ORIGINAL RESEARCH

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What is the Role of Mucocutaneous Manifestations in the Clinical Presentation of Monogenic Autoinflammatory Diseases? A Single-center Experience

Monogenik Otoenflamatuvar Hastalıkların Klinik Prezentasyonunda Mukokutanöz Bulguların Payı Nedir? Tek Merkez Deneyimi

Oya Köker[1], Nuray Aktay Ayaz[2]

[1]Marmara University, Pendik Training and Research Hospital, Clinic of Pediatric Rheumatology, İstanbul, Turkey
[2]İstanbul University Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Turkey

Abstract

Objective: The aim of the study was to determine the distribution, frequency, and characteristics of mucocutaneous manifestations along with other clinical and laboratory data in the presentation of monogenic autoinflammatory diseases.

Method: The study was performed with the patients being followed up with a diagnosis of autoinflammatory diseases at the Pediatric Rheumatology Department in İstanbul University Faculty of Medicine. Medical records on clinical and laboratory characteristics covering the date range from January 1, 2018 to September 1, 2021 were retrospectively reviewed.

Results: The study cohort (n=97) demonstrated a distribution as familial Mediterranean fever (n=64, 66%), mevalonate kinase deficiency (n=16, 16.5%), cryopyrin-associated periodic syndromes (n=11, 11.3%), and TNF receptor-associated periodic syndrome (n=6, 6.2%). Among the entire cohort, 59.8% was female. The median age at diagnosis and at the study were 71 (3-195) and 147 (34-253) months, respectively. Mucocutaneous involvement (34%, n=33) appeared as erysipelas-like, urticaria-like, maculopapular or morbilliform in character. The location and extent of rash differed between the subgroups, limited to a localized area in patients with familial Mediterranean fever, but scattered in patients with cryopyrin-associated periodic syndromes.

Conclusion: The location and character of the mucocutaneous signs demonstrated a consistent distribution according to the subgroups. Skin

Öz

Amaç: Çalışmanın amacı monogenik otoenflamatuvar hastalıkların sunumunda mukokütanöz bulguların dağılımını, sıklığını ve özelliklerini diğer klinik ve laboratuvar verilerle birlikte belirlemekti.

Yöntem: Çalışma İstanbul Üniversitesi Tıp Fakültesi Çocuk Romatoloji Bilim Dalı'nda otoenflamatuvar hastalık tanısı ile takip edilen hastalarla gerçekleştirildi. 1 Ocak 2018-1 Eylül 2021 tarih aralığındaki klinik ve laboratuvar özelliklerin ayrıntılarına ilişkin medikal kayıtlar geriye dönük olarak incelendi.

Bulgular: Çalışma kohortu (n=97) ailesel Akdeniz ateşi (n=64, %66), mevalonat kinaz eksikliği (n=16, %16,5), kriyopirin ilişkili periyodik sendromlar (n=11, %11,3), TNF reseptörü ilişkili periyodik sendrom (n=6, %6,2) şeklinde dağılım göstermiştir. Çalışma grubunun %59,8'i kız hastalardı. Tanı anındaki ve çalışmadaki ortanca yaşlar sırasıyla 71 (3-195) ve 147 (34-253) aydı. Mukokütanöz tutulum (%34, n=33) erizipel benzeri, ürtiker benzeri, makülopapüler veya morbilliform karakterdeydi. Döküntülerin yeri ve yaygınlığı alt gruplar arasında farklılık gösterdi; ailesel Akdeniz ateşi olan hastalarda lokalize alanla sınırlıyken, kriyopirin ilişkili periyodik sendrom tanılı hastalarda dağınık yerleşimliydi.

Sonuç: Mukokütanöz bulguların yeri ve karakteri alt gruplara göre tutarlı bir dağılım göstermiştir. Deri bulguları hemen hemen tüm alt tiplere eşlik eder ve hastalığın alt bölümlerine ve patolojik mekanizmasına ilişkin bir ipucu sağlayabilir.

Address for Correspondence: Oya Köker, Marmara University, Pendik Training and Research Hospital, Clinic of Pediatric Rheumatology, İstanbul, Turkey
E-mail: oyakoker@hotmail.com **ORCID:** orcid.org/0000-0002-0101-9585 **Received:** 04.01.2022 **Accepted:** 02.03.2022

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manifestations accompany almost all subtypes and may provide a clue regarding the subdivision and pathological mechanism of the disease.

Keywords: Autoinflammatory diseases, mucocutaneous manifestations, pediatric rheumatology

Anahtar kelimeler: Mukokutanöz belirtiler, otoenflamatuvar hastalıklar, pediyatrik romatoloji

Introduction

Autoinflammatory diseases are a group of disorders associated with an overactivation of the cytokines and other components of the innate immune system and clinically characterized by uncontrolled systemic inflammation leading to recurrent episodes of fever along with the involvement of the joints, eyes, skin, and serosal surfaces (1). The term "autoinflammatory diseases" was first used in 1999 to describe a group of rare diseases driven by autoinflammatory mechanisms (2,3). Since then, with deepening awareness of the genetic polymorphisms and their association with proteins of the inflammasome complex and other regulatory proteins, the diseases have begun to be more identified, and the spectrum has continued to grow.

Monogenic, polygenic, and multifactorial disorders are among the range of autoinflammatory diseases. The classical monogenic group consists of familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD) and cryopyrin-associated periodic syndromes (CAPS) derived from various mutations in a single gene leading to unregulated innate immunity and overexpression of interleukin (IL)-1β (4). Clinical inflammation is recurrent or rarely persistent, usually manifested by fever and involvement of the serous membranes. Mucocutaneous lesions are the hallmark of the spectrum as they may have a role in the initial presentation or the activation stage of autoinflammatory diseases.

The cutaneous features may solely be the dominant sign in the clinical picture or one of the indispensable manifestations guiding the differential diagnosis. In contrast to the overlapping clinical features such as fever and joint involvement, the cutaneous signs in monogenic diseases may display a consistent morphological and topographic distribution among the subgroups and provide a clue regarding the subdivision and pathological mechanism of the disease. However, in these diseases, genotype and phenotype correlation is not always compatible, and may lead to individual differences and heterogeneous clinical presentations (5). The aim of this study is to determine the distribution, frequency, and characteristics of mucocutaneous features along with other clinical and laboratory data in the presentation and the course of monogenic autoinflammatory diseases.

Materials and Methods

Patient Selection

The study was performed with the patients being followed up with a diagnosis of autoinflammatory diseases at the Pediatric Rheumatology Department in İstanbul University Faculty of Medicine. In the definition of the patients, genotype, clinical manifestations, and expert opinion were regarded in the light of recommended classification criteria (6, 7). Special attention has been given to include patients who were diagnosed after excluding all existing causes, and who did not have any signs that would raise diagnostic suspicion during the follow-up and treatment process.

Autoinflammatory diseases other than monogenic periodic syndromes were not included in the study. Since the diagnoses may demonstrate a wide age distribution, patients between the ages of 0-18 years were included in the study. The patients with missing or insufficient data and without regular follow-up were excluded from the study. Each participant and his/her legal representative approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study. Approval was obtained from the Ethics Committee of İstanbul University Faculty of Medicine for the study (2021-622903).

Data Collection

Medical records covering the date range from January 1, 2018 to September 1, 2021 were retrospectively reviewed. The details of clinical and laboratory characteristics were recorded by using a standardized form for all subjects. Demographic (age, gender) and disease-related data (age at diagnosis, duration of symptoms before the diagnosis, disease duration from the diagnosis to the time of the study, disease pattern, detailed history of initial symptoms, medication history) were assessed. It was verified whether the physical signs within the criteria were accurately and consistently documented at the time of the diagnosis. Baseline laboratory data including leukocyte and platelet

count, C-reactive protein, erythrocyte sedimentation rate, serum amyloid a were investigated both from their own records and from the hospital database.

Genetic Analyses

Genetic tests were primarily ordered based on clinical pictures and laboratory data of the patients. In case of suspicion of FMF, genomic DNA from peripheral blood samples of the suspected patients was genotyped for the specific candidate gene MEFV using Sanger sequencing. For patients who were clinically incompatible with the MEFV mutation, who displayed episodes of atypical inflammation and who did not respond to colchicine therapy and who were suggestive of other monogenic types, a gene panel including NLRP3, MVK, TNFRSF1A, NLRP12, PSTPIP1, NOD2, ELANE, IL1RN, MEFV, LPIN2, TNFRSF11A, CARD14, PSMB8, IL10RA, IL10RB, NLRP7 or whole-exome sequencing method was utilized. Variants found in patients were analyzed by searching on the ClinVar or the Infevers.

Statistical Analysis

Statistical analyses were performed by using the IBM SPSS Statistics for Windows 21.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA) and Microsoft Excel (Redmond, WA). The visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were performed to analyze the distribution of the variables. The demographic and clinical data were evaluated using descriptive analysis, and the data are presented as percentage (%), median with minimum and maximum values. In the comparison and assessment of the data, non-parametric tests, and Kruskal-Wallis test were performed. Statistical significance was defined as p-value <0.05.

Results

Nine patients were excluded from the study because of missing or insufficient data, while 97 patients with the diagnosis of monogenic autoinflammatory diseases were enrolled. The study cohort demonstrated a distribution as FMF (n=64, 66%), MKD (n=16, 16.5%), CAPS (n=11, 11.3%), TRAPS (n=6, 6.2%).

Among the entire cohort, 59.8% were female. The median age at diagnosis and at the study were 71 (3-195) and 147 (34-253) months, respectively. The median disease duration was 78 (13-207) months. According to gender distribution, the ratio of females n (%) among the groups were 41 (64.1) in FMF patients, 7 (63.6) in CAPS patients, 9 (56.3) in MKD patients and 1 (16.7) in TRAPS patients. The age at the study by months were 160 (51-253) in FMF, 156 (54-216) in CAPS, 96 (34-180) in MKD and 94 (50-160) in TRAPS. The current age revealed a significant difference among the subgroups (p=0.00), yet there was no difference in terms of gender distribution (p=0.84). The age at the diagnosis by months were 72 (13-195) in FMF, 96 (3-185) in CAPS, 41.5 (6-120) in MKD and 54 (36-132) in TRAPS. The disease duration by months was 75 (13-207) in FMF, 80 (47-170) in CAPS, 81 (31-174) in MKD and 66.5 (30-98) in TRAPS. There was no significant difference between the subgroups in terms of the age at diagnosis and the disease duration with p=0.16 and p=0.81, respectively. Early signs and symptoms with initial laboratory data of the entire cohort were demonstrated in Table 1. The table illustrates the general distribution of the different characters of the skin involvement. Distribution of clinical and demographic manifestations among the subgroups is presented in Table 2 with the details of mucocutaneous signs.

Discussion

Autoinflammatory diseases have a wide distribution within themselves, therewithal, skin lesions diversify according to subgroups. Although monogenic autoinflammatory diseases often have cutaneous manifestations as part of their presentation, clinical data and studies on dermatological involvement are limited. As presenting the clinical presentation of monogenic autoinflammatory diseases, we aimed to determine the presence, rate, and distribution of mucocutaneous features in the portrayal.

The study cohort, comprised of different monogenic autoinflammatory diseases, frequently exhibited fever as expected, and serositis in the initial presentation. The reason behind the superiority of serositis over other symptoms is that FMF constituting the majority of the cohort most often presents with episodes of peritonitis. On the other hand, pleural and pericardial involvement are rarer manifestations in monogenic autoinflammatory diseases (4). Fever and joint involvement mostly as arthralgia were the primary complaints in the presentation of the disease. Neurological symptoms rarely accompany monogenic autoinflammatory diseases excluding moderate and severe forms of CAPS (8). In our cohort, although rare, neurologic manifestations such as febrile convulsions and headache were observed among non-FMF autoinflammatory diseases. Mucocutaneous lesions were among the most striking presentations with a frequency of 34%. Skin involvement may be included in the initial picture as a key symptom, or conversely, can be incorporated into the clinical picture

Table 2. Demographic and clinical manifestations according to the subgroups of monogenic autoinflammatory diseases

AIDs (n=97)	FMF (n=64)	CAPS (n=11)	MKD (n=16)	TRAPS (n=6)	p
Gender (female)	41 (64.1)	7 (63.6)	9 (56.3)	1 (16.7)	p=0.84
Age at the study (m)	160 (51-253)	156 (54-216)	96 (34-180)	94 (50-160)	p=0.00
Age at the diagnosis (m)	72 (13-195)	96 (3-185)	41.5 (6-120)	54 (36-132)	p=0.16
Disease duration (m)	75 (13-207)	80 (47-170)	81 (31-174)	66.5 (30-98)	p=0.81
Fever	36 (56.3)	8 (72.7)	16 (100)	6 (100)	
Duration (days)	3 (1-10)	3 (1-7)	4 (2-10)	5.5 (2-8)	
Cutaneous involvement	5 (7.8)	9 (81.8)	3 (18.8)	2 (33.3)	p=0.00
Character	Erysipelas-like	Diffuse erythematous, edematous plaques	Intensive maculopapular, morbilliform	Macules	
Location and Distribution	The anterior-lower surface of the tibia, ankle	Face, trunk, symmetrically on the extremities	Trunk, upper and lower extremities	Trunk and upper extremities	
Duration (days)	4 (3-7)	3 (1-24)	3 (2-5)	6 (4-8)	
Scar	None	77%	None	50%	
Oral mucosa	3 (4.7)	3 (27.3)	5 (31.3)	3 (50)	p=0.001
Lymphadenopathy	-	1 (9.1)	3 (18.8)	-	
Organomegaly	-	-	2 (12.5)	-	
Peritonitis	56 (87.5)	1 (9.1)	-	-	
Bouts of diarrhea	-	1 (9.1)	9 (56.3)	-	
Arthralgia	31 (48.4)	9 (81.8)	9 (56.3)	4 (66.7)	
Arthritis	9 (14.1)	5 (45.5)	2 (12.5)	2 (33.3)	
Duration (days)	3 (1-15)	7 (2-17)	4 (2-7)	6 (4-10)	
Muscle involvement	9 (14.1)	-	3 (18.8)	3 (50)	
Neurological involvement	-	2 (18.2)	3 (18.8)	2 (33.3)	
Eye involvement	-	-	-	3 (50)	
Wbc ($x10^9$/L)	7.98 (3.61-29.6)	10.8 (6.2-24)	11.09 (5.9-18.2)	11 (10.2-14)	
Neutrophil (%)	55 (27-80)	52 (30-78)	55 (38-80)	53.5 (25-56)	
Platelet ($x10^9$/L)	302 (161-667)	303 (255-519)	298 (108-392)	354 (208-402)	
CRP (mg/L)	2,1 (0-151)	14 (1-299)	72 (1-222)	23 (5-61)	
ESR (mm/h)	13 (1-110)	17 (2-140)	31 (5-100)	37 (18-48)	
SAA (mg/L)	5.2 (0-1200)	23.5 (1-349)	8.5 (0-233)	1 (0-4)	

WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SAA: Serum amyloid a. Kruskal-Wallis test was used to compare demographic and clinical features and mucocutaneous manifestations

after months or even years (9). In another single-center study in which autoinflammatory diseases were evaluated comprehensively, skin lesions were more prominent with a frequency of 76% (10). The rate and distribution of clinical manifestations in the cohort were presumably influenced by the prevalence of subgroups.

Differential diagnosis of autoinflammatory diseases is not always feasible due to their non-specific and overlapping features. The presentation of the disease may manifest a heterogeneous picture, notably when individual differences are considered, and genetic tests with a long turnaround time may not be guiding at the early stage of diagnosis. Furthermore, the diagnostic performance of genetic tests is not fully comprehensive and pathogenic variants may display variable expression. Nonetheless, the medical history of persistent or recurrent episodes of inflammation is the hallmark for diagnosis.

Still, at least 40% of patients with a possible autoinflammatory disease do not comply with any of the known diseases and are considered as the ''undifferentiated'' group (1). Although the symptoms overlap significantly in the clinical presentation of different diseases, some clues in the clinical picture can determine the subtype of hereditary periodic fever syndrome. Although it does not occupy considerable

Table 1. Clinical presentation of the cohort of monogenic autoinflammatory diseases

Entire cohort	**n=97**
Clinical presentation	**n (%)**
Fever	66 (68)
Cutaneous involvement	19 (19.6)
Maculopapular	8 (8.2)
Urticarial	5 (5.1)
Morbilliform	1 (1)
Erysipela-like rash	5 (5.1)
Oral mucosal involvement	14 (14.4)
Lymphadenopathy	4 (4.1)
Hepatomegaly and/or splenomegaly	2 (1.9)
Serositis	57 (58.8)
Diarrhea	10 (10.3)
Joint involvement	53 (54.6)
Muscle involvement	15 (15.5)
Neurological involvement	7 (7.2)
Eye involvement	3 (3.1)
Baseline laboratory data	**Med (min-max)**
Wbc (x10^9/L)	8.820 (3.610-29.600)
Neutrophil (%)	55 (25-80)
Platelet count (x10^9/L)	303,000 (108,000-667,000)
CRP (mg/L)	5.1 (0-299)
ESR (mm/h)	16 (1-140)
SAA (mg/L)	5.1 (0-1200)

WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SAA: Serum amyloid a

space in the general presentation, distinct types of cutaneous and mucosal involvement were remarkable in the cohort. Correspondingly, the study groups differed from each other in terms of rash characteristics. The recurrent episodes of a specific type of rash may be a guide in determining the subgroup of systemic autoinflammatory diseases at diagnosis.

FMF is the most common monogenic autoinflammatory disease with short-term and self-limiting episodes. Erysipelas-like erythema accompanies approximately 20% of disease attacks in children, but their frequency may vary geographically (11-13). The lesion appears as tender and erythematous plaque, 10-15 centimeters in diameter located below the knee and on the dorsal aspect of the feet (12,14). In a patient presenting with inflammatory attacks of rash, the query of the location may be a guide in determining the subtype of the autoinflammatory disease as FMF rash is typically distributed on the lower extremities. As a result of a 10-year retrospective study, Gezgin Yildirim et al. (15) detected erysipelas-like erythema in 59 of 782 patients and emphasized that 11 (18.6%) of them were the initial symptoms. As in our cohort, this rate may be lower at the onset and the cutaneous involvement may be included in the course of the disease. However, since it is the pathognomonic cutaneous sign, its initial presence is substantial for the diagnosis. Of note, the presence of vascular rash or mucosal involvement in FMF requires further evaluation in terms of IgA vasculitis, polyarteritis nodosa and Behçet's disease (16,17). On the other hand, Ben-Chetrit and Yazici (18) have suggested that it could be considered as an atypical manifestation of the disease rather than comorbidity.

The inflammatory episodes of TRAPS have longer duration compared to FMF. Cutaneous lesions may present as large erythematous migratory patches or plaques. A study including 25 TRAPS patients aged 4 to 56 years demonstrated that precursor skin lesions emerged in the first 2 years of life and lasted for a mean of 13 days. In our patients with TRAPS, macules were distributed on the trunk and upper extremities with a median duration of 6 days. Scar was observed in our cohort, but the sample size was insufficient to determine the rate.

Mucocutaneous involvement occurs in 70% of the patients with MKD. Non-specific maculopapular or morbilliform eruptions located on the extremities and trunk are the most common but diverse skin lesions can be observed. Aphthous oral ulcers and sometimes genital ulcers are seen in 50% of patients (19). The skin involvement of our patients exhibited a typical distribution. Oral mucosa involvement was detected in 31.3%, but genital ulcer was not observed in the cohort. In an international study evaluating the clinical characteristics at disease onset and diagnosis of patients with MKD, the rate of rash was %13 (n=5) (20). More research is required to describe the distribution and diversity of skin manifestations in MKD.

CAPS represent three phenotypes of varying severity. The typical cutaneous sign, defined clinicopathologically as neutrophilic urticarial dermatosis, is the most significant shared feature of the three entities (21,22). Skin involvement is expected to predominate in the initial picture of the disease complex. Urticaria-like lesions, symmetrical and widespread distribution, and histopathological demonstration of neutrophils are crucial for the diagnosis (22). Patients with a diagnosis of CAPS in our cohort presented with diffuse urticaria-like erythematous plaques lasting up to 24 days, the majority of which healed with scarring. Particularly, resistant recurrent urticaria without

an antihistaminic response, accompanied by signs of inflammation, should be examined for CAPS (22).

Autoinflammatory diseases may display overlapping symptoms. The number of studies on clinical presentations is limited. Since there are various mutations for each subtype, the study was designed according to clinical classification and definition and gene analyses were not presented separately. Except for FMF, the prevalence of other subtypes is quite low. Although the current study is based on a small sample of participants and non-homogeneous distribution, it represents a comprehensive analysis of the initial symptoms, signs, and mucocutaneous lesions.

Conclusion

The clinical framework and classification of autoinflammatory diseases are growing day by day through the identification of new molecular mechanisms. Monogenic autoinflammatory diseases can be recognized by recurrent episodes of inflammation. Recognizing the system and organ involvement in these attacks aids in the diagnosis. Mucocutaneous signs were not frequently included in the presentation of the disease in our study cohort, but the location and character of the lesions demonstrated a consistent distribution according to the subgroups. Skin manifestations accompany almost all subtypes and may provide a clue regarding the subdivision and pathological mechanism of the disease. Hence, the awareness of the distinctive mucocutaneous manifestations and their correlation with subgroups provides a convenient definition, well-timed control of the underlying condition.

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Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of İstanbul University Faculty of Medicine for the study (2021-622903).

Informed Consent: Each participant and his/her legal representative have approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.A.A., O.K., Design: N.A.A., O.K., Data Collection or Processing: O.K., Analysis or Interpretation: N.A.A., O.K., Writing: O.K.

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