	9 (81.8)	ND	21/36 (58.3)
Partial	ND	ND	8 (36.4)	2/11 (18.2)	ND	ND	ND	3/13 (23.1)	1 (9.1)	ND	7/36 (19.4)
None	ND	ND	6 (27.2)	3/11 (27.3)	ND	ND	ND	5/13 (38.5)	1 (9.1)	ND	8/36 (22.2)

Abbreviations: ND=No data.

§ In this study, 56 (42.1%) patients were treated with glucocorticoids and 17 (12.8%) with anakinra (no response rate was provided).

In this series, 78 (58.7%) patients had variants of uncertain significance in the MEFV gene (33 of them were compound heterozygous variants or complex heterozygous genotypes) and 49 (36.8%) missense variants were detected in other genes, including *TNFRSF1A*, *NLRP3*, *NLRP12* and *NLRC4* genes.

¦ Prednisone was used in 29 (21.8%) patients and colchicine in 44 (33.1%) patients (no response rate was provided).

* At the end of the study, among patients with partial or no response to anakinra, remission was achieved with canakinumab (n = 2), tocilizumab (n = 2), infliximab, methotrexate, baricitinib and allogeneic bone marrow transplant (n = 1 each), and 3 patients died.

** Results are given for the 50 patients initially included, although 4 of them were finally diagnosed with monogenic autoinflammatory diseases.

Indeed, a recurrent non-pruriginous macular (sometimes papular) eruption involving the trunk associated with increased inflammatory markers in adult patients, named as systemic inflammatory trunk recurrent acute macular eruption (SITRAME), has recently emerged as a new undifferentiated autoinflammatory disease [55].

After identifying patients with adult PFAPA syndrome as those usually presenting with fever, throat manifestations, oral aphthae and lymphadenopathy, mostly cervical adenitis, the remaining undifferentiated autoinflammatory diseases in adult patients were grouped in four phenotype groups: a) Predominantly fever phenotype; b) Predominantly abdominal/pleuritic pain phenotype; c) Predominantly pericarditis phenotype; and d) Complex syndrome phenotype. Overall, it is remarkable that the predominantly fever phenotype consisted in episodes of recurrent fever with additional musculoskeletal manifestations in almost two-third of patients; the predominantly abdominal/pleuritic pain phenotype presented mainly with abdominal pain, and fever was detected in only a third of patients; the predominantly pericarditis phenotype was characterized by recurrent or maintained pericarditis, accompanied by fever in two-third of cases; and the complex syndrome phenotype comprised patients with systemic and organ-specific manifestations, more difficult to diagnose since they needed imaging tests and biopsies in most cases, and also more difficult to treat, since all patients needing additional immunosuppressive (cytotoxic or biologic) agents belonged to this complex group. Of note, fever was not constant in patients with undifferentiated autoinflammatory diseases, and was more commonly absent in those with serosal (abdominal, pleural or pericardial) involvement.

Although CPR and ESR values were increased during attacks and returned back to normal in most patients of all groups, still a third of patients in all phenotype groups disclosed normal acute reactant levels during attacks. The reduced inflammatory response in some of these patients could be explained in part by the fact that these disorders in adults might exhibit milder clinical and biological presentations, as previously observed in adult forms of monogenic autoinflammatory diseases compared with the same conditions with pediatric onset [7–16]. These a priori incoherent responses may be also reflecting the unknown mechanisms of these complex systemic diseases in adult patients.

The response to the used drugs was different depending on the phenotype group. In the predominantly fever phenotype, initial treatment with prednisone and colchicine were associated with complete responses in 30% and 25% of cases, respectively. Anakinra was useful in two thirds of subjects. In patients with predominantly abdominal/pleuritic pain phenotype, colchicine was the agent chosen as first line therapy achieving complete responses in 77.8% of patients. Prednisone was also effective in half of patients. Only one patient received anakinra with good results. Patients with the predominantly pericarditis phenotype were initially treated more often with colchicine, but complete responses were observed only in a third of cases of cases. Prednisone was effective in most cases, with complete responses in 42.9% of them. In these subjects, anakinra was a good alternative, with complete response in 83.3% of patients treated. These good results are in line with those from previous larger cohort studies on idiopathic recurrent acute pericarditis treated with anakinra [43–46]. Patients with a complex syndrome phenotype were mainly treated with prednisone and colchicine, with complete responses in 21.9% and 25.7% of patients, respectively. Anakinra was used 40% of patients, being of help in two thirds (with complete response in 44.4%) of them. In patients with adult PFAPA syndrome phenotype, prednisone on demand, as the first chosen therapy, was associated with a complete response in almost two-third of cases. Colchicine was also effective in more than half of subjects. Anakinra was of some help in 87.5% of patients, with 62.5% of complete responses. Based on ours and previous observations, in patients with adult PFAPA syndrome, prednisone on demand has shown to be the main option to control the flares, and colchicine seems to contribute to avoid or ameliorate the frequency and intensity of attacks in most patients [47]. Anti-IL-1 blockade with anakinra and canakinumab has also shown to be an effective option in isolated cases and small series of patients not able to achieve full control of the disease with colchicine and prednisone [47–50].

Overall, preliminary recommendations for treating undifferentiated autoinflammatory diseases would include colchicine, prednisone

(mainly on demand) and anakinra as effective drugs, since they control >80% of patients with these conditions. Only a small proportion of patients will need to explore other therapeutic options, maybe due to the participation of other pathogenic pathways. In order to validate these results, similar studies need to be replicated in larger, international and multicenter collaborative studies, such as the AutoInflammatory Diseases Alliance (AIDA) Network/Registry for PFAPA syndrome and undifferentiated autoinflammatory diseases [51,52].

Limitations of this study include the retrospective nature of the study design and the low number of patients in some disease phenotypes not permitting to drawn firm conclusions or recommendations. Conversely, the strengths of the present study rely in the analysis of the largest series of adult patients with undifferentiated autoinflammatory diseases from a single reference center. Consequently, homogeneous criteria were followed by the same team of physicians in the diagnostic process and all therapeutic strategies used.

Although a definite diagnosis of rare diseases is always difficult to achieve, both in children and adults, the diagnostic process of undiagnosed diseases in adult patients results even more challenging. By gathering patients with similar patterns of presentation and therapeutic responses, a potential window of opportunity is open for testing different drugs based in functional studies targeting different molecules involved in inflammatory pathways. In this sense, the study of NF-κB and interferon signatures, inflammasome functional assays, cytokine patterns, and advanced genomic, proteomic and other omic studies in adult patients with undifferentiated autoinflammatory diseases and their affected relatives may increase the likelihood of understanding the molecular basis, finding biomarker candidates and diagnosing “new monogenic autoinflammatory diseases”. To conclude, with the description and characterization of different phenotypes of undifferentiated autoinflammatory diseases, we expect to increase the awareness of physicians for an early identification of these conditions, and also to provide the best known therapeutic options until more knowledge is acquired.

Disclosure statement

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Declaration of competing interest

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Data availability

Data will be made available on request.

References

[1] Mcdermott MF, Aksentijevich I, Galon J, Mcdermott EM, Ogunkolade BW, Centola M, et al. 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.

[2] Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 2002;10:417–26.

[3] Lin B, Goldbach-Mansky R. Pathogenic insights from genetic causes of autoinflammatory inflammasomopathies and interferonopathies. J Allergy Clin Immunol 2022;149:819–32.

[4] Aksentijevich I, Soriano A, Hernández-Rodríguez J. Editorial: autoinflammatory diseases: from genes to bedside. Front Immunol 2020;11:1177.

[5] Aksentijevich I, Zhou Q. NF-kappaB pathway in autoinflammatory diseases: dysregulation of protein modifications by ubiquitin defines a new category of autoinflammatory diseases. Front Immunol 2017;8:399.

[6] Goldbach-Mansky R, Kastner DL. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. J Allergy Clin Immunol 2009;124:1141–9. quiz 50–1.

[7] Hernández-Rodríguez J, Ruíz-Ortiz E, Tomé A, Espinosa G, González-Roca E, Mensa-Vilaró A, et al. Clinical and genetic characterization of the autoinflammatory diseases diagnosed in an adult reference center. Autoimmun Rev 2016;15:9–15.

[8] Hernández-Rodríguez J, Ruiz-Ortiz E, Yagüe J. Monogenic autoinflammatory diseases: general concepts and presentation in adult patients. Med Clin (Barc) 2018;150:67–74.

[9] Cantarini L, Rigante D. Adult-onset autoinflammatory disorders: a still debated entity? Clin Exp Rheumatol 2015;33:137–40.

[10] Muscari I, Iacoponi F, Cantarini L, Lucherini OM, Simonini G, Brizi MG, et al. The diagnostic evaluation of patients with potential adult-onset autoinflammatory disorders: our experience and review of the literature. Autoimmun Rev 2012;12:10–3.

[11] Sayarlioglu M, Cefle A, Inanc M, Kamali S, Dalkilic E, Gul A, et al. Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases. Int J Clin Pract 2005;59:202–5.

[12] Comak E, Akman S, Koyun M, Dogan CS, Gokceoglu AU, Arikan Y, et al. Clinical evaluation of R202Q alteration of MEFV genes in Turkish children. Clin Rheumatol 2014;33:1765–71.

[13] Cantarini L, Rigante D, Merlini G, Vitale A, Caso F, Lucherini OM, et al. The expanding spectrum of low-penetrance TNFRSF1A gene variants in adults presenting with recurrent inflammatory attacks: clinical manifestations and long-term follow-up. Semin Arthritis Rheum 2014;43:818–23.

[14] Ruiz-Ortiz E, Iglesias E, Soriano A, Buján S, Español-Rego M, Castellanos-Moreira R, et al. Disease phenotype and outcome depending on the age at disease onset in patients carrying the R92Q low-penetrance variant in TNFRSF1A gene. Front Immunol 2017;8:299.

[15] Naselli A, Penco F, Cantarini L, Insalaco A, Alessio M, Tommasini A, et al. Clinical characteristics of patients carrying the Q703K variant of the NLRP3 gene: a 10-year multicentric national study. J Rheumatol 2016;43:1093–100.

[16] Toplak N, Frenkel J, Ozen S, Lachmann HJ, Woo P, Kone-Paut I, et al. An international registry on autoinflammatory diseases: the Eurofever experience. Ann Rheum Dis 2012;71:1177–82.

[17] Betrains A, Staels F, Schrijvers R, Meyts I, Humblet-Baron S, De Langhe E, et al. Systemic autoinflammatory disease in adults. Autoimmun Rev 2021;20:102774.

[18] Mcgonagle D, Mcdermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3:e297.

[19] Goldbach-Mansky R. Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1. Clin Exp Immunol 2012;167:391–404.

[20] Giacomelli R, Caporali R, Ciccia F, Colafrancesco S, Dagna L, Govoni M, et al. Expert consensus on the treatment of patients with adult-onset still's disease with the goal of achieving an early and long-term remission. Autoimmun Rev 2023;22:103400.

[21] Neel A, Henry B, Barbarot S, Masseau A, Perrin F, Bernier C, et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: a French multicenter study. Autoimmun Rev 2014;13:1035–41.

[22] Cavalli G, Colafrancesco S, Emmi G, Imazio M, Lopalco G, Maggio MC, et al. Interleukin 1alpha: a comprehensive review on the role of IL-1alpha in the pathogenesis and treatment of autoimmune and inflammatory diseases. Autoimmun Rev 2021;20:102763.

[23] De Pauli S, Lega S, Pastore S, Grasso DL, Bianco AMR, Severini GM, et al. Neither hereditary periodic fever nor periodic fever, aphthae, pharingitis, adenitis: undifferentiated periodic fever in a tertiary pediatric center. World J Clin Pediatr 2018;7:49–55.

[24] Hidaka Y, Fujimoto K, Matsuo N, Koga T, Kaieda S, Yamasaki S, et al. Clinical phenotypes and genetic analyses for diagnosis of systemic autoinflammatory diseases in adult patients with unexplained fever. Mod Rheumatol 2021;31:704–9.

[25] Marques MC, Egeli BH, Wobma H, Ribeiro C, Anderson E, Hausmann JS, et al. Features predicting colchicine efficacy in treatment of children with undefined systemic autoinflammatory disease: a retrospective cohort study. Eur J Rheumatol 2022;9:116–21.

[26] Ter Haar NM, Eijkelboom C, Cantarini L, Papa R, Brogan PA, Kone-Paut I, et al. Clinical characteristics and genetic analyses of 187 patients with undefined autoinflammatory diseases. Ann Rheum Dis 2019;78:1405–11.

[27] Simon A, Van Der Meer JW, Vesely R, Myrdal U, Yoshimura K, Duys P, et al. Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes. Rheumatology (Oxford) 2006;45:269–73.

[28] Demir F, Dogan OA, Demirkol YK, Tekkus KE, Canbek S, Karadag SG, et al. Genetic panel screening in patients with clinically unclassified systemic autoinflammatory diseases. Clin Rheumatol 2020;39:3733–45.
[29] Kosukcu C, Taskiran EZ, Batu ED, Sag E, Bilginer Y, Alikasifoglu M, et al. Whole exome sequencing in unclassified autoinflammatory diseases: more monogenic diseases in the pipeline? Rheumatology (Oxford) 2021;60:607–16.
[30] Sutera D, Bustaffa M, Papa R, Matucci-Cerinic C, Matarese S, D'orsi C, et al. Clinical characterization, long-term follow-up, and response to treatment of patients with syndrome of undifferentiated recurrent fever (SURF). Semin Arthritis Rheum 2022; 55:152024.
[31] Papa R, Penco F, Volpi S, Sutera D, Caorsi R, Gattorno M. Syndrome of undifferentiated recurrent fever (SURF): an emerging group of autoinflammatory recurrent fevers. J Clin Med 2021;10:1963.
[32] Aksentijevich I, Mcdermott MF. Lessons from characterization and treatment of the autoinflammatory syndromes. Curr Opin Rheumatol 2017;29:187–94.
[33] Chandrakasan S, Chiwane S, Adams M, Fathalla BM. Clinical and genetic profile of children with periodic fever syndromes from a single medical center in south East Michigan. J Clin Immunol 2014;34:104–13.
[34] Papa R, Rusmini M, Volpi S, Caorsi R, Picco P, Grossi A, et al. Next generation sequencing panel in undifferentiated autoinflammatory diseases identifies patients with colchicine-responder recurrent fevers. Rheumatology (Oxford) 2020;59: 344–60.
[35] Garg S, Wynne K, Omoyinmi E, Eleftheriou D, Brogan P. Efficacy and safety of anakinra for undifferentiated autoinflammatory diseases in children: a retrospective case review. Rheumatol Adv Pract 2019;3:rkz004.
[36] Harrison SR, Mcgonagle D, Nizam S, Jarrett S, Van Der Hilst J, Mcdermott MF, et al. Anakinra as a diagnostic challenge and treatment option for systemic autoinflammatory disorders of undefined etiology. JCI Insight 2016;1:e86336.
[37] Papa R, Doglio M, Lachmann HJ, Ozen S, Frenkel J, Simon A, et al. A web-based collection of genotype-phenotype associations in hereditary recurrent fevers from the Eurofever registry. Orphanet J Rare Dis 2017;12:167.
[38] Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019; 78:1025–32.
[39] Manthiram K, Lapidus S, Edwards K. Unraveling the pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis through genetic, immunologic, and microbiologic discoveries: an update. Curr Opin Rheumatol 2017;29:493–9.
[40] Hofer M, Pillet P, Cochard MM, Berg S, Krol P, Kone-Paut I, et al. International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients. Rheumatology (Oxford) 2014; 53:1125–9.
[41] Cantarini L, Vitale A, Sicignano LL, Emmi G, Verrecchia E, Patisso I, et al. Diagnostic criteria for adult-onset periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. Front Immunol 2017;8:1018.
[42] Rigante D, Vitale A, Lucherini OM, Cantarini L. The hereditary autoinflammatory disorders uncovered. Autoimmun Rev 2014;13:892–900.
[43] Cantarini L, Lopalco G, Selmi C, Napodano S, De Rosa G, Caso F, et al. Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis. Autoimmun Rev 2015;14:90–7.
[44] Brucato A, Emmi G, Cantarini L, Di Lenarda A, Gattorno M, Lopalco G, et al. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. Intern Emerg Med 2018;13:475–89.
[45] Imazio M, Andreis A, De Ferrari GM, Cremer PC, Mardigyan V, Maestroni S, et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: the IRAP (international registry of Anakinra for pericarditis) study. Eur J Prev Cardiol 2020;27:956–64.
[46] Lopalco G, Rigante D, Cantarini L, Imazio M, Lopalco A, Emmi G, et al. The autoinflammatory side of recurrent pericarditis: enlightening the pathogenesis for a more rational treatment. Trends Cardiovasc Med 2021;31:265–74.
[47] Soriano A, Soriano M, Espinosa G, Manna R, Emmi G, Cantarini L, et al. Current therapeutic options for the main monogenic autoinflammatory diseases and PFAPA syndrome: evidence-based approach and proposal of a practical guide. Front Immunol 2020;11:865.
[48] Lopalco G, Rigante D, Vitale A, Caso F, Iannone F, Cantarini L. Canakinumab efficacy in refractory adult-onset PFAPA syndrome. Int J Rheum Dis 2017;20: 1050–1.
[49] Sopeña B, Araújo O, Freire M, Barrera-López L, Hernández-Rodríguez J. Efficacy of canakinumab in a patient with adult-onset glucocorticoid-resistant periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. Mod Rheumatol Case Rep 2023;7:276–9.
[50] Gaggiano C, Rigante D, Sota J, Grosso S, Cantarini L. Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review. Clin Rheumatol 2019;38: 11–7.
[51] La Torre F, Sota J, Insalaco A, Conti G, Del Giudice E, Lubrano R, et al. Preliminary data revealing efficacy of *Streptococcus salivarius* K12 (SSK12) in periodic fever, Aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: a multicenter study from the AIDA network PFAPA syndrome registry. Front Med (Lausanne) 2023;10:1105605.
[52] Della Casa F, Vitale A, Lopalco G, Ruscitti P, Ciccia F, Emmi G, et al. Development and implementation of the AIDA international registry for patients with undifferentiated systemic autoinflammatory diseases. Front Med (Lausanne) 2022; 9:908501.
[53] Savic S, Coe J, Laws P. Autoinflammation: Interferonopathies and other autoinflammatory diseases. J Invest Dermatol 2022;142:781–92.
[54] Figueras-Nart I, Mascaró JMJ, Solanich X, Hernández-Rodríguez J. Dermatologic and dermatopathologic features of monogenic autoinflammatory diseases. Front Immunol 2019;8.
[55] Soria A, Amsler E, Garel B, Moguelet P, Tieulie N, Cordoliani F, et al. Systemic inflammatory trunk recurrent acute macular eruption (SITRAME): a new auto-inflammatory syndrome in adult? J Eur Acad Dermatol Venereol 2023;37. e538-e42.