Original Article

Features predicting colchicine efficacy in treatment of children with undefined systemic autoinflammatory disease: A retrospective cohort study

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Abstract

Objective: Patients with undefined systemic autoinflammatory diseases (uSAIDs) are challenging to manage, as there are no guidelines or recommendations for targeted therapy. We aimed to evaluate the efficacy of empiric treatment with colchicine in our single-center uSAID population in the United States, as well as the patient characteristics associated with the most robust colchicine response.

Methods: Children with uSAID ≤18 years old at initial evaluation during 2000-2019 were included if they received ≥3 months of colchicine therapy. Data on demographics, clinical features, laboratory/genetic studies, and treatment responses were collected. Most statistics were based on chi-square analyses for categorical data. Complete response to colchicine was defined as resolution of episodes or the presence of minor residual symptoms that did not require any further therapy. A partial response was defined as a decrease in the frequency, severity, or length of episodes but still necessitating additional therapy. Patients were considered nonresponders if they did not experience any improvement with colchicine at target therapeutic dosing.

Results: We identified 133 children diagnosed with uSAID who met our inclusion criteria. The median time to starting empiric colchicine was 5 months from the diagnosis of autoinflammatory disease. 92.5% (n = 123) of patients had a beneficial response to colchicine, including 46.6% (n = 62) partial responders and 45.9% (n = 61) complete responders. The presence of a nonurticarial rash was associated with an incomplete colchicine response (29.2% (n = 21) vs 13.1% (n = 8), $P = .025$). The presence of a heterozygous *MEFV* mutation in patients who did not fit Familial Mediterranean Fever diagnostic criteria (n = 25) appeared to be associated with a greater likelihood of complete colchicine response, although this was not statistically significant (62.5% (n = 14) vs 42.6% (n = 11), $P = .08$). In *MEFV* mutation-negative patients, a nonurticarial rash was even more strongly associated with incomplete colchicine response, with an OR of 27.53 (CI [1.59-477], $P = .023$). The presence of oral ulcers also corresponded to incomplete colchicine response, although this did not reach clinical significance (38.9% (n = 28) vs 24.6% (n = 15), $P = .08$). There was no significant association between episode duration or frequency and colchicine response.

Conclusion: Colchicine leads to clinical benefits in most children with uSAID. We, thus, recommend an early trial of colchicine in newly diagnosed patients with uSAID.

Keywords: Colchicine, fever, hereditary autoinflammatory diseases, inflammation

Introduction

Systemic autoinflammatory diseases (SAIDs) are characterized by a dysregulated innate immune response resulting in unprovoked episodes of fever and inflammation. The term "autoinflammation" was first described in 1999 after the identification of the causative genes for familial Mediterranean fever (FMF) in 1997, followed by TNF-Receptor-Associated Periodic Syndrome (TRAPS) in 1999. Over 45 monogenic SAIDs have now been described,[1,2] along with several disorders that are polygenic and clinically defined (e.g., periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA)).[3]

With an increasing ability to recognize clinical patterns and the widespread availability of genetic testing, it has become possible to rationally select targeted therapeutics for many of these diseases.[4] For example, syndromes related to inflammasome dysregulation, such as cryopyrin-associated periodic syndromes (CAPSs) and mevalonate kinase deficiency, benefit from interleukin-1 blockade. In contrast, type I interferonopathies such as STING Associated Vasculopathy with onset in Infancy and Chronic Atypical

Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature syndrome tend to respond to Janus kinase inhibitors.[5–7]

Despite the vast progress that has been made in disease classification, many patients with SAID do not fit within any clinically or genetically defined syndrome. These patients are often referred to as having "undifferentiated" or "undefined" SAID (uSAID), and they pose a challenging clinical dilemma as it is unclear how they should be treated; most clinical trials exclude patients without a precise diagnosis.[1,8] Patients with uSAID are thought to account for about 50% of patients seen in autoinflammatory disease clinics.[8]

Colchicine is an ancient medicine that has been used for joint pain since 1500 B.C.E.[9] Derived from the *Colchicum autumnale* plant, colchicine is FDA approved to treat FMF and gout. An abundance of data also supports its use in other inflammatory disorders such as Behçet's syndrome and cutaneous vasculitis.[9,10] The mechanism of action is thought to result from impairing microtubule dynamics and the expression of adhesion molecules, thus reducing neutrophil trafficking and downregulating inflammatory pathways such as the NOD-like receptor protein 3 inflammasome.[9] Colchicine is readily available, inexpensive, and has a favorable safety profile; as such, it is often trialed as empiric therapy for uSAID. However, the patient and clinical characteristics that are most predictive of a good response to colchicine are still poorly understood.[11]

The Autoinflammatory Disease Clinic at Boston Children's Hospital follows several hundred children with SAID per year, of which about 50% have an uSAID. This study aims to assess the efficacy of colchicine treatment and identify features that predict a favorable response in patients with uSAID.

Main Points

- We present the largest study of empiric colchicine treatment in children with uSAID (n = 133).

- 92.5% of children had a beneficial response to colchicine, with 45.9% of these showing a complete response.

- A nonurticarial rash was a negative predictor of complete colchicine response, particularly in children without heterozygous *MEFV* mutations.

- Based on our findings, we recommend an early trial of colchicine for children with uSAID.

Methods

Study participants
This was a single-center retrospective study of pediatric patients (age ≤18 at first visit) referred to the Autoinflammatory Diseases Clinic of the Rheumatology Program at Boston Children's Hospital from 2000 to 2019 who were diagnosed with an uSAID and received empiric treatment with colchicine for at least 3 months. Subjects were identified by i2b2 technology for billing codes and keywords related to colchicine, followed by a manual chart review to confirm diagnosis and treatment course. Ethics approval for this study was obtained at Boston Children's Hospital institutional IRB protocol (P00028772) for analyzing the deidentified retrospective patient data.

Defining uSAID
For diagnosis of uSAID, patients could not meet clinical or clinical and genetic criteria for previously described autoinflammatory diseases (CAPS, TRAPS, FMF, etc.) per the 2019 Gattorno criteria.[12] Patients with heterozygous mutations in *MEFV* (or other recessive genes) were included if they did not meet clinical criteria for the disease. For example, patients with one confirmatory MEFV mutation could not have the following: duration of episodes between 1 and 3 days, arthritis, chest pain, or abdominal pain. Patients also could not meet clinical criteria for PFAPA, which requires the patient to fulfill seven out of eight clinical criteria (presence of pharyngotonsillitis, duration of episodes from 3 to 6 days, cervical lymphadenitis, periodicity, and absence of diarrhea, chest pain, skin rash, and arthritis).

Data collection
Deidentified data were collected and stored using REDCap (Center Drive, Nashville, TN) electronic data capture tools hosted at Boston Children's Hospital (BCH).[13,14] Variables that were documented included patient demographics (race, ethnicity, and country of origin), clinical attributes (fever pattern, associated symptoms, and prior management), laboratory studies, and treatment course.

Complete vs partial response
A complete response to colchicine was defined as having a complete cessation of episodes or if patients had minor residual symptoms that did not require any further therapy. A partial response to colchicine was defined as a decrease in the frequency, severity, or length of episodes but still necessitating additional therapy, such as corticosteroids or NSAIDs. Patients were considered nonresponders if they did not experience any

improvement with colchicine at target therapeutic dosing. For the sake of statistical comparison, partial- and non-responders were combined into a group called "incomplete responders."

Statistical analysis
For categorical data, the absolute number (frequency) was compared between groups via a Pearson Chi-square analysis or Fisher Exact test. Continuous variables were assessed for normality via the Shapiro–Wilk test. For continuous data that were not normally distributed, the Mann–Whitney U test was used to make comparisons. To evaluate if there were any homogeneous patient subgroups, categorical principal component analysis was used. The variables with at least 20% frequency in the cohort were factored into the analysis. Both the study participant and the variable variance were reduced into a two-dimensional Euclidian plot. Following this step, clustering of the binomial variables was done. A *P*-value <.05 was used to define significance for all analyses. All statistical analyses were performed in R version 3.6.0. Categorical principal component analysis and clustering were conducted via the package "Factoshiny" in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient cohort
From 2000 to 2019, there were ~1,200 patients identified at BCH when medical records were screened for the term "colchicine." These records were then analyzed for diagnosis of uSAID and colchicine use for ≥3 months. Some patients' charts included colchicine as a possible therapy to consider, but it was never actually initiated, and these patients were excluded. The most common defined syndromes for patients who were subsequently excluded were PFAPA, FMF, IgA vasculitis (previously known as Henoch–Schoenlein purpura), and recurrent pericarditis. Fewer than 20 patients started colchicine but discontinued it before 3 months due to gastrointestinal side effects. Altogether, 133 patients met our criteria for further analysis. All patients remained alive while followed at our center.

Demographic data
Of the 133 patients in our cohort, 53.4% (n = 71) were female (Table 1). The median age of disease onset was 34 months (IQR 12-72). Racial/ethnic backgrounds were as follows: 92.7% (n = 102) were White, 5.5% (n = 6) were Asian, and 0.9% (one patient) were black. Ten patients (7.5%) identified as Latinx

Table 1. Demographic Features of uSAID Patients (n = 133)

Feature	Number (%)
Female	71 (53.4)
Ethnicity (known = 110)[*]	
Hispanic or Latino	10 (9.3)
Non-Hispanic or Latino	100 (90.7)
Race (known = 114)[†]	
White	102 (92.7)
Black	1 (0.9)
Asian	6 (5.5)
Native American/Alaskan Native	5 (4.5)
Native Hawaiian/other Pacific Islander	0 (0)
Growth delay	11(8.6)
Developmental delay	10 (8.2)
Family history of recurrent fever	26 (20.6)
Family history of autoimmune disease	
Inflammatory bowel disease	25 (18.8)
Thyroid disease	38 (28.6)
Systemic lupus erythematosus	22 (16.5)
Rheumatoid arthritis	42 (31.6)
Psoriasis	23 (17.3)
Celiac disease	10 (7.5)
Age at disease onset (months), median (IQR)	34 (12-72)
Age at diagnosis (months), median (IQR)	74.5 (39.5-127.25)
Delay in diagnosis (months), median (IQR)	32 (18.25-55.5)
Time to colchicine treatment (months), median (IQR)	5 (1-15.5)
Youngest age to start colchicine treatment (months)	15

[*]Four patients had mixed Hispanic/European roots.
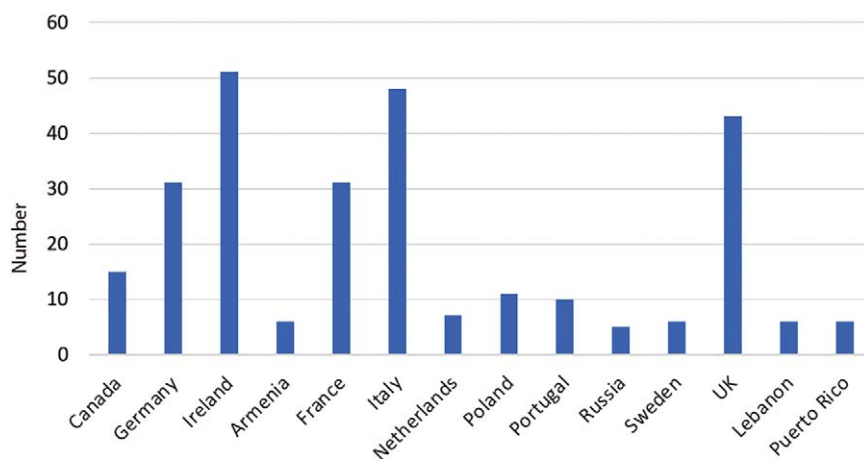[†]Some patients were multiracial (entered for each).

Figure 1. Geographic region of ancestry. Many patients had multiple ancestral roots. Only countries with n > 5 were included in the chart.

and 16 (12%) identified as Ashkenazi Jewish. Detailed data on countries of origin are shown in Figure 1. Patients often had multiple ancestral roots, with the most common being Italian (n = 52, 45%) and Irish (n = 48, 41%).

Clinical features

The median age at diagnosis of autoinflammatory disease at BCH was 74.5 months (IQR 39.5-127.25). The median delay in diagnosis from symptom onset was 32 months (IQR 18.25-55.5). Fewer than 10% of patients had a growth or developmental delay. The main clinical features are shown in Table 2. For the entire cohort, the median duration of autoinflammatory disease flare was 4 days (IQR 3, 5), and the median interval between episodes was 28 days (IQR 18, 35). The most common clinical features during flares were fever (95.5%, n = 127), abdominal pain (51.9%, n = 69), headache (39.8%, n = 53), fatigue (36.1%,

n = 48), arthralgia (36.1%, n = 48), and rash (33.8%, n = 45).

To better understand if certain clinical features clustered together, principal component analysis was performed, the results of which are shown in Supplementary Figure 1. Only 25% of the variance could be explained by this analysis, suggesting that there were no distinct clusters of symptoms shared amongst patients.

Laboratory and genetic features

Basic laboratory studies were collected from the first visit, during which patients were often at their baseline state of health (Supplementary Table 1). These showed mild elevations in absolute lymphocyte count, absolute eosinophil count, and platelet count in a subset of the population. The absolute neutrophil count was generally normal. One hundred and eight children (81.2%) had genetic testing performed; most underwent commercially available genetic panels for autoinflammatory diseases, while a few underwent whole-exome sequencing. Many patients had variants of unknown significance or were heterozygous for pathologic variants that did not fully explain their phenotype.[15] This was true for *MEFV* mutations found in 25/133 (18.8%) patients. The list of *MEFV* mutations and associated clinical features is shown in Supplementary Table 2.

Predictors of colchicine response

The median time to initiation of colchicine after the initial autoinflammatory clinic visit at BCH was 5 months. Overall, 10 patients were nonresponders (7.5%), 62 showed partial response (46.6%), and 61 (45.9%) had a complete response to therapy. A minority of patients required advancement to IL-1 or TNF-α inhibition (12.8% (n = 17) and 3% (n = 4), respectively). Fifty-six patients (42.1%) were at least temporarily managed with corticosteroid treatment as an abortive agent. A comparison of patients with complete versus incomplete response (including non- or partial responders) is shown in Table 2. There was no significant association between episode duration or frequency and colchicine response.

However, there was a significant association between the presence of rash and incomplete colchicine response (41.7% (n = 30) vs 24.6% (n = 15), P = .038), particularly if it was a non-urticarial rash (29.2% (n = 21) vs 13.1% (n = 8), P = .025), see Table 2. In fact, having a non-urticarial rash corresponded to a 2.72 greater odds of incomplete colchicine response (C.I. [1.10-6.71], P = .028). This effect was even more pronounced in patients who were negative for a heterozygous *MEFV* mutation, with an odds ratio of incomplete response to

Table 2. Clinical Features Associated with Colchicine Response in uSAID Patients

Clinical Features of Episodes	Total Cohort (n = 133)	Partial/ Nonresponder (n = 72)	Complete Responder (n = 61)	P value
Timing (median, IQR)				
Duration (days)	4 (3, 5)	4 (3, 6)	3.75 (3, 5)	.69
Frequency (days)	28 (18.13, 35)	22.75 (18, 35)	30 (21.75, 35.75)	.4
Constitutional (%)				
Fever	127 (95.5)	69 (95.8)	58 (95.1)	.84
Fatigue	48 (36.1)	28 (38.9)	20 (32.7)	.47
Mucocutaneous				
Oral ulcers	43 (32.3)	28 (38.9)	15 (24.6)	.08
Genital ulcers	4 (3.1)	3 (4.2)	1 (1.6)	.40
Pharyngitis	36 (27.1)	19 (26.4)	17 (27.9)	.85
Rash	45 (33.8)	30 (41.7)	15 (24.6)	.038
Urticarial rash	16 (12.1)	9 (12.5)	7 (11.5)	.86
Nonurticarial rash	29 (21.8)	21 (29.2)	8 (13.1)	.025
Conjunctivitis	12 (9.0)	7 (9.7)	5 (8.2)	.76
Gastrointestinal				
Abdominal pain	69 (51.9)	36 (50.0)	33 (54.1)	.64
Vomiting	39 (29.3)	20 (27.8)	19 (31.1)	.67
Diarrhea	17 (12.8)	12 (16.7)	5 (8.2)	.14
Musculoskeletal				
Myalgia	37 (27.8)	19 (26.4)	18 (29.5)	.69
Arthralgia	48 (36.1)	23 (31.9)	25 (41.0)	.28
Leg pain	24 (18.0)	11 (15.3)	13 (21.3)	.37
Lymphoid				
Lymphadenopathy	35 (26.3)	22 (30.6)	13 (21.3)	.23
Cardiorespiratory				
Chest pain	10 (7.5)	5 (6.9)	5 (8.2)	.78
Cough	4 (3.0)	2 (2.8)	2 (3.3)	.87
Neurologic				
Headache	53 (39.8)	31 (43.1)	22 (36.1)	.41

colchicine of 27.53 (CI [1.59-477], P = .023) (85.7% vs 50.6%).

The presence of oral ulcers also corresponded to incomplete colchicine response, although this did not reach clinical significance (38.9% (n = 28) vs 24.6% (n = 15), P = .08). Conversely, the presence of a heterozygous *MEFV* mutation appeared to have a higher likelihood of complete response, although this also missed statistical significance (62.5% (n = 14) vs 42.6% (n = 11), P = .08). Within those with MEFV mutations, patients who were incomplete responders tended to have the E148Q variant.

Discussion

Over the last two decades, there have been many advances in the clinical description and management of SAIDs. Nevertheless, almost half of patients with SAIDs do not neatly fit into classic syndromes. Patients with uSAID are a challenge to providers, as there is little evidence to base treatment. Colchicine is an inexpensive, well-tolerated medication with a long track record of being an effective anti-inflammatory agent. In this study, we evaluated the efficacy of colchicine use in our uSAID population. As demonstrated by our attempt at PCA analysis, our population was expectedly heterogenous, but we sought to identify individual features that might be correlated with incomplete or complete colchicine response. To our knowledge, this is the largest North American study on children with uSAID and the largest to focus on the empiric use of colchicine.

In our clinic, colchicine is often the first empiric agent to be offered and trialed for uSAID, usually within 5 months of diagnosis. A notable finding of our study is that 92.5% of patients had a favorable response, with almost half of patients demonstrating a complete response. Colchicine was well-tolerated, particularly when started at a lower dose and titrated up to therapeutic dosing. While other studies have demonstrated the efficacy of anakinra or tonsillectomy for some patients with uSAID, we favor initiating treatment with colchicine instead, as it is an oral medication with a good safety profile.[16–18] It is also less costly and a good option for families concerned about surgical risks.

Our uSAID population shared many features with patients described in a Eurofever study on uSAID in 2019, with similar frequencies of mucocutaneous, neurologic, and gastrointestinal symptoms.[8] In that study, which included 49 patients who received colchicine, a good response to colchicine was associated with shorter inflammatory episodes. In our study, this trend was not found (P = .69). Our larger cohort also enabled us to probe the relationship of clinical features and genetic variants on the treatment response.

Gene panel analysis identified many variants of unclear significance. There were 25 children with heterozygous *MEFV* mutations who did not meet clinical criteria for FMF. Their response rate to colchicine was generally better than that of our uSAID population at large, except for patients with E148Q mutations. This mutation, which is located on exon 2, is not considered as pathogenic as exon 10 mutations. Indeed, in a study of 646 children with FMF, only six patients had homozygous E148Q mutations, and M694V/E148Q compound heterozygosity presented similarly to those with M694V alone.[19] Some of our patients with E148Q also had compound heterozygosity at position P369S on exon 3, which has also been shown to be associated with a variable phenotype and only incomplete response to colchicine.[20]

Curiously, the presence of a rash—specifically nonurticarial rash—was correlated with a significantly decreased likelihood of complete colchicine response, particularly in *MEFV* mutation-negative patients (OR 27.5). While some of these rashes were erythematous or violaceous, many fell into a Behçet's disease-like spectrum of acneiform, pustular, or erythema nodosum like (while not otherwise meeting criteria for Behçet's disease). On the other hand, children with an urticarial rash were more likely to respond to colchicine, which is not surprising given the generally beneficial effect colchicine has shown for urticarial vasculitis.[21]

In our preliminary analysis, there were hints of a negative correlation between complete colchicine response and the presence of oral ulcers, although this did not quite meet significance when we increased our sample.[22] This finding was in line with a small American cohort of uSAID patients, in which having features of PFAPA syndrome was negatively correlated with colchicine response.[18] Together these findings are interesting since colchicine

is a standard treatment for aphthous ulcers in Behçet's disease and chronic aphthous stomatitis, both of which are thought to be on a spectrum with PFAPA.[23] However, as has recently been reviewed, the benefit of colchicine for these indications may be modest at best.[24,25]

One strength of our study is the large number of patients who were seen at a single center. However, we had a poor representation of Asian, Latinx, and Black patients in our uSAID population, with most patients being white with European ancestry. The literature on these metrics in SAID is primarily focused on patient ancestry in FMF and TRAPS, with different mutations found worldwide.[26–29] However, the ancestry, race, and ethnicity of patients with uSAID have not yet been entirely determined, recognizing that these latter two are flawed social proxies of genetic ancestry. PFAPA is a classic polygenic uSAID, and studies on the family history in children with PFAPA were composed of a primarily white (94%) population.[30] More data are needed to determine the disease prevalence in different demographics to help identify if there may be any disparities in access to care at our center and elsewhere.

A limitation intrinsic to studying patients with undefined autoinflammatory diseases is the lack of diagnostic criteria and dependence on clinical judgment of the treating physician. Nevertheless, we believe this is partially mitigated by our experience diagnosing uSAID as one of the largest autoinflammatory clinics in North America.

Another important limitation is that we selected patients who had taken colchicine for at least 3 months. This was intentional, as a trial less than 3 months may not have enabled a patient to reach therapeutic dosing and be followed long enough to see a clinical benefit. Of the 1,200 patients we screened, fewer than 20 discontinued colchicine before completing 3 months of therapy due to gastrointestinal side effects. However, we acknowledge that our data may be slightly biased toward favoring colchicine based on our inclusion criteria. Finally, as a retrospective study, there is always the possibility for selection bias; however, we are reassured by the diversity in the clinical presentation of the cohort described, which is consistent with colchicine being regarded as one of the first-line empiric agents for uSAID at our center.

In conclusion, the findings of our study support the early use of colchicine in children with uSAID, as it generally leads to a partial—if not complete—response and is inexpensive and well-tolerated. While the presence of a *MEFV* mutation appeared to correlate with a higher rate of complete colchicine response, many patients who did not carry *MEFV* mutations still benefited. However, patients without *MEFV* mutations with nonurticarial rash were more likely to have an incomplete colchicine response, although additional data are needed to confirm our findings and determine more effective treatments for these patients.

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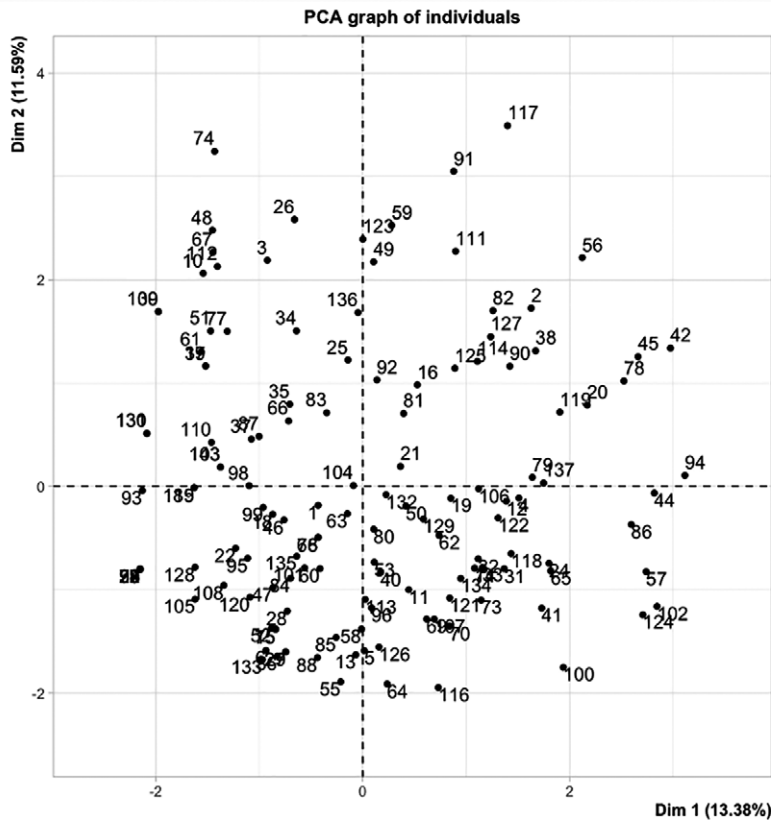
Supplementary Figure 1. PCA analysis of clinical features that were seen in at least 20% of patients. There were no clear clusters that explained a significant amount of the variance.

Laboratory Study	Number (%)
Hemoglobin	
Normal	69 (85.2)
Increased	8 (9.9)
Decreased	4 (4.9)
WBC	
Normal	55 (69.6)
Increased	18 (22.8)
Decreased	6 (7.6)
Neutrophil	
Normal	53 (63.9)
Increased	11 (13.3)
Decreased	19 (22.9)
Lymphocyte	
Normal	33 (39.8)
Increased	49 (59.0)
Decreased	1 (1.2)
Monocyte	
Normal	21 (77.8)
Increased	5 (18.5)
Decreased	1 (3.7)
Eosinophil	
Normal	44 (54.3)
Increased	32 (39.5)
Decreased	5 (6.2)
Platelet	
Normal	51 (60.7)
Increased	32 (38.1)
Decreased	1 (1.2)
CRP	
Normal	71 (87.7)
Increased	10 (12.3)
ESR	
Normal	71 (91.0)
Increased	7 (9.0)

Supplementary Table 1. Relative Lab Values for Age at the Initial Visit during Usual State of Health

Supplementary Table 2. List of MEFV Mutations and Associated Clinical Features in Addition to Fevers

MEFV Mutation + Other	Clinical Features	Episode (Days)	Ancestry	Response
E148Q	Abdominal pain, vomiting, anorexia	8	Cambodia	Complete
E148Q	Ulcers, pharyngitis, urticarial rash	4	France, Italy, UK, native	Partial
E148Q	Myalgia	3.5	Portugal	Partial
E148Q and I591T (compound HZ)	Pharyngitis, rash, LAD, abdominal pain, arthralgia, myalgia, HA	17.5	Viet Nam	Partial
E148Q and L110P (compound HZ)	Oral ulcers, urticarial rash, arthralgia, abdominal pain, HA	17.5	China	Partial
E148Q	Torticollis	unknown	Ashkenazi Jewish	Complete
E148Q and P369 + SLC37A4: N27S	Vomiting, anorexia	4	French, Canada, native, UK	Partial
E148Q and P369S	Pharyngitis, abdominal pain, fatigue	3.5	Greece	Partial
S154P + SCL9A3: A230T	Urticarial rash, arthralgia, oligoarthritis, fatigue, preorbital edema	4.5	Italian	Partial
R329H	Oral ulcer, rash, vomiting	7	Germany, Ireland, Italy, UK	Partial
S339F + TNFRSF1A: IVS4 + 7	Pharyngitis	5.5	France, Ireland, Italy, Eastern Europe	Complete
I591T	Oral ulcers, rash, vomiting	5	French, Canada, Ireland, Italy, UK	Partial
I591T	Rash, arthralgia, myalgia, fatigue	3	Austria, Israel, Norway	Complete
M694V + TNFRSF1A: R92Q	Conjunctivitis, urticarial rash, sore throat	2	Armenia, UK	Complete
M694V	Rash, myalgia, abdominal pain, diarrhea	3.5	France, Ireland, Italy, Portugal, UK	Complete
K695R	Arthralgia, headache	2	Guatemala, Greece, Italy, Turkey	Complete
K695R	Oral ulcer, rash, chest pain, LAD, arthralgia, abdominal pain, HA	3.5	France, Italy, Poland	Complete
V726A + NOD2: A860T	Pharyngitis, rash, sore throat	4	Unknown	Complete
V726A	Eczematous rash, Raynaud's, ill-defined pain	unknown	Germany, Ireland, Ashkenazi Jewish	Complete
V726A + IL2RA D26H	Vomiting, diarrhea, abdominal pain, anorexia	3	Ashkenazi Jewish	Complete
A744S	Pharyngitis, urticarial rash, sore throat, chest pain, arthralgia, myalgia, abdominal pain, fatigue	unknown	Ecuador, Germany, Ireland, Italy, UK	Partial
MEFV (IVS8-4 g > a) + LPIN2 P886L	Rash, arthralgia, myalgia, HA	2	Puerto Rico	Partial
Unknown HZ	Anorexia, fatigue	4	Syria, Lebanon	Complete
Unknown HZ	Abdominal pain, leg heaviness	3.5	Unknown	Complete
Unknown HZ	Oral ulcers, pharyngitis, neck and leg pain, HA	3	Cuba, Italy, Eastern Mediterranean	Complete

HZ, heterozygous; LAD, lymphadenopathy; HA, headache.