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Review Article

Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) and PAPA-Like Syndromes: Systematic Review of the Literature

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Abstract

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare autosomal dominant autoinflammatory disorder caused by mutations in the PSTPIP1/CD2BP1 gene. We systematically reviewed 93 patients with PAPA and PAPA-like syndrome. Most patients were male (65.9%) mainly born to non-consanguineous parents. The median (IQR) age at the onset of symptoms and diagnosis was 6.0 (2.0-8.0) and 25.0 (7.0-32.0) years, respectively. 62.5% of patients were presented with arthropathies and septic arthritis was the most common (54.2%) initial diagnosis. Joint disorders were the most common findings (n=71, 78.9%) starting at the median (IQR) age of 4.0 (2.0-8.0) years, mainly in the knee (56.5%), ankle (36.9%), and elbow (47.8%).

Skin involvement (62 (66.7%)) initially presented at a median (IQR) age of 12.0 (20.-10.0) years and included pyoderma gangrenosum (n=41, 44.1%), acne (n=43, 46.2%), and nodulocystic acne (n=19, 20.4%).

There was a stronger association between skin manifestations and the development of the classic triad (P<0.001) compared to joint disorders (P=0.05) and patients with lower age of onset were more prone to the progression of the complete triad (P=0.18). Corticosteroids (n=45, 50.0%) with or without anakinra (33.3%) were the treatments applied in the majority of patients.

PAPA/PAPA-like syndromes involve mainly non-axial joints in early childhood and later skin in the second decade of life. Only 26.4% of the patients manifested the classical triad of PAPA syndrome. There is no clear genotype-phenotype association in these disorders. More studies are required to investigate the therapeutic options in PAPA/PAPA-like syndromes.

Keywords: PAPA; PSTPIP1; Pyogenic Sterile Arthritis; Pyoderma Gangrenosum; Acne; PAPA-Like Syndrome

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Introduction

PAPA (pyogenic sterile arthritis, pyoderma gangrenosum, and acne) syndrome is a rare systemic autoinflammatory syndrome that is inherited in an autosomal dominant fashion (1). It is caused by a mutation in the proline serine threonine phosphatase- interacting protein 1 (PSTPIP1)/CD2-binding protein 1(CD2BP1) gene located on chromosome 15 (2). PAPA syndrome was first described in 1997 by Lindor et al (3) and described as recurrent attacks of noninfectious pyogenic arthritis usually with associated dermatologic findings that most commonly involve acne vulgaris, but may also include pyoderma gangrenosum (PG). This syndrome clinically manifests as early-onset episodic attacks of acute aseptic arthritis in the first two decades of life (4). This syndrome has variable manifestations therefore the treatment varies included corticosteroids, intra-articular steroid injections , non steroidal anti-inflammatory drugs (NSAIDs) and biologic agents such as anakinra, methothrexate ,infliximab ,adalimumab ,cyclosporine ,etanercept,tacrolimus , colchicine , canakinumab , colchicine ,canakinumab and others

In this study, we aim to systematically review demographic, clinical, and laboratory features of patients with PAPA and PAPA-like syndrome reported in the literature.

Methods

A systematic literature search was conducted in PubMed, Web of Science, and Scopus databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method (**Figure 1**). The following search terms were applied in various combinations: "Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne", "PAPA syndrome", "PAPA-like syndrome", "Pyogenic arthritis, pyoderma gangrenosum, and severe cystic acne", and "PSTPIP1". Overall 1818 articles were found and after the removal of 1060 duplicate articles, 757 articles remained for the initial screening of titles and abstracts. Reference lists of all full-text articles and major reviews were searched manually for additional studies. Articles written in the English language with at least one patient with PAPA or PAPA-like syndrome diagnosis were included in the study. Studies using animal models, reviews, conference papers, and articles in languages other than English were excluded. In addition, Patients with Suppurative Hidradenitis Psoriatic arthritis, Ulcerative Colitis, Crohn disease, Spondyloarthritis, Leukocytoclastic vasculitis, autoimmune hepatitis and primary sclerosing cholangitis were excluded. The informed consent for participation was obtained from the patient and his parents. Ethical Approval was not applicable.

Results

Demographic Findings

Overall, 93 patients from 45 articles published during 1997 – 2022 years, were enrolled in the study and were categorized as PAPA (n=79) and PAPA-like (n=14) syndromes. The study of the origin of reported patients was mainly the United States in 33 (35.4%) and Italy in 18 (19.4%) patients and the others were distributed among different countries.

The male:female ratio was almost 2 (60 (65.9%) male and 31 (34.1%) female). All except seven patients were born to non-consanguineous parents. Most of the patients with available life status were alive (79 of 82, 96.3%). The median (interquartile range: IQR) age at the study time was 22.0

(10.0-36.0). The median (IQR) age at the onset of symptoms was 4.0 (2.0-8.0) years and the median (IQR) age at the diagnosis was 15.0 (7.0-32.0) years, with a median (IQR) diagnostic delay of 9.8 (3.0-20.0) years. Lower age at onset of symptoms did not predispose patients to a higher mortality rate (p=0.831). (**Table 1**)

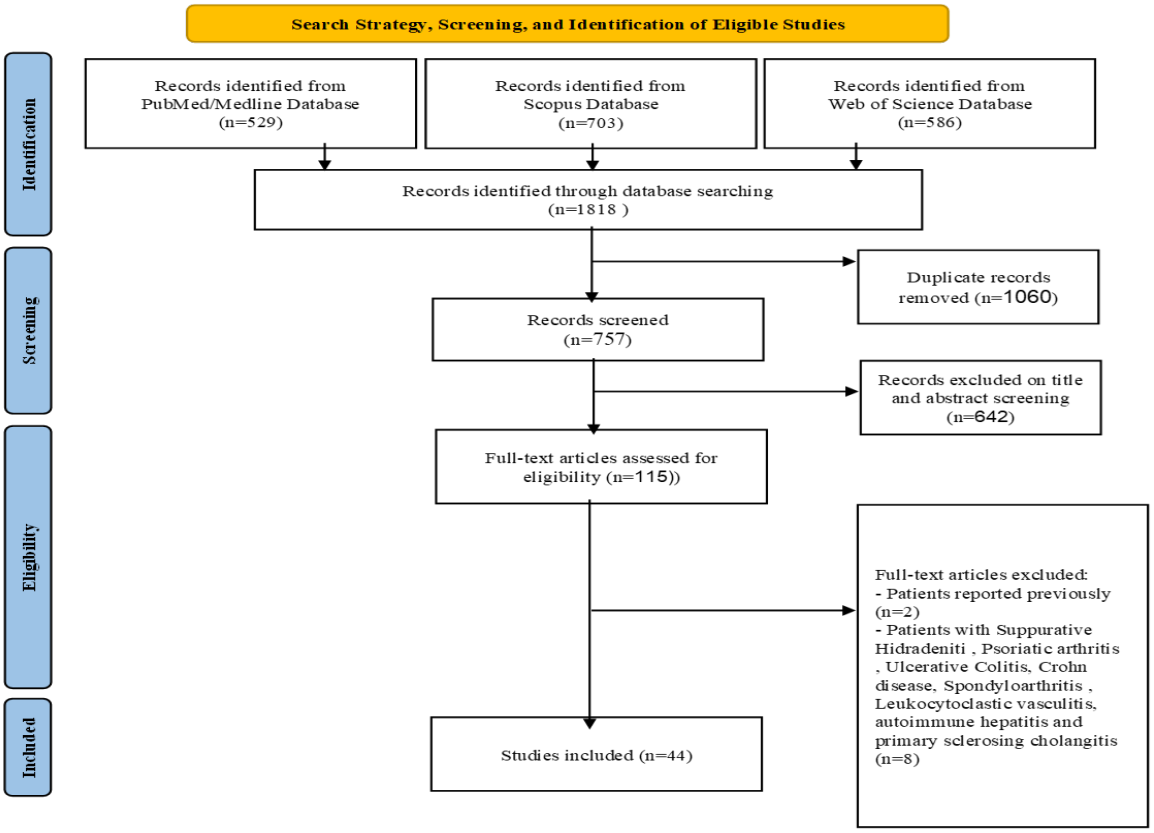

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Clinical Findings

First presentation of disease was mentioned in 69 patients and included arthropathies (n=40, 58%), skin lesions (n=17, 24.6%), and post-vaccination pathergy, febrile attacks, and infectious disorders each in 4 (5.8%) patients.The initial diagnosis was available in 24 patients and the disorder was considered as septic arthritis (n=13, 54.2%), juvenile idiopathic arthritis (JIA) (n=3, 12.5%), sepsis (n=3, 12.5%), osteomyelitis (n=2, 8.3%), familial mediterranean fever (FMF) (n=2, 8.3%), and chronic recurrent multifocal osteomyelitis (CRMO) (n=1, 4.2). The classic triad was observed in 25 (26.9%) patients (Figure 2).

Joint involvement was reported in 76 (83.5%) patients with a median (IQR) age of onset at 5 (2-10) years. In 47 out of 76 patients, the pattern of joint involvement was mentioned, which was oligoarticular (n=22, 46.8%), monoarticular (n=14, 29.8%), and polyarticular (n=11, 23.4%) forms. History of trauma was positive in 11 of 76 (14.5%) patients and almost half of patients suffered from recurrent arthritis (37 of 76, 49.3%). The most common joints involoved in order of frequency were knee (n=26, 56.5%), ankle (n=17, 36.9%), elbow (n=22, 47.8%), metacarpophalangeal (n=8, 17.3%), hip (n=8, 17.3%), wrist (n=7, 15.2%), and shoulder (n=4, 8.6%) joints.

Skin involvement was reported in 62 (66.7%) patients and initially presented at a median (IQR) age of 11 (6-14) years. Skin disorders mainly included pyoderma gangrenosum (n=41, 44.1%) mainly in the lower extremities and head/neck, acne (n=43, 46.2%) mainly on the face and upper back, and nodulocystic acne (n=19, 20.4%).

There was a stronger association between skin manifestations and the development of classic triad (P<0.001) compared to joint disorders (P=0.006).

Another complications were abscess (n=18,

19.4%), anemia (n=10, 10.8%), recurrent fever (n=10, 10.8%), osteomyelitis (n=8, 8.6%), organomegaly (n=6, 6.5%), septic arthritis (n=5, 5.4%), autoimmunity (4, 4.3%), and allergy, vasculopathy, and malignancy each in two patients (2.2%). (**Table 2**)

Table 1. Demographic data of patients with PAPA syndrome

Parameters (no. of evaluated patients)	Results
Country of living (%) (n = 93)	United States (35.4), Italy (19.4), Germany and China (6.3) and others
Sex ratio, m/f, n (%) (n = 93)	60 (65.9)/31 (34.1)
Consanguinity, n (%)(n = 93)	7(7.6)
Familial case, n (%)(n = 93)	50(53.8)
Alive/dead, n (%)(n = 82)	79 (96.3)
Age (y) (n = 93)	Min =1.60, max = 68.00, median (IQR) = 13.00 (10.50-36.00)
Age at onset (y) (n = 93)	Min =.00, max =50.00 , median (IQR) = 10.50 (2.00-8.00)
Age at diagnosis (y) (n = 93)	Min =2.00, max =63.00 , median (IQR) = 13.00 (7.00-32.00)
Delay in diagnosis (y) (n = 93)	Min =.00, max =51.00 , median (IQR) = 25.00 (3.00-20.00)
Age at presentation of joint joint involvement (y) (n = 93)	Min =1.00, max =50.00 , median (IQR) = 20.50 (2.00- 10.00)
Age at presentation of skin involvement (y) (n = 93)	Min =.08, max =56.00 , median (IQR) = 8.00 (6.00- 14.00)
Age at presentation of pyoderma gangrenosum (y) (n = 93)	Min =5.00, max =52.00 , median (IQR) = 18.00 (10.25- 18.00)
Age at presentation of acne (y) (n = 93)	Min =2.90, max =31.00 , median (IQR) = 8.00 (11.00- 18.00)

F, female; m, male; max, maximum; min, minimum; nk, not known. Note: for age, age at onset, age at diagnosis, and delay in diagnosis, the median is shown (with 25th and 75th percentiles).

Laboratory and genetic Findings

Elevated levels of inflammatory markers such as estimated sedimentation rate (ESR) (27 of 30, 90%) and C-reactive protein (CRP) (43 of 48, 89.5%) was reported in the majority of patients with available laboratory data, and leukocytosis was reported in 11 out of 26 (42.3%) patients. Auto-antibodies were evaluated in 10 patients and were negative. Joint analysis revealed high cell count with negative culture in all 18 evaluated patients.

Among all 93 included patients in this study, 81 patients had the features of PAPA syndrome, and the remaining had the PAPA-like phenotype. A genetic diagnosis was identified in 87 patients, whereas the other six were diagnosed based on the patient's clinical presentation. After excluding cases where gene testing was not performed, two patients with the phenotype of PAPA did not have a mutation in the PSTPIP1 gene. Seventy-one patients had mutations in the PSTPIP1 gene, and one had a mutation in the MEFV gene. The responsible gene for causing the disease was not mentioned in 18 patients, eight patients with PAPA and 10 with PAPA-like syndrome. In terms of genotype, although genetic analyses were performed in most of the studies, genetic mutations were only reported in 58 of the 92 cases, and we did not have access to the genetic details of the remaining patients. Overall, 10 different PSTPIP1 gene mutations including c. 688G>A, c.748G>A, c.748G>C, c.657A>C, c.1213C>T, c.605G >A, c.36+68 G>A, c.356A>G, c.736G>A, c.964 G>C reported in 55 patients with PAPA syndrome. c.688G>A and c.748G>C mutations were the most commonly identified genetic defects. A rare homozygous missense mutation (c.1222G>A; p. Val408Ile) of the PSTPIP1 gene was detected in two cases of PAPA syndrome. Whole-genome sequencing revealed a novel homozygous PSTPIP1 mutation (c.773G>C; p. Gly258Ala) in one patient with the phenotype of PAPA-like syndrome. Furthermore, c.773G>C was also detected in heterozygous form in a pyoderma gan-

grenosum (PG) patient. Gene testing showed a heterozygous pathogenic variant in the MEFV gene (c.2080A>G; p. Met694Val) in a patient with pyogenic arthritis, PG, and acne. PSTPIP1 testing was negative in this patient (**Table 3**).

Table 2. Clinical manifestations of patients with PAPA syndrome

Parameters (no. Of evaluated patients)	Results, n (%)
Joint involvement(n=91)	76(83.5)
Trauma(n=91)	11(12.1)
History of recurrent arthritis(n=90)	37(44.1)
Pyoderma gangrenosum(n=93)	41(44.1)
Skin disorders(n=93)	62(66.7)
Acne(n=93)	43(46.2)
Nodulocystic, acne fulminans or severe(n=93)	19(20.4)
Abscess(n=93)	18(19.4)
Recurrent fever(n=93)	10(10.8)
Osteomyelitis(n=93)	8(8.6)
Septic arthritis(n=93)	5(5.4)
Vasculopathy(n=93)	2(2.2)
Candidiasis(n=93)	1(1.1)
Respiratory manifest(n=93)	1(1.1)
Allergy(n=93)	1(1.1)
Autoimmunity(n=93)	4(4.3)
Organomegaly(n=93)	6(6.5)
Hematologic oncologic disorders(n=96)	14(14.6)
Ear, nose, throat manifestation(n=93)	3(3.1)
Vasculopathy(n=93)	2(2.2)
Candidiasis(n=93)	1(1.1)
Sepsis(n=93)	4(4.3)

Treatment and outcome

Immunosuppressive/anti-inflammatory agents included corticosteroids (n=47, 50.5%), intra-articular steroid injections (n=12, 12.9%), non steroidal anti-inflammatory drugs (NSAIDs) (n=21, 22.6%), and biologic agents such as anakinra (31.2%), methothrexate (14%), infliximab (6.5%), adalimumab (8.6%), cyclosporine (7.8%), etanercept (6.5%), tacrolimus (6.5%), colchicine (5.4%), canakinumab (3.2%), and others (4.3%). 13 (14%) patients required surgeries and three patients were reported to be dead at adulthood due to acute myeloid leukemia (AML) or sepsis-related multiorgan failures.

Discussion

We reviewed a total of 93 patients with PAPA and PAPA-like syndromes. Almost all patients were born to consanguineous parents. Despite the disease onset in early childhood (median age of 4 years), the diagnosis was established at the median age of 15 years with a diagnostic delay of almost a decade. Contrary to earlier reports with an older age at diagnosis and longer diagnostic delay (5, 6). This delay could result from the gradual development of the disease over years; given pyoderma gangrenosum and acne as important components of the classic triad of PAPA syndrome presented in the second decade of life and

 2-table3.jpg

Table 3. Genetic analysis of patients with PAPA syndrome

Gene	Mutation	Protein	Patient(s)	Phenotype	Clinical significance
PSTPIP1					
	c.964 G>C	p. E250Q	2	PAPA	Not mentioned
	c.688G>A	p. A230T	20	PAPA	Pathogenic
	c.657A>C	p. Q219H	1	PAPA	likely benign
	c.1213C>T	p. A405C	1	PAPA	VUS
	c.605G>A	p. A202Q	1	PAPA	VUS
	c.748G>A	p. E250K	7	PAPA/ PAPA-like	Pathogenic
	c.748G>C	p. E250Q	16	PAPA	Pathogenic
	c.356A>G	p. Y119C	1	PAPA	Pathogenic
	c.773G>C	p. G258A	2	PAPA-like	Benign
	c.1222G>A	p. V408I	2	PAPA	VUS
	c.736G>A	p. D246N	1	PAPA	Likely Pathogenic
	c.36+68 G>A	Not mentioned	1	PAPA	Benign
	c.770A>G	p. E256G	3	PAPA	Likely pathogenic
MEFV					
	c.2080A>G	p.M694V	1	PAPA-like	Likely pathogenic

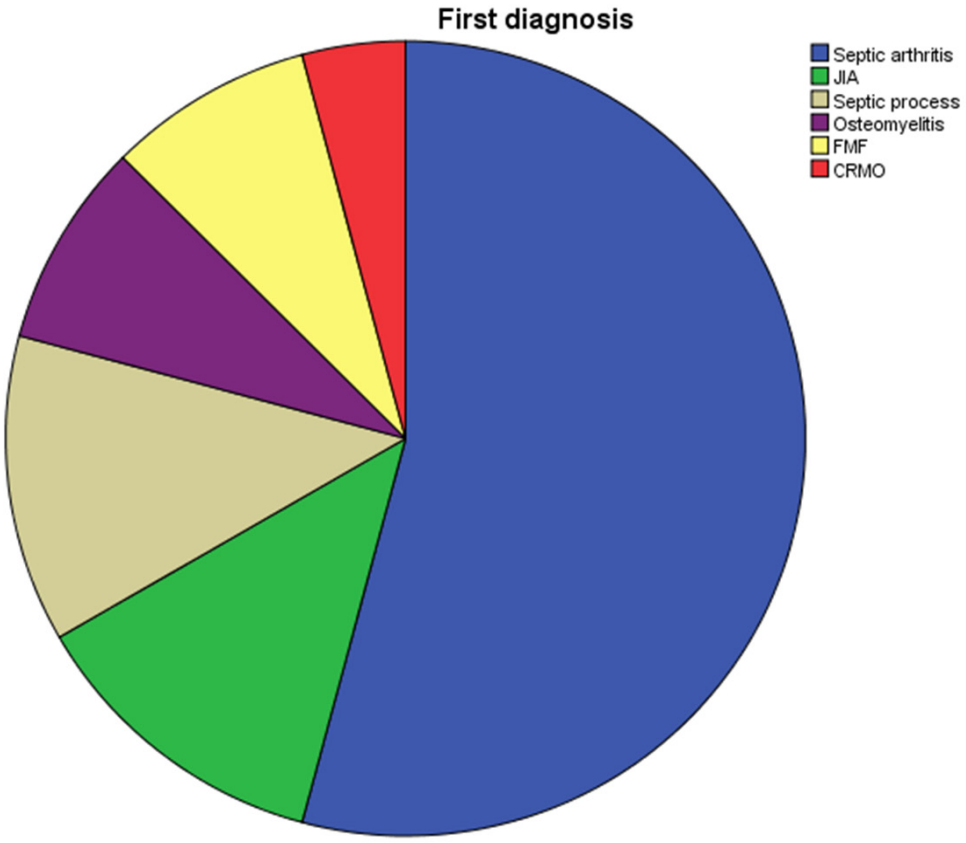

Figure 2. First presentation and first diagnosis of the patients

delayed the diagnosis. . Likewise, previous studies expressed that skin disorders generally start early in puberty and persist onward (7).

Joint involvements were the earliest and most prevalent manifestation among most patients with PAPA and PAPA-like syndromes. Consistent with former reports (8, 9), both big and small, especially non-axial, joints were involved in these patients. Considering patients mainly experienced arthropathy as their initial presentation, they were primarily diagnosed with septic arthritis before further evaluation.

Skin disorders were the second prevalent manifestations, predominantly characterized by pyoderma gangrenosum (44.1%) and acne (46.2%) and distributed in different sites. Interestingly, skin lesions were the first presentation in 24.6% of patients which disrupts the expected sequence of PAPA syndrome development (10). Even though less than one-third of the patients had the classical triad of PAPA syndrome, patients with skin lesions were significantly more prone to develop this triad, especially in patients with lower age of onset. However, the peneterance and the type of disease manifestations may vary within cases (7).

In recent years, the variety of autoinflammatory diseases has increased, likely due to variations in the PSTPIP1gene with heterogeneous manifestations. PAPA syndrome is one of these associated inflammatory diseases with different numbers of variants, based on reports from different databases. There are several variant databases that support data on disease-associated variants. Until now, 25 variants have been reported for the PSTPIP1 gene in the Infevers database (http://fmf.igh.enrs.fr/ISSAID/infevers/). Moreover, 259 variants in PSTPIP1-associated PAPA syndrome are present in the ClinVar Miner database (http://clinvarminer.genetics.utah.edu/variants). Given that the clinical approach to the diagnosis of PAPA syndrome is challenging due to its diverse clinical features, genetic sequencing is required for accurate diagnosis. Due to the rarity of PAPA syndrome, there are no comprehensive studies on the genetic mutations related to reported cases. Evidence from different studies suggests that PSTPIP1 variants, including p.A230T, p.E250Q, p.E256G, p.D246N, and p.D266N, are currently the most pathogenic mutations in PAPA syndrome (11). A230T and E250Q are the most reported pathogenic mutations in the literature, which significantly increase the binding of PSTPIP1 to pyrin (12). A230T is a non-conservative amino acid substitution, which is likely to have an effect on protein secondary structure. In contrast, p.D246N, p.E256G, and p.D266N have been defined as the other PAPA-causing mutations. p.D246N, as a novel de novo missense mutation in the coiled-coil domain of the PSTPIP1 gene, was reported in a boy with clinical features of PAPA syndrome; therefore, this mutation may be the cause of symptoms in the child (13). It should be noted that pathogenic mutations linked to PAPA syndrome are located within the coiled-coil region of the PSTPIP1 gene (14). In contrast to pathogenic PSTPIP1 mutations that cause PAPA syndrome, a homozygous PSTPIP1 mutation (c.773GC and p. Gly258Ala) led to a novel phenotype associated with a PAPA-like syndrome (15). Genetic analysis, in this case, revealed a recessive inheritance pattern of PSTPIP1 mutation that previously was reported as heterozygous polymorphism in a patient with pyoderma gangrenosum (PG) (16). Several studies have reported that the p.Gly258Ala substitution in homozygous carriers can significantly alter the dimerization of the PSTPIP1 protein (15, 17). A heterozygous missense mutation p. (Val408Ile) of the PSTPIP1 gene was reported in two siblings. V408I is an amino acid substitution mutation, which is not likely to have effect on secondary protein structure. To date, it is not clear whether this variant is a pathogenic or a benign variant. Using next-generation sequencing, a homozygous mutation p.M680I of exon 10 in the MEFV gene and the heterozygous missense mutation p. (Val408Ile) of the PSTPIP1 gene were detected in two siblings. The presence of PAPA syndrome associated with FMF, as observed in the two siblings, and considering the rarity of the Val408Ile mutation, may amplify clinical symptoms, and the evolution of both diseases and a common pathway is suggested for linked between FMF and PAPA syndrome (18). In silico analysis revealed that, E250K variant has a deleterious effect on the protein function of the PSTPIP1 gene. This variant has been reported many times in patients with PAPA syndrome or hyperzincaemia/hypercal-protectinemia (Hz/Hc). The glutamic acid residue is crucial for PSTPIP1 protein function, and missense substitutions at this position

may be pathogenic. Molecular analysis of the PSTPIP1 gene in this study showed that six patients had heterozygous E250K mutations with PAPA syndrome phenotype and one heterozygous de novo mutation (19), which showed a specific condition distinct from classical PAPA syndrome (20). A different missense substitution at this codon, p.E250Q has also been described as a pathogenic mutation. In our study, two patients with manifestations of PAPA syndrome did not exhibit mutations in the PSTPIP1 gene. This unusual condition has been described primarily in European countries (21). In these cases, additional factors other than the known mutations, such as inflammatory pathways, maybe contribute to this situation. It should be noted that PAPA syndrome is regarded as an autoinflammatory disease, and CD2BP has been reported as a part of an inflammatory pathway.

Patients with PAPA/ PAPA-like syndrome are in autoimmune inflammatory states (22). Therefore, increased inflammatory markers consisting of ESR, CRP, and leukocytosis were reported in a majority of patients with available laboratory data. However, auto-antibodies and the culture of the joint analysis in patients were negative, rejecting autoimmunity and infections as the underlying pathomechanisms of the disease (22).

The reported patients were treated with systemic corticosteroids (n=47, 50.5%), intra-articular steroid injections (n=12, 12.9%), non steroidal anti-inflammatory drugs (NSAIDs) (n=21, 22.6%), and biologic agents such as anakinra (31.2%), methothrexate (14%), infliximab (6.5%), adalimumab (8.6%), cyclosporine (7.8%), etanercept (6.5%), tacrolimus (6.5%), colchicine (5.4%), canakinumab (3.2%) and others (4.3%), particularly in refractory cases. Although a standard therapeutic approach has not been established for PAPA/PAPA-like syndromes, promising results were observed in some studies including cost-effective therapies (23-25). Yet, more studies are required to investigate the treatment options in PAPA/PAPA-like syndromes.

Finally, it should be mentioned that the studies mainly originated from developed countries where diagnostic tools and therapeutic options are more accessible and therefore, it could affect the interpretation of the data.

In summary, PAPA and PAPA-like syndromes are rare autoimmune/autoinflammatory diseases involving mainly non-axial joints in early childhood and later skin in the second decade of life. However, less than one-third of the patients manifested the classical triad of PAPA syndrome. There is no clear genotype-phenotype association in these disorders. Inflammatory indices are elevated in the blood, however, no sign of auto-antibodies or infectious microorganisms were detected in the patients. Currently, corticosteroids and biologic agents are the selected treatments in these patients. Whilst, no standard therapeutic approach has not yet been established for PAPA and PAPA-like syndromes.

Ethics approval and consent to participate

The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences with ethic code: IR.SBMU.NRITLD.REC.1400.111, and written informed consent was obtained from all participants or their parents before enrolling to the study.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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