SIMILARITIES AND DIFFERENCES BETWEEN FAMILIAL MEDITERRANEAN FEVER AND BEHÇET'S DISEASE

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Abstract

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease, mainly affecting populations originating from the Eastern Mediterranean region. Behçet's Disease (BD) is grouped in polygenic autoinflammatory diseases. It is a systemic vasculitis that affects all types and sizes of blood vessels. The aim of this article is to shed light on similarities and differences between FMF and BD. BD is frequently reported along the ancient Silk Road, extending from the Far East to the Mediterranean basin. Several studies have searched for the association between FMF and BD. FMF is caused by mutations of the Mediterranean Fever (MEFV) gene while an increased frequency of MEFV mutations is reported in BD patients. Although BD and FMF share some epidemiological and pathophysiological features, there are distinct clinical characteristics of these nosological entities. Mucocutaneous manifestations, especially recurrent oral ulcers, are the most common symptom in BD patients whereas fever accompanied by serosal inflammation is the main clinical presentation in FMF patients.

Keywords: Familial Mediterranean fever, Behçet disease, MEFV gene, COVID-19

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ABBREVIATIONS

Behçet's disease: BD
Familial Mediterranean Fever: FMF
Human leukocyte antigen gene encoding B*51: HLA B51
Endoplasmic reticulum aminopeptidases 1: ERAP1
International Criteria for Behçet's Disease: ICBD
Interleukin: IL
International Study Group: ISG
Mediterranean Fever: MEFV
Pediatric BD: PEDBD
Toll-like receptors: TLRs
Tumor necrosis factor: TNF
Variants of uncertain significance: VUS

INTRODUCTION

Familial Mediterranean fever (FMF) and Behçet's disease (BD) are autoinflammatory diseases common in the Mediterranean region. They do share some features and may co-occur in one patient. Distinct characteristics of these diseases make the differential diagnosis easier.

FMF is the most common autoinflammatory disease with autosomal recessive inheritance. It mainly affects populations originating from the Mediterranean region, predominantly Armenians, Turks, Jews, and Arabs [1]. FMF is caused by mutations of the Mediterranean Fever (MEFV) gene that encodes pyrin. Pyrin acts as a pattern recognition receptor that assembles the inflammasome

complex [2, 3]. Gain-of-function mutations of MEFV cause pyrin inflammasome activation, leading to an increase in caspase-1 activation and interleukin 1 β (IL-1 β) release [2].

Generally, FMF is characterized by self-resolving inflammatory attacks which last 1-3 days. Patients are usually free of symptoms between attacks. A typical attack consists of fever accompanied by peritonitis, pleuritis, arthritis, erysipelas-like erythema, or rarely by pericarditis [4]. Clinical presentation and course of the disease may differ across various ethnic groups and individuals [5]. Genotype affects the disease phenotype. For instance, M694V homozygotes often present with severe disease, amyloidosis, and frequent attacks, necessitating higher doses of colchicine [6-8]. Also, FMF patients may suffer from other manifestations such as protracted febrile myalgia, spondyloarthropathy, and vasculitic rash [9].

FMF diagnosis is mainly based on clinical presentations. MEFV gene analysis could support the clinical diagnosis. The latest set of FMF classification criteria combines clinical manifestations and genotype [10]. FMF classification is based on the presence of confirmatory MEFV genotype and at least one of the following: duration of attacks lasts 1–3 days, arthritis, chest pain, or abdominal pain. If the patient has non-confirmatory MEFV genotype (compound heterozygous for a single pathogenic MEFV mutation variants and a single mutation variant of uncertain significance (VUS), or biallelic VUS, or heterozygous for a single pathogenic MEFV mutation variant), the presence of at least two of the mentioned parameters is required for FMF diagnosis.

Colchicine is the frontline therapy to suppress inflammation and prevent attacks and complications in FMF [11]. Colchicine resistance, defined as one or more attacks per month during three months or persistent systemic inflammation between attacks, is detected in about 5% of patients [12-14]. Biological drugs, especially anti-IL-1 agents, are used to treat colchicine resistant/intolerant patients [15].

BD is a systemic vasculitis with autoinflammatory features. It is frequently reported along the ancient Silk Road, extending from the Far East to the Mediterranean basin [16]. The genetic predisposition to BD is well known, with the human leukocyte antigen gene encoding B*51 (HLA B51) playing a critical role. HLA B51 is not pathognomonic for BD since its positivity reaches 20% in healthy subjects. This marker simply supports BD diagnosis [17].

Endoplasmic reticulum aminopeptidase 1 (ERAP1) is another enzyme that plays a pathogenic role in BD. It facilitates the processing and delivery of peptides to HLA molecules. The presence of ERAP1 polymorphisms that lead to an unfolded protein response of HLA B51 triggers endoplasmic stress and activates the inflammation via the IL-23/IL-17 pathway.

BD is a multisystemic disease with heterogeneous clinical presentations. Recurrent oral ulcers are reported in almost all patients with BD, including 87-98% of them presenting with such symptoms in the disease debut [18]. The lesions are round or oval painful ulcers with erythematous borders located on lips, tongue, cheeks, or palate. Multiple ulcers are common, but single ulcers are also possible. Genital ulcers are reported in 55-83% of cases as the second most common features of BD [19-22]. Genital lesions tend to be deeper with irregular margins and healing with scars.

Cutaneous signs may present as erythema nodosum-like lesions, papulopustular elements, and folliculitis. Pathergy test positivity, which is not pathognomonic for BD, varies widely across cohorts [23].

Ocular involvement may present with anterior and posterior uveitis, or panuveitis. BD uveitis may lead to the loss of vision. Neurological features have a broad clinical spectrum, ranging from isolated headaches, benign elevated intracranial pressure, cerebral venous thrombosis, meningoencephalitis, psychiatric disturbances, cranial nerve palsy, to parenchymal lesions in the brain stem, spinal cord, basal ganglia, and cerebral white matter [24, 25].

Vascular involvement can affect all sizes of arterial and venous vessels. Aside from deep vein thrombosis, which is the most common vascular manifestation, superficial vein thrombosis, arterial thrombosis, and arterial aneurysm may also develop [26].

A spectrum of other manifestations has been identified, including articular symptoms, gastrointestinal involvement, pericarditis, myocarditis, pulmonary involvement, and glomerulonephritis [27-29].

Several classification criteria of BD have been proposed [30]. The most widely used sets of criteria for adult patients are those of the International Study Group (ISG) [31] and the International Criteria for BD (ICBD) [32]. According to the ISG, a patient must have oral ulceration and two of the following four parameters for the classification of BD: genital ulceration, eye manifestations, skin lesions, and positive pathergy test [31]. In the revised ICBD criteria [33], two points were

scored for genital ulceration, oral aphthosis, and ocular findings, and one point each for skin lesions, vascular lesions, and neurological findings. In the presence of pathergy test positivity, one point was added. A score of four and more points is required for the diagnosis of BD [34]. The sensitivity and specificity of the most recent version of ICBBD is 94.8% and 90.5%, respectively [34]. All these criteria are developed for adults, and there was a need for a new set of criteria for pediatric BD.

The Pediatric BD (PEDBD) study established the classification criteria for pediatric patients in 2015. Three of the following six items are required to classify a patient as having pediatric BD: recurrent oral aphthosis (at least three attacks per year), genital aphthosis, skin involvement, ocular involvement, neurological signs, or vascular findings [20]. The sensitivity and specificity of

these criteria in pediatric BD patients have been reported as 91.7% and 42.9%, respectively, in the validation study.

The management strategy may differ in BD depending on the type and severity of organ involvement. Topical corticosteroids and colchicine are commonly preferred to treat mucocutaneous findings. Other treatment options include systemic corticosteroids, apremilast, azathioprine, anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) agents, cyclophosphamide, cyclosporine A, and interferon α [18, 35].

SIMILARITIES BETWEEN FMF AND BD

FMF is the prototype of the monogenic autoinflammatory diseases while BD is grouped in polygenic autoinflammatory diseases (Table 1).

Table 1. Distinguishing features of FMF and BD

	FMF	BD
Inheritance mode	Monogenic autoinflammatory disease	Polygenic autoinflammatory disease
MEFV gene mutations	Associated with the disease	Increased frequency of mutations
Epidemiology	Common in the Mediterranean region	Common along the ancient Silk Road extending to the Mediterranean basin
Pathogenesis	Increased production of IL-1 β by the overactive pyrin inflammasome	An unfolded protein response of HLA-B51 Association with Toll-like receptors 2, 4, and 9 Higher levels of IL-1 β
Age of disease onset	Early childhood	Late childhood-adulthood
Key clinical features	Periodic fever, serositis, arthritis	Recurrent oral and genital ulceration, uveitis, skin lesions, neurological and vascular involvement
Treatment	Colchicine Anti-IL-1 treatment in colchicine-resistant FMF patients	Differ depending on the type and severity of organ involvement Colchicine for mucocutaneous findings Other treatment agents; apremilast, azathioprine, anti-TNF α agents, cyclophosphamide, cyclosporine A, interferon α

Abbreviations: FMF; Familial Mediterranean Fever, BD; Behçet's disease, IL; interleukin, TNF; tumor necrosis factor.

The increased frequency of MEFV mutations in BD patients and the presence of FMF as a comorbidity in BD patients have been demonstrated in several studies [36, 37]. MEFV mutations are reported as susceptibility factors for vascular involvement in BD [38, 39]. Coexistence of BD and FMF has also been reported in the literature. Schwartz et al. reported 39 patients with BD and FMF and stated that response to colchicine treatment was lower among patients with both FMF and BD compared to patients with only FMF [40]. And, skin, central nervous system, and gastrointestinal

involvements were more common in patients with FMF and BD compared to patients with only BD [40]. Akpolat et al. also reported a BD patient with homozygous M680I mutations who developed amyloidosis [41]. BD and FMF also share some epidemiological and pathophysiological features. BD is most common along the Silk road, extending from the Far East to Mediterranean basin countries [16]. FMF is also highly prevalent in countries of the Mediterranean basin [42]. On the other hand, IL-1 has a role in the pathogenesis of both FMF and BD. Increased production of IL-1 β by the overactive Pyrin

inflammasome is the central process in FMF pathogenesis [42]. The higher levels of IL-1 β were also found in BD patients with both active and inactive disease compared to healthy controls [43]. Also, Toll-like receptors (TLRs) 2, 4, and 9 have been implicated in BD pathogenesis [44]. The gene polymorphisms of TLR4 and TLR9 were more frequent in BD patients than in healthy controls [45, 46]. The interaction of TLR2 and 4 with their ligands cause increased IL-1 β production via NLRP3 inflammasome in active BD patients [47, 48]. Colchicine is the mainstay of FMF treatment [42]. It is also frequently used in the treatment of mucocutaneous manifestations of BD [49].

DIFFERENCES BETWEEN FMF AND BD

FMF phenotype usually becomes apparent in early childhood while the age of onset is older in BD [49]. Fever and recurrent serosal inflammation, which are the main manifestations of FMF, are not prominent in BD. On the other hand, uveitis, vasculitis, and neurological involvement are more specific to BD. Regarding treatment, anti-IL-1 drugs form the primary therapeutic option in treating colchicine-resistant FMF while there are limited data regarding the efficacy of *anti-IL-1 drugs* in BD patients. Fabiani et al. reported that 25 of 36 BD patients who used anti IL-1 treatment had a complete response in the 3-month follow-up. Eighteen patients continued treatment for at least 12 months with a response to treatment. However, in the remaining patients, treatment was discontinued within the first year due to the inefficacy [50]. Similarly, anti-IL-1 treatment was administered to nine BD patients, refractory to standard therapies and TNF blockers. A rapid improvement was observed. However, most patients experienced relapse within several months [51].

FMF AND BD DURING THE COVID-19 PANDEMIC

The COVID-19 outbreak has created a global health crisis. There have been concerns about the influence of COVID-19 on patients with rheumatologic diseases, especially those receiving immunosuppressive therapy [52]. Espinosa et al. reported four BD patients with mild clinical presentations of COVID-19 [53]. Two of them were receiving immunosuppressive agents, and two of them were receiving colchicine [53]. Brito et al. also reported a BD patient with a mild form of COVID-19 who was on anti-TNF treatment [53, 54]. Currently, there are no strict guidelines regarding the management of immunosuppressive agents during the COVID-19 pandemic. However, it is recommended to continue

immunosuppressive therapy unless the infection is present [55]. Bourguiba et al. evaluated the clinical course of 27 patients with COVID-19 in a cohort of 342 FMF patients. They stated that these patients did not appear to have an additional risk factor for severe SARS-CoV-2 infection compared to the general population [56]. Similarly, Kobak et al. reported an FMF patient suffering from COVID-19 infection with mild symptoms [57].

Individuals carrying a MEFV mutation might have a selection advantage against plaque [58, 59]. It is unknown whether the presence of MEFV mutations causes an advantage against COVID-19. Importantly, colchicine has been used in COVID-19. The results of several studies have supported the benefit of colchicine in COVID-19 [60, 61]. In a randomized placebo-controlled trial, colchicine use has been associated with statistically significant reductions in the risk of death and hospitalization compared to placebo [60, 61]. Current studies do not suggest a decreased or increased risk in BD or FMF patients for the occurrence of COVID-19 or COVID-19-related complications compared to the healthy population.

CONCLUSION

BD and FMF share some epidemiological and pathophysiological features. And, MEFV mutations, primarily associated with FMF, are probably genetic susceptibility factors in BD. There are distinct clinical features of both diseases that make the differential diagnosis easier.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work; and the acquisition, analysis, or interpretation of data for the work -UKA, EDB. Drafting the work and revising it critically for important intellectual content -UKA, EDB. Final approval of the version to be published -UKA, EDB. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved-UKA, EDB.

CONFLICTS OF INTEREST

EDB receives consultancy fees from Novartis. Other than that, both authors declare that they do not have any financial and non-financial conflicts to disclose.

DISCLAIMER

No part of this review is copied or published elsewhere in whole or in part.

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ОТБАСЫ МЕДИТРАНИЯЛЫҚ ҚЫЗЫЛЫҚ ЖӘНЕ АРА АУРУЫ АРАСЫНДАҒЫ ҰҚСАСТЫҚТАР МЕН АЙЫРМАШЫЛЫҚТАР

Түйіндеме

Отбасы медитраниялық қызылдық (ОМҚ) – көбінесе Шығыс Жерорта теңіз аумағындағы халқына зақым келтіретін, ең таралған моногендік аутоқабыну ауруы. Бехчет ауруы (БА) полигендік аутоқабыну ауруларға жатады, бұл барлық түрдегі және өлшемді қан тамырларын зақымдаушы жүйелік васкулит болып саналады. Бұл мақаланың мақсаты ОМҚ мен БА арасындағы ұқсастықтар мен айырмашылықтарды қарастыру болып табылады. Қиыр Шығыстан Жерорта теңіздік алабына дейін созылған ежелгі Жібек жолы аймағында БА жиі кездеседі. Қазіргі таңда ОМҚ мен БА арасындағы байланысты зерттеуге арналған зерттеулер бар. MEd Mediterranean FeVer (MEFV) генінің мутациясынан ОМҚ туындайтыны айқындалған, сондай-ақ БА шалдыққан емделушілерде MEFV гені мутациясының жоғарғы жиілігі байқалады. ОМҚ мен БА-да біршама жалпы эпидемиологиялық және патофизиологиялық сипаттамалары болғанымен, нозология мәліметтерінде бір-бірінен бірқатар ерекшеленетін клиникалық белгілері бар. Тері-шырышты көріністер, әсіресе ауыз қуысындағы қайталамалы жара БА-ға шалдыққан емделушілердің ең жиі белгісі болып табылады, ал сероздық қабынумен қоса өтетін безгек ОМҚ шалдыққан емделушілердің негізгі клиникалық көрінісі болып саналады.

Түйінді сөздер: Отбасы медитраниялық қызылдық, Бехчет ауруы, MEFV гені, COVID-19

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СХОДСТВА И РАЗЛИЧИЯ МЕЖДУ СЕМЕЙНОЙ СРЕДИЗЕМНОМОРСКОЙ ЛИХОРАДКОЙ И БОЛЕЗНЬЮ БЕХЧЕТА

Резюме

Семейная средиземноморская лихорадка (ССЛ) - наиболее распространенное моногенное аутовоспалительное заболевание, поражающее преимущественно население, проживающее в регионе Восточного Средиземноморья. Болезнь Бехчета (ББ) относится к полигенным аутовоспалительным заболеваниям, это системный васкулит, поражающий кровеносные сосуды всех типов и размеров. Цель данной статьи заключается в рассмотрении сходств и различий между ССЛ и ББ. ББ часто встречается на территории древнего Шелкового пути, простирающейся от Дальнего Востока до Средиземноморского бассейна. На данный момент есть исследования, посвященные изучению связи между ССЛ и ББ. Было выявлено, что ССЛ вызывается мутациями гена MEd Mediterranean FeVer (MEFV), у пациентов с ББ также отмечается повышенная частота мутаций гена MEFV. Хотя ССЛ и ББ имеют некоторые общие эпидемиологические и патофизиологические характеристики, данные нозологии имеют ряд отличающихся друг от друга клинических признаков. Кожно-слизистые проявления, особенно рецидивирующие язвы в полости рта, являются наиболее частым симптомом у пациентов с ББ, тогда как лихорадка, сопровождающаяся серозным воспалением, является основным клиническим проявлением у пациентов с ССЛ.

Ключевые слова: Семейная средиземноморская лихорадка, болезнь Бехчета, ген MEFV, COVID-19

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