SHORT COMMUNICATION

Dermatological Comorbidities in Patients with Familiar Mediterranean Fever

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Familial Mediterranean fever (FMF) is a well-defined autoinflammatory disease characterized by recurrent febrile episodes and serositis resulting from marenostrin-encoding fever (MEFV) gene mutations located on chromosome 16p13.3, leading to dysregulated inflammasome activity and systemic inflammation (1). While FMF is renowned for its systemic symptoms, its cutaneous manifestations, such as erythema elevatum diutinum (2), urticaria (3), Henoch-Schönlein purpura, polyarteritis nodosa, and episodic purpuric lesions (4), are less prominently recognized. These manifestations indicate a wider influence of FMF on the skin, an aspect that has received limited attention in medical research. This paper seeks to investigate additional dermatological comorbidities linked to FMF.

MATERIALS AND METHODS

This study utilized data from Leumit Health Services (LHS), a national healthcare provider in Israel. The study cohort was extracted from over 1,000,000 individuals insured by LHS from January 2001 until December 2023. The study employed International Classification of Diseases 9th revision (ICD-9) codes to identify cases of FMF. Specifically, the code 277.31 was utilized. The FMF group included patients with a documented FMF diagnosis by board-certified rheumatologists according to the Tel Hashomer criteria for a diagnosis of FMF (5). The control group comprised individuals without FMF randomized with a ratio of 1:4. Rigorous matching based on age, gender, socioeconomic status, and first year of LHS membership was performed to ensure comparability between the 2 groups. ICD-9 codes recorded in electronic health records were used to compare the lifelong prevalence of dermatological comorbidities. The Leumit Health Services Institutional Ethics Committee approved the study.

Statistical analysis

Differences in demographic and clinical characteristics between groups were analysed using independent sample t-tests for normally distributed continuous variables. For categorical variables, proportions were tested using Fisher's exact test. Odds ratios and 95% confidence intervals (95% CIs) were calculated. All statistical analyses were conducted using R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Our study compared the demographics of 3,324 patients with FMF and 13,296 controls. The age and gender distribution across both groups was similar, with an average age of 36.9 ± 20.1 years, and 51.1% females in both FMF patients and controls. The average BMI was slightly lower in the FMF group (22.3 ± 6.1) compared with the controls (22.7 ± 6.2) ($p = 0.001$).

Our analysis of the lifelong prevalence of dermatological comorbidities in patients with FMF compared with controls is presented in **Table I**. In the category of inflammatory skin diseases, FMF patients showed a higher prevalence of atopic dermatitis (14.6% vs 12.6%, OR 1.19 [CI 1.06 to 1.33]; $p = 0.002$), contact dermatitis (25.1% vs 22.8%, OR 1.13 [CI 1.04 to 1.24]; $p = 0.006$), seborrheic dermatitis (9.60% vs 8.45%, OR 1.15 [CI 1.01 to 1.31]; $p = 0.039$), and psoriasis (4.27% vs 3.52%, OR 1.22 [CI 1.00 to 1.49]; $p = 0.044$). Acne was also more common in FMF patients (22.6% vs 19.3%, OR 1.22 [CI 1.11 to 1.34]; $p < 0.001$), as were erythema nodosum (0.57% vs 0.18%, OR 3.18 [CI 1.64 to 5.06]; $p < 0.001$) and hidradenitis suppurativa (0.57% vs 0.15%, OR 3.82 [CI 1.92 to 7.54]; $p < 0.001$). Acute urticaria was another condition with a significantly higher prevalence in the FMF group (13.5% vs 10.4%, OR 1.13 [CI 1.20 to 1.51]; $p < 0.001$).

In infectious skin diseases, cellulitis (33.6% vs 23.3%, OR 1.66 [CI 1.53 to 1.81]; $p < 0.001$), herpes simplex (14.8% vs 11.2%, OR 1.37 [CI 1.23 to1.53]; $p < 0.001$), and herpes zoster (5.81% vs 4.76%, OR 1.23 [CI 1.04 to 1.46]; $p = 0.014$) were more prevalent among FMF patients.

Regarding autoimmune diseases, lupus erythematosus (systemic) was notably more common in FMF patients (0.57% vs 0.20%, OR 2.93 [CI 1.53 tox 5.52]; $p < 0.001$), as was Behcet disease (1.053% vs 0.075% in controls, OR 14.13 [6.84 to 32.04], $p < 0.001$), and alopecia areata (3.25% vs 1.74%, OR 1.89 [CI 1.49 to 2.39]; $p < 0.001$). However, no significant differences were observed in the prevalence of discoid lupus erythematosus, dermatomyositis, systemic and localized scleroderma, pemphigus, bullous pemphigoid, dermatitis herpetiformis, vitiligo, and chronic spontaneous urticaria.

No significant differences were observed between the 2 groups in neoplastic skin diseases.

DISCUSSION

Our study presents novel insights into the dermatological comorbidities associated with FMF, expanding the understanding of this autoinflammatory disease beyond its classical systemic manifestations. The significant findings of higher prevalence rates of certain dermatological conditions in FMF patients compared with controls un-

Table I. Lifelong prevalence of dermatological comorbidities in patients with familial Mediterranean fever (FMF)

Dermatological comorbidities	FMF *N* = 3,324 *n* (%)	Control *N* = 13,296 *n* (%)	*p*-value	OR [95% CI]
Inflammatory skin diseases				
Atopic dermatitis	485 (14.6)	1,669 (12.6)	0.002	1.19 [1.06–1.33]
Contact dermatitis	835 (25.1)	3,038 (22.8)	0.006	1.13 [1.04–1.24]
Seborrheic dermatitis	319 (9.60)	1,124 (8.45)	0.039	1.15 [1.01–1.31]
Lichen planus	10 (0.30)	62 (0.47)	0.237	0.64 [0.29–1.27]
Psoriasis	142 (4.27)	468 (3.52)	0.044	1.22 [1.00–1.49]
Pityriasis rosea	69 (2.08)	228 (1.71)	0.164	1.21 [0.91–1.60]
Erythema multiforme	10 (0.30)	22 (0.17)	0.121	1.82 [0.77–4.01]
Acne	750 (22.6)	2,565 (19.3)	<0.001	1.22 [1.11–1.34]
Rosacea	27 (0.81)	121 (0.91)	0.679	0.89 [0.56–1.36]
Erythema nodosum	19 (0.57)	24 (0.18)	<0.001	3.18 [1.64–6.06]
Hidradenitis suppurativa	19 (0.57)	20 (0.15)	<0.001	3.82 [1.92–7.54]
Acute urticaria	450 (13.5)	1,382 (10.4)	<0.001	1.35 [1.20–1.51]
Infectious skin diseases				
Impetigo	283 (8.51)	1,122 (8.44)	0.889	1.01 [0.88–1.16]
Cellulitis	1,118 (33.6)	3,104 (23.3)	<0.001	1.66 [1.53–1.81]
Dermatophytosis (ringworm)	1,044 (31.4)	3,959 (29.8)	0.069	1.08 [0.99–1.17]
Onychomycosis	237 (7.13)	1021 (7.68)	0.285	0.92 [0.79–1.07]
Candidiasis	71 (2.14)	223 (1.68)	0.077	1.28 [0.96–1.68]
Herpes simplex	492 (14.8)	1,494 (11.2)	<0.001	1.37 [1.23–1.53]
Herpes zoster	193 (5.81)	633 (4.76)	0.014	1.23 [1.04–1.46]
Molluscum contagiosum	206 (6.20)	808 (6.08)	0.807	1.02 [0.87–1.20]
Autoimmune diseases				
Lupus erythematosus (systemic)	19 (0.57)	26 (0.20)	0.001	2.93 [1.53–5.52]
Lupus erythematosus (discoid)	0	2 (0.015)	0.885	0.80 [0.04–16.66]
Dermatomyositis	1 (0.03)	16 (0.12)	0.224	0.25 [0.01–1.61]
Scleroderma (systemic)	3 (0.09)	12 (0.09)	0.999	1.00 [0.18–3.71]
Scleroderma (localized)	0	3 (0.02)	0.711	0.57 [0.03–11.06]
Behcet disease	35 (1.053)	10 (0.075)	<0.001	14.13 [6.84–32.04]
Pemphigus	1 (0.03)	2 (0.015)	0.488	2.00 [0.03–38.48]
Bullous pemphigoid	0	1 (0.01)	0.860	1.33 [0.05–32.73]
Dermatitis herpetiformis	2 (0.060)	11 (0.083)	0.999	0.73 [0.08–3.33]
Alopecia areata	108 (3.25)	232 (1.74)	<0.001	1.89 [1.49–2.39]
Vitiligo	27 (0.81)	86 (0.65)	0.289	1.26 [0.78–1.96]
Chronic spontaneous urticaria	43 (1.29)	129 (0.97)	0.104	1.34 [0.95–1.89]
Neoplastic skin diseases				
Mycosis fungoides	4 (0.12)	22 (0.17)	0.557	0.73 [0.25–2.11]
Melanoma	5 (0.15)	23 (0.17)	0.869	0.87 [0.26–2.34]
Basal cell carcinoma	19 (0.57)	84 (0.63)	0.805	0.90 [0.52–1.50]
Squamous cell carcinoma	10 (0.30)	28 (0.21)	0.314	1.43 [0.62–3.04]
Kaposi's sarcoma	0	1 (0.01)	0.860	1.33 [0.05–32.73]

derscore the multifaceted nature of FMF and its broader impact on skin health.

One of the most notable findings is the increased prevalence of inflammatory skin diseases in FMF patients. Previous research on children with FMF did not show an increase in atopic dermatitis (AD) (6). At the same time, we observed higher lifelong prevalence rates of AD, contact dermatitis, and seborrheic dermatitis in FMF. Our study supports the previous observation that psoriasis (7), erythema nodosum (8), and hidradenitis suppurativa (9) are more common in FMF patients than in the normal population. Our observation suggests a possible link between the dysregulated inflammasome activity in FMF and the pathogenesis of these skin conditions (10). This correlation could be attributed to the systemic inflammation and altered immune response inherent in FMF, which may predispose patients to these dermatological conditions.

The study also revealed a higher prevalence of infectious skin diseases, such as cellulitis, herpes simplex, and herpes zoster, in the FMF cohort. This finding could indicate an altered skin barrier or immune dysregulation in FMF patients, making them more susceptible to skin infections (11). Nevertheless, while providing effective treatment for FMF, colchicine and anti-IL-1 drugs (anakinra, canakinumab, rilonacept) are associated with the reactivation of latent viral infections and exacerbation or new onset of psoriasis and other dermatological conditions by modulating the immune system and inflammatory pathways (12).

In skin autoimmune diseases, the significantly higher prevalence of systemic lupus erythematosus, Behcet disease, and alopecia areata in FMF patients is particularly intriguing. Several case series and small studies have reported associations between FMF and autoimmune disorders (13). Our findings may reflect a shared pathophysiological mechanism between FMF and autoimmune skin diseases, potentially involving MHC-I-opathies but not MHC-II-associated autoimmunity (14).

Although a previous study found a significantly lower incidence of cancer in FMF patients than in the general population of Israel (15), our study did not observe significant differences in the prevalence of neoplastic skin diseases between FMF patients and controls. This finding warrants further investigation.

It is essential to acknowledge the limitations of the current study. As a retrospective cohort study, it is subject to limitations inherent in data availability and potential confounding factors. In addition, using ICD-9 codes to identify dermatological comorbidities may introduce inaccuracies or misclassification. However, the large sample size and rigorous matching process enhance the reliability and generalizability of these findings. While previous studies' results acknowledge dermatological issues as potential comorbidities in FMF, none present a dedicated, real-world study thoroughly characterizing and quantifying these skin conditions without relying on ICD coding.

Overall, our study highlights the importance of dermatological evaluation in patients with FMF and suggests that dermatologists should be aware of the increased risk of certain skin conditions in this patient population. Further studies are needed to elucidate the exact pathophysiological links and to explore potential therapeutic implications for managing these comorbidities in FMF patients.

The authors have no conflicts of interest to declare.

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