Association Between Pruritus and Fibromyalgia: Results of a Population-Based, Cross-Sectional Study

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PRACTICE **POINTS**

- Dermatologists should be aware of the connection between fibromyalgia, pruritus, and related conditions to improve patient care.
- The association between fibromyalgia and pruritus underscores the importance of employing multidisciplinary treatment strategies for managing these conditions.

Fibromyalgia is a common musculoskeletal condition that affects up to 3% of the worldwide population. Its pathogenesis is not entirely clear but is thought to involve neurogenic inflammation as well as aberrations in peripheral nerves and central pain mechanisms. It is believed that the same mechanism that causes hypersensitivity and pain in patients with fibromyalgia also predisposes them to pruritus. This population-based, retrospective, cross-sectional study was performed using a computerized database encompassing more than 4.5 million patients to examine the association between fibromyalgia and pruritus as well as pruritus-related skin conditions.

Pruritus, which is defined as an itching sensation that elicits a desire to scratch, is the most common cutaneous condition. Pruritus is considered chronic when it lasts for more than 6 weeks.[1] Etiologies implicated in chronic pruritus include but are not limited to primary skin diseases such as atopic dermatitis, systemic causes, neuropathic disorders, and psychogenic reasons.[2] In approximately 8% to 35% of patients, the cause of pruritus remains elusive despite intensive investigation.[3] The mechanisms of itch are multifaceted and include complex neural pathways.[4] Although itch and pain share many similarities, they have distinct pathways based on their spinal connections.[5] Nevertheless, both conditions show a wide overlap of receptors on peripheral nerve endings and activated brain parts.[6,7] Fibromyalgia, the third most common musculoskeletal condition, affects 2% to 3% of the population worldwide and is at least 7 times more common in females.[8,9] Its pathogenesis is not entirely clear but is thought to involve neurogenic inflammation, aberrations in peripheral nerves, and central pain mechanisms. Fibromyalgia is characterized by a plethora of symptoms including chronic widespread pain, autonomic disturbances, persistent fatigue and sleep disturbances, and hyperalgesia, as well as somatic and psychiatric symptoms.[10]

Fibromyalgia is accompanied by altered skin features including increased counts of mast cells and excessive degranulation,[11] neurogenic inflammation with elevated cytokine expression,[12] disrupted collagen metabolism,[13] and microcirculation abnormalities.[14] There has been limited research exploring the dermatologic manifestations of fibromyalgia. One retrospective study that included

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Drs. Aronov and Freud report no conflict of interest. Dr. Valdman-Grinshpoun has served as an advisor, consultant, or speaker for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Janssen, Kamada Pharmaceuticals, MDS Pharma Services, Novartis, Pfizer, and Sanofi. Dr. Cohen has received research grants from AbbVie, Janssen, Novartis, and Sanofi, and also has served as an advisor, consultant, or speaker for AbbVie, Amgen, Boehringer Ingelheim, Dexcel Pharma, Eli Lilly and Company, Janssen, Kamedis, Neopharm, Novartis, Perrigo, Pfizer, Rafa Laboratories Ltd, Sanofi, Sirbal, and Taro Pharmaceutical Industries Ltd. Dr. Czarnowicki has served as an advisor, consultant, or speaker for AbbVie, Neopharm, Novartis, Rafa Laboratories Ltd, and Sanofi.

The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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Cutis. 2024 August;114(2):55-59, E2. doi:10.12788/cutis.1075

845 patients with fibromyalgia reported increased occurrence of "neurodermatoses," including pruritus, neurotic excoriations, prurigo nodules, and lichen simplex chronicus (LSC), among other cutaneous comorbidities.[15] Another small study demonstrated an increased incidence of xerosis and neurotic excoriations in females with fibromyalgia.[16] A paucity of large epidemiologic studies demonstrating the fibromyalgia-pruritus connection may lead to misdiagnosis, misinterpretation, and undertreatment of these patients.

Up to 49% of fibromyalgia patients experience small-fiber neuropathy.[17] Electrophysiologic measurements, quantitative sensory testing, pain-related evoked potentials, and skin biopsies showed that patients with fibromyalgia have compromised small-fiber function, impaired pathways carrying fiber pain signals, and reduced skin innervation and regenerating fibers.[18,19] Accordingly, pruritus that has been reported in fibromyalgia is believed to be of neuropathic origin.[15] Overall, it is suspected that the same mechanism that causes hypersensitivity and pain in fibromyalgia patients also predisposes them to pruritus. Similar systemic treatments (eg, analgesics, antidepressants, anticonvulsants) prescribed for both conditions support this theory.[20-25]

Our large cross-sectional study sought to establish the association between fibromyalgia and pruritus as well as related pruritic conditions.

Methods

Study Design and Setting—We conducted a cross-sectional retrospective study using data-mining techniques to access information from the Clalit Health Services (CHS) database. Clalit Health Services is the largest health maintenance organization in Israel. It encompasses an extensive database with continuous real-time input from medical, administrative, and pharmaceutical computerized operating systems, which helps facilitate data collection for epidemiologic studies. A chronic disease register is gathered from these data sources and continuously updated and validated through logistic checks. The current study was approved by the institutional review board of the CHS (approval #0212-17-com2). Informed consent was not required because the data were de-identified and this was a noninterventional observational study.

Study Population and Covariates—Medical records of CHS enrollees were screened for the diagnosis of fibromyalgia, and data on prevalent cases of fibromyalgia were retrieved. The diagnosis of fibromyalgia was based on the documentation of a fibromyalgia-specific diagnostic code registered by a board-certified rheumatologist. A control group of individuals without fibromyalgia was selected through 1:2 matching based on age, sex, and primary care clinic. The control group was randomly selected from the list of CHS members frequency-matched to cases, excluding case patients with fibromyalgia. Age matching was grounded on the exact year of birth (1-year strata).

Other covariates in the analysis included pruritus-related skin disorders, including prurigo nodularis, neurotic excoriations, and LSC. There were 3 socioeconomic status categories according to patients' poverty index: low, intermediate, and high.[26]

Statistical Analysis—The distribution of sociodemographic and clinical features was compared between patients with fibromyalgia and controls using the χ^2 test for sex and socioeconomic status and the *t* test for age. Conditional logistic regression then was used to calculate adjusted odds ratio (OR) and 95% CI to compare patients with fibromyalgia and controls with respect to the presence of pruritic comorbidities. All statistical analyses were performed using SPSS software (version 26). $P<.05$ was considered statistically significant in all tests.

Results

Our study population comprised 4971 patients with fibromyalgia and 9896 age- and sex-matched controls. Proportional to the reported female predominance among patients with fibromyalgia,[27] 4479 (90.1%) patients with fibromyalgia were females and a similar proportion was documented among controls ($P=.99$). There was a slightly higher proportion of unmarried patients among those with fibromyalgia compared with controls (41.9% vs 39.4%; $P=.004$). Socioeconomic status was matched between patients and controls ($P=.99$). Descriptive characteristics of the study population are presented in Table 1.

We assessed the presence of pruritus as well as 3 other pruritus-related skin disorders—prurigo nodularis, neurotic excoriations, and LSC—among patients with fibromyalgia and controls. Logistic regression was used to evaluate the independent association between fibromyalgia and pruritus. Table 2 presents the results of multivariate logistic regression models and summarizes the adjusted ORs for pruritic conditions in patients with fibromyalgia and different demographic features across the entire study sample. Fibromyalgia demonstrated strong independent associations with pruritus (OR, 1.8; 95% CI, 1.8-2.4; $P<.001$), prurigo nodularis (OR, 2.9; 95% CI, 1.1-8.4; $P=.038$), and LSC (OR, 1.5; 95% CI, 1.1-2.1; $P=.01$); the association with neurotic excoriations was not significant. Female sex significantly increased the risk for pruritus (OR 1.3; 95% CI, 1.0-1.6; $P=.039$), while age slightly increased the odds for pruritus (OR, 1.0; 95% CI, 1.0-1.04; $P<.001$), neurotic excoriations (OR, 1.0; 95% CI, 1.0-1.1; $P=.046$), and LSC (OR, 1.0; 95% CI, 1.01-1.04; $P=.006$). Finally, socioeconomic status was inversely correlated with pruritus (OR, 1.1; 95% CI, 1.1-1.5; $P=.002$).

Frequencies and ORs for the association between fibromyalgia and pruritus with associated pruritic disorders stratified by exclusion of pruritic dermatologic and/or systemic diseases that may induce itch are presented in the eTable. Analyzing the entire study cohort, significant increases were observed in the odds of all 4 pruritic disorders analyzed. The frequency of pruritus was almost double in patients with fibromyalgia compared

TABLE 1. Descriptive Characteristics of the Study Population

Variable	Fibromyalgia group (n=4971)	Control group (n=9896)	*P* value
Sex, n (%)			
Male	492 (9.9)	981 (9.9)	NS
Female	4479 (90.1)	8915 (90.1)	
Age, y			
Mean (SD)	49.8 (10.6)	49.8 (10.6)	NS
Median	52	52	
Range	18–65	18–65	
Marital status, n (%)			
Married	2890 (58.1)	5995 (60.6)	.004
Unmarried	2081 (41.9)	3901 (39.4)	
Socioeconomic status, n (%)			
Low	2624 (52.8)	5230 (52.8)	NS
Intermediate	1625 (32.7)	3225 (32.6)	
High	720 (14.5)	1437 (14.5)	
BMI			
Mean (SD)	28.7 (6.2)	28 (6.1)	<.0001
Median	28.1	27.2	
Range	15.1–65.3	14.9–89.8	

Abbreviations: BMI, body mass index; NS, not significant.

with controls (11.7% vs 6.0%; OR, 2.1; 95% CI, 1.8-2.3; *P*<.0001). Prurigo nodularis (0.2% vs 0.1%; OR, 2.9; 95% CI, 1.1-8.4; *P*=.05), neurotic excoriations (0.6% vs 0.3%; OR, 1.9; 95% CI, 1.1-3.1; *P*=.018), and LSC (1.3% vs 0.8%; OR, 1.5; 95% CI, 1.1-2.1; *P*=.01) frequencies were all higher in patients with fibromyalgia than controls. When primary skin disorders that may cause itch (eg, pemphigus vulgaris, Darier disease, dermatitis, eczema, ichthyosis, psoriasis, parapsoriasis, urticaria, xerosis, atopic dermatitis, dermatitis herpetiformis, lichen planus) were excluded, the prevalence of pruritus in patients with fibromyalgia was still 1.97 times greater than in the controls (6.9% vs. 3.5%; OR, 2.0; 95% CI, 1.7-2.4; *P*<.0001). These results remained unchanged even when excluding pruritic dermatologic disorders as well as systemic diseases associated with pruritus (eg, chronic renal failure, dialysis, hyperthyroidism, hyperparathyroidism/hypoparathyroidism, hypothyroidism). Patients with fibromyalgia still displayed a significantly higher prevalence of pruritus compared with the control group (6.6% vs 3.3%; OR, 2.1; 95% CI, 1.7-2.6; *P*<.0001).

Comment

A wide range of skin manifestations have been associated with fibromyalgia, but the exact mechanisms remain unclear. Nevertheless, it is conceivable that autonomic nervous system dysfunction,[28-31] amplified cutaneous opioid receptor activity,[32] and an elevated presence of cutaneous mast cells with excessive degranulation may partially explain the frequent occurrence of pruritus and related skin disorders such as neurotic excoriations, prurigo nodularis, and LSC in individuals with fibromyalgia.[15,16] In line with these findings, our study—which was based on data from the largest health maintenance organization in Israel—demonstrated an increased prevalence of pruritus and related pruritic disorders among individuals diagnosed with fibromyalgia.

This cross-sectional study links pruritus with fibromyalgia. Few preliminary epidemiologic studies have shown an increased occurrence of cutaneous manifestations in patients with fibromyalgia. One chart review that looked at skin findings in patients with fibromyalgia revealed 32 distinct cutaneous manifestations, and pruritus was the major concern in 3.3% of 845 patients.[15]

A focused cross-sectional study involving only women (66 with fibromyalgia and 79 healthy controls) discovered 14 skin conditions that were more common in those with fibromyalgia. Notably, xerosis and neurotic excoriations were more prevalent compared to the control group.[16]

The brain and the skin—both derivatives of the embryonic ectoderm[33,34]—are linked by pruritus. Although itch has its dedicated neurons, there is a wide-ranging overlap of brain-activated areas between pain and itch,[6] and the neural anatomy of pain and itch are closely related in both the peripheral and central nervous systems[35-37]; for example, diseases of the central nervous system are accompanied by pruritus in as many as 15% of cases, while postherpetic neuralgia can result in chronic pain, itching, or a combination of both.[38,39] Other instances include notalgia paresthetica and brachioradial pruritus.[38] Additionally, there is a noteworthy psychologic impact associated with both itch and pain,[40,41] with both psychosomatic and psychologic factors implicated in chronic pruritus and in fibromyalgia.[42] Lastly, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system are altered in both fibromyalgia and pruritus.[43-45]

Tey et al[45] characterized the itch experienced in fibromyalgia as functional, which is described as pruritus associated with a somatoform disorder. In our study, we found a higher prevalence of pruritus among patients with fibromyalgia, and this association remained significant (*P*<.05) even when excluding other pruritic skin

TABLE 2. Multivariate Analysis of the Association Between Fibromyalgia and Pruritus-Related Skin Disorders[a]

	Pruritus			Prurigo nodularis			Neurotic excoriations			Lichen simplex chronicus		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Fibromyalgia	1.8	1.8-2.4	<.001	2.9	1.1-8.4	.038	1.9	1.1-3.1	NS	1.5	1.1-2.1	.01
Female sex	1.3	1.0-1.6	.039	1580868.7	0	NS	1.5	0.5-4.1	NS	0.6	0.4-0.9	.028
Age, y	1.0	1.0-1.04	<.001	1.1	1.0-1.1	NS	1.0	1.0-1.1	.046	1.0	1.01-1.04	.006
Socioeconomic status												
Low	1			1			1			1		
Intermediate	0.9	0.9-1.2	NS	0.9	0.3-2.6	NS	1.1	0.6-1.9	.046	0.9	0.6-1.3	NS
High	1.1	1.1-1.5	.002	0.4	0.1-2.9	NS	1.0	0.5-2.2	NS	1.1	0.7-1.7	NS

Abbreviations: NS, not significant; OR, odds ratio.

[a]All adjusted ORs.

conditions and systemic diseases that can trigger itching. In addition, our logistic regression analyses revealed independent associations between fibromyalgia and pruritus, prurigo nodularis, and LSC.

According to Twycross et al,[46] there are 4 clinical categories of itch, which may coexist[7]: pruritoceptive (originating in the skin), neuropathic (originating in pathology located along the afferent pathway), neurogenic (central origin but lacks a neural pathology), and psychogenic.[47] Skin biopsy findings in patients with fibromyalgia include increased mast cell counts[11] and degranulation,[48] increased expression of δ and κ opioid receptors,[32] vasoconstriction within tender points,[49] and elevated IL-1β, IL-6, or tumor necrosis factor α by reverse transcriptase-polymerase chain reaction.[12] A case recently was presented by Görg et al[50] involving a female patient with fibromyalgia who had been experiencing chronic pruritus, which the authors attributed to small-fiber neuropathy based on evidence from a skin biopsy indicating a reduced number of intraepidermal nerves and the fact that the itching originated around tender points. Altogether, the observed alterations may work together to make patients with fibromyalgia more susceptible to various skin-related comorbidities in general, especially those related to pruritus. Eventually, it might be the case that several itch categories and related pathomechanisms are involved in the pruritus phenotype of patients with fibromyalgia.

Age-related alterations in nerve fibers, lower immune function, xerosis, polypharmacy, and increased frequency of systemic diseases with age are just a few of the factors that may predispose older individuals to pruritus.[51,52] Indeed, our logistic regression model showed that age was significantly and independently associated with pruritus ($P<.001$), neurotic excoriations ($P=.046$), and LSC ($P=.006$). Female sex also was significantly linked with pruritus ($P=.039$). Intriguingly, high socioeconomic status was significantly associated with the diagnosis of pruritus ($P=.002$), possibly due to easier access to medical care.

There is a considerable overlap between the therapeutic approaches used in pruritus, pruritus-related skin disorders, and fibromyalgia. Antidepressants, anxiolytics, analgesics, and antiepileptics have been used to address both conditions.[45] The association between these conditions advocates for a multidisciplinary approach in patients with fibromyalgia and potentially supports the rationale for unified therapeutics for both conditions.

Conclusion

Our findings indicate an association between fibromyalgia and pruritus as well as associated pruritic skin disorders. Given the convoluted and largely undiscovered mechanisms underlying fibromyalgia, managing patients with this condition may present substantial challenges.[53] The data presented here support the implementation of a multidisciplinary treatment approach for patients with fibromyalgia. This approach should focus on managing fibromyalgia pain as well as addressing its concurrent skin-related conditions. It is advisable to consider treatments such as antiepileptics (eg, pregabalin, gabapentin) that specifically target neuropathic disorders in affected patients. These treatments may hold promise for alleviating fibromyalgia-related pain[54] and mitigating its related cutaneous comorbidities, especially pruritus.

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APPENDIX

eTABLE. Sensitivity Analysis of the Association Between Fibromyalgia and Pruritus-Related Skin Disorders

	Diagnosis			
Patient group	**Pruritus**	**Prurigo nodularis**	**Neurotic excoriations**	**Lichen simplex chronicus**
Entire study population				
Fibromyalgia group, n (%)(n=4971)	582 (11.7)	9 (0.2)	31 (0.6)	64 (1.3)
Control group, n (%)(n=9896)	594 (6.0)	6 (0.1)	29 (0.3)	83 (0.8)
OR (95% CI)	2.1 (1.8-2.3)	2.9 (1.1-8.4)	1.9 (1.1-3.1)	1.5 (1.1-2.1)
P value	<.0001	.05	.018	.01
Exclusion of pruritic dermatologic diseases[a]				
Fibromyalgia group, n (%)(n=3092)	214 (6.9)	3 (0.1)	10 (0.3)	17 (0.5)
Control group, n (%)(n=7088)	250 (3.5)	2 (0.0)	14 (0.2)	16 (0.2)
OR (95% CI)	2.0 (1.7-2.4)	3.4 (0.6-20.6)	1.6 (0.7-3.7)	2.4 (1.2-4.8)
P value	<.0001	NS	NS	.012
Exclusion of pruritic dermatologic diseases[a] or systemic diseases[b] that may induce itch				
Fibromyalgia group, n (%)(n=2635)	175 (6.6)	3 (0.1)	8 (0.3)	13 (0.5)
Control group, n (%)(n=6277)	206 (3.3)	2 (0.0)	14 (0.2)	15 (0.2)
OR (95% CI)	2.1 (1.7-2.6)	3.6 (0.6-21.4)	1.4 (0.6-3.2)	2.1 (0.9-4.3)
P value	<.0001	NS	NS	NS

Abbreviations: NS, not significant; OR, odds ratio.

[a]Pemphigus vulgaris, Darier disease, dermatitis, eczema, ichthyosis, psoriasis, parapsoriasis, urticaria, xerosis, atopic dermatitis, dermatitis herpetiformis, lichen planus.

[b]Chronic renal failure, dialysis, hyperthyroidism, hyperparathyroidism/hypoparathyroidism, hypothyroidism.