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"Zooming" in the association between rosacea and fibromyalgia syndrome: ıs it worth mentioning?

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SUMMARY

OBJECTIVE: We aimed to detect the frequency of fibromyalgia syndrome in patients with rosacea and determine whether this frequency was affected by the severity of rosacea and the quality of life.

METHODS: In this prospective, controlled, cross-sectional study, a total of 94 consecutive rosacea cases and 87 age- and sex-matched controls were enrolled. The severity of rosacea was assessed in light of the findings of the National Rosacea Society Ethics Committee. Dermatology Life Quality Index and Rosacea-specific Quality-of-Life instrument had been applied to the cases of rosacea. The diagnosis of fibromyalgia syndrome was established according to the 2016 revised fibromyalgia diagnostic criteria, and the Fibromyalgia Impact Questionnaire was used to determine the functional disability.

RESULTS: The frequency of fibromyalgia syndrome was higher in the rosacea group than in the control group (p=0.01), and Dermatology Life Quality Index and Rosacea-specific Quality-of-Life instrument were higher in patients with rosacea with fibromyalgia syndrome (p=0.006 and p=0.004, respectively). A statistically significant weak positive correlation was observed between Dermatology Quality-of-Life Index, Rosacea-specific Quality-of-Life instrument, and Fibromyalgia Impact Questionnaire; symptom severity scale scores; and fibromyalgia score (r=0.35, r=0.259, and r=0.32 and r=0.376, r=0.305, and r=0.312, respectively).

CONCLUSION: The patients with rosacea have higher rates and disability scores of fibromyalgia syndrome than healthy controls, independent of rosacea severity, and quality of life is correlated with fibromyalgia scores. We might point out that fibromyalgia syndrome accompanying rosacea has more restrictions in their daily routine activities than rosacea alone. As such, physicians should be aware of the possible coexistence of rosacea and fibromyalgia syndrome.

KEYWORDS: Rosacea. Fibromyalgia. Thyroid gland. Thyroidology. Pathology.

INTRODUCTION

Rosacea, *per se*, is a chronic inflammatory disease of the central facial skin characterized by flushing attacks, persistent erythema, papules, pustules, telangiectasias, less frequent phymatous changes, and eye involvement[1]. In a recent systematic review, its prevalence was predicted at 5.5% of the adult population, and both sexes are affected equally[2]. Rosacea can lead to low self-esteem, anxiety, and depression, and stigmatism frequently impairs the quality of life seriously[1]. The most common diseases accompanying rosacea were depression, anxiety disorder, hypertension, dyslipidemia, diabetes mellitus, hypothyroidism, migraine, and rheumatoid arthritis. Rosacea and thyroid disorders are also similar in accompanying metabolic status and inflammatory pathways. Augmented expression of inflammatory markers involving matrix metalloproteinases (MMP), particularly MMP-9, has been demonstrated in rosacea as well as in hypothyroid hormonal status in thyroidology[3,4].

The pathogenesis of rosacea is multifactorial, with genetic predisposition, dysregulation in innate and adaptive immunity, and neuroinflammatory mechanisms[5]. The stimulation of transient receptor potential vanilloid 1-4 (TRPV1-4) and transient receptor potential ankyrin 1 (TRPA1) receptors, localized on sensorial neurons and keratinocytes, leads to the secretion of neuromediators such as capsaicin, calcitonin-gene related peptide, and substance P, which results in neurogenic inflammation and vasodilatation[5,6]. Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread and chronic musculoskeletal pain, accompanied by sleep disturbance, fatigue,

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morning stiffness, and cognitive disorders, whose prevalence varies between 2 and 3%[7]. The coexistence of FMS with diseases in which emotional factors play a role in the etiology, such as dysmenorrhea; migraine; irritable bowel syndrome; psychiatric diseases such as depression, anxiety, and panic attacks; and chronic inflammatory and autoimmune diseases like lupus erythematosus, rheumatoid arthritis, coronary artery disease, and diabetes mellitus have been described[8,9]. FMS and hypothyroidism share certain clinical characteristics like musculoskeletal pain and fatigue, and thyroid autoimmunity is more common in FMS[10]. Skin findings, including hyperhidrosis and pruritus, have been reported in cases with FMS[11]. Although the pathophysiology of FMS is unclear, the disease may be associated with alterations in peripheral cutaneous nerve fibers and dysfunction. In addition, neurogenic inflammation is higher in the skin biopsies of the cases with FMS[12].

The presence of neurogenic inflammation is a common pathogenetic factor in both rosacea and FMS. Furthermore, the association of both diseases with autoimmunity, chronic inflammation, and psychological stress is clear. Hence, we purposed to investigate the frequency of FMS in patients with rosacea and the association between the FMS and rosacea duration, severity, and quality of life.

METHODS

Ethical aspects

The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Giresun University under the 1205.07. KAEK-116/2019 approval number.

Study design

In our setting, a total of 94 consecutive rosacea patients and 87 age- and sex-matched controls had been enrolled in this prospective, controlled, cross-sectional study. The exclusion criteria included a history of malignancy, musculoskeletal, neurological, endocrinological, rheumatic diseases, major depression, congestive heart failure, other cutaneous diseases, younger than 18 years old, pregnant women, and receiving any treatment for rosacea within the last 3 months. As such, all the patients with rosacea were examined by the same dermatologists and classified into four subtypes according to the *National Rosacea Society* classification criteria[13]. The rosacea clinical scoring system established by the *American Rosacea Society* in 2004 was used to evaluate the clinical severity of rosacea. In this scoring system, signs and symptoms are graded from 0 to 3 as absent, mild, moderate, and severe, which leads to the rosacea severity score being classified as 0–9 mild, 10–18 moderate, and ≥19 severe[14,15].

The Rosacea-specific Quality-of-Life (RosQol) scale and Dermatology Quality-of-Life Index (DQLI) were used to evaluate the effect of rosacea on quality of life. DQLI is a questionnaire consisting of 10 questions regarding symptoms and emotions, daily activities, leisure activities, work and school, personal relationships, and treatment in the previous week. The scoring is "quite a lot=3 points", "lot=2 points", "mild=1 point", "none=0 points", and "not related=0 points", and the total score of the scale, which can vary from 0 to 30, is the sum of the scores of each question[16]. RosQol consists of 21 questions and 3 sub-dimensions such as the emotions dimension (7 items), the functions dimension (3 items), and the symptoms dimension (11 items). The answer options are structured in a five-point Likert style as "never (0 points)", "rarely (1 point)", "sometimes (2 points)", "often (3 points)", and "always (4 points)", constituting a total score ranging from 0 to 84[16]. High scores in DQLI and RosQol indicate low quality of life[16,17].

The 2016 American College of Rheumatology (ACR) diagnostic criteria were used as diagnostic criteria. The scale used in the 2016 ACR diagnostic criteria consists of two parts: (i) the Widespread Pain Index (WPI) and (ii) the Symptom Severity Scale (SSS), which leads to a total fibromyalgia score (FS). FMS was diagnosed as possessing generalized pain and symptoms for 3 months, with pain in at least four of the five anatomic locations determined except for the chin, chest, and abdomen (WPI ≥7 with SSS ≥5 or WPI 4–6 with SSS ≥9) in light of the 2016 ACR diagnostic criteria[18]. To this end, the fibromyalgia impact questionnaire (FIQ), consisting of 10 self-administered scales related to physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being, was applied to all the participants in order to determine the FMS-related effect rate and functional restriction. A score between 0 and 100 is possible from the survey. The average score of a patient diagnosed with FMS is 50, and an increase in the score means that the disease is affected[19].

Statistical analysis

Statistical analyses were performed using the SPSS software, version 23. Parametric, nonparametric, and categorical parameters were presented respectively as mean±standard deviation (SD), median [interquartile range (IQR)], and numbers (%). Analysis of skewness and kurtosis was used to test the assumption of normality, and values between -1.5 and +1.5 were considered to provide the assumption of normality. Mann-Whitney U test was used when the data did not support the assumption of normality, whereas t-test was used for the opposite. The chi-square

and Fisher's exact tests were used to identify the significance of the relationships between categorical variables. The Spearman correlation coefficient was used to evaluate the relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 22 (23.4%) cases of rosacea were diagnosed with FMS, while 8 members of the healthy control group (9.2%) also had FMS. The frequency of FMS and FIQ scores were significantly higher in rosacea than in the control (p=0.01 and p=0.01, respectively) (Table 1). The papulopustular rosacea was recognized as the most frequent subtype (53.2%), while the disease severity was moderate in 55.3% of the cases. The mean rosacea severity score was detected as 12.35±4.44, and their clinical characteristics are summarized in Table 2. No difference was recognized between the cases with and without FMS in the rosacea group in age, sex, duration of rosacea, family history, subtype, and severity of rosacea. Of note, DLQI and RosQol were higher in rosacea with FMS (p=0.006 and p=0.004, respectively) (Table 2). Notably, a statistically significant weak positive correlation was detected between DQLI, RosQol, FIQ, SSS scores, and FS (r=0.35, r=0.259, and r=0.32 and r=0.376, r=0.305, and r=0.312, respectively) (Table 3).

DISCUSSION

Rosacea is a common chronic inflammatory skin disease progressing with unclear pathogenesis and associated with multiple comorbidities, including neurologic, psychiatric, and rheumatologic diseases such as migraine, anxiety, depression, hypothyroidism, rheumatoid arthritis, and lupus erythematosus[3,4]. FMS is a clinical condition with widespread pain, usually accompanied by somatic and emotional symptoms[7]. Rosacea and FMS share similar commonalities in the chronic course, pathogenesis, association with several comorbidities, and triggering factors[3,4,7]. Both rosacea and FMS can be aggravated by emotional stress and environmental factors such as heat, cold, and light[6,7]. A study, which is a cross-sectional study incorporating 100 females with rosacea and 100 female controls, has investigated the association between rosacea and FMS to date. This study used the 2010 ACR criteria for diagnosing FMS, revealing FMS was higher in the rosacea (37% in the rosacea and 21% in the control, p=0.019)[20]. Similarly, our preliminary results revealed that rosacea had FMS (23.4%) at higher rates than the healthy control (9.2%), and the frequency of FMS was higher than in the normal population, estimated at around 2–3%[7]. The authors reported a higher frequency of FMS (37%), compared to our findings,of 23.4%[20]. We estimate this high level might be due to FMS being incorporated solely in female cases and utilizing different diagnostic criteria for FMS in the aforementioned study. In addition, they reported no difference in FIQ scores between the patients and the control group[20]. Contrarily, we recognized higher FIQ scores in cases with rosacea than in controls.

Numerous factors have been reported to contribute to rosacea's molecular and histopathologic mechanisms. Of note, the innate immune system and neurovascular dysregulation have been regarded as being primarily implicated in the pathology

Table 1. The presence of fibromyalgia and assessment of widespread pain index, symptom severity scale, fibromyalgia score, and fibromyalgia impact questionnaire score in rosacea and control group.

	Rosacea (n=94)	Control (n=87)	p-value
Age (years), mean±SD	40.90±14.42	41.06±13.73	0.942
Sex			
Female	77 (81.9%)	72 (82.8%)	0.882
Male	17 (18.1%)	15 (17.1%)	
Diagnosed with FMS	22 (23.4%)	8 (9.2%)	**0.010**
Female	20 (90.9%)	8 (100%)	
Male	2 (9.1%)	0 (0%)	
WPI, median (IQR)	1.00 (0.00–6.25)	1.00 (0.00–3.00)	0.557
SSS, mean±SD	4.58±3.23	3.94±2.75	0.157
FS, median (IQR)	6.50 (3.00–12.50)	5.00 (3.00–8.00)	0.157
FIQ, mean±SD	34.25±23.09	26.09±19.21	**0.010**

FMS: fibromyalgia syndrome; WPI: widespread pain index; SSS: symptom severity scale; FS: fibromyalgia score; FIQ: fibromyalgia impact questionnaire. Bold indicates statistically significant p-values.

Table 2. Comparison of patients with and without fibromyalgia syndrome according to the demographic, clinical characteristics, dermatology life quality index, and Rosacea-specific Quality-of-Life instrument in the patient group with rosacea.

	Rosacea with FMS (n=22)	Rosacea without FMS (n=72)	Total (n=94)	p-value
Age, years, mean±SD	44.32±12.71	39.86±14.83	40.90±14.42	0.206
Sex				
Female, n (%)	20 (90.9)	57 (79.2)	77 (81.9)	0.343*
Male, n (%)	2 (9.1)	15 (20.8)	17 (18.1)	
Duration of rosacea, years, median (IQR)	3.00 (1.00–4.25)	2 (1.00–6.75)	2 (1–5.25)	0.658
Positive family history, n (%)	6 (27.3)	20 (27.8)	26 (27.7)	0.963
Rosacea subtype, n (%)				
Erythematotelengiectatic	11 (50)	31 (43.06)	42 (44.68)	0.654
Papulopustular	11 (50)	39 (54.17)	50 (53.2)	
Phymatous	0	2 (2.78)	2 (2.13)	
Ocular†	9 (40.91)	18 (25)	27 (28.72)	
Rosacea severity, n (%)				
Mild	8 (36.36)	23 (31.94)	31 (32.98)	0.874
Moderate	12 (54.54)	40 (55.56)	52 (55.32)	
Severe	2 (9.10)	9 (12.5)	11 (11.70)	
Rosacea severity score, mean±SD	12.18±4.66	12.40±4.40	12.35±4.44	0.838
DLQI, median (IQR)	7.50 (4.75–10.75)	4.00 (3.00–8.75)	5 (3–9)	**0.006**
RosQol, mean±SD	54.73±16.78	41.88±18.40	44.88±18.75	**0.004**

IQR: interquartile range; SD: standard deviation; DLQI: dermatology life quality index; RosQol: Rosacea-specific Quality-of-Life instrument; FMS: fibromyalgia syndrome. *Fisher's exact test. †Some patients had ocular rosacea accompanying other subtypes, pure ocular rosacea was absent. Bold indicates statistically significant p-value.

Table 3. Correlation of rosacea findings and fibromyalgia scores (n=94).

	FIQ	SSS	FS
Duration of rosacea, years	0.009	0.100	0.050
Rosacea severity score	0.057	0.040	–0.016
RosQol	0.376**	0.305**	0.312**
DQLI	0.350**	0.259*	0.320**

DLQI: dermatology life quality index; RosQol: Rosacea-specific Quality-of-Life instrument; SSS: symptom severity scale; FS: fibromyalgia score; FIQ: fibromyalgia impact questionnaire. **p<0.001, *p<0.05.

of rosacea. Microscopically, a mild-to-moderate perivascular lymphocytic infiltrate or granulomatous inflammation is exhibited, while occasional plasma cells resemble an important clue for diagnostic purposes. Active pustular lesions are akin to superficial folliculitis, whereas older lesions frequently resemble granulomatous perifolliculitis. In addition, increased neurogenic inflammation in histopathology, which is correlated with allodynia, sleep disturbance, fatigue, and a decrease in the pain threshold, emerges in the skin in FMS cases[21,22]. Herewith, we suggest that the increased frequency and impact rate of FMS that we have detected in patients with rosacea may be due to increased neurogenic inflammation and increased neuropeptide levels, which play a common role in the pathogenesis of both rosacea and FMS.

In the present study, rosacea with FMS was detected to possess a lower quality of life than those without FMS, though there was no difference in terms of severity, duration, and type of rosacea. We found a positive correlation between the DLQI and RosQol and the FIQ score and SSS. Of note, the SSS scale includes emotional, cognitive, and psychological components such as fatigue, sleep disturbance, and depression[18]. Some authors reported that a positive correlation was being recognized between DLQI and FIQ scores, similar to our preliminary results (r=0.39; p=0.017)[20]. Although both studies had similar results, we believe that the inclusion of rosacea patients who did not receive any treatment is the strength of our study. Various studies have revealed that psychiatric comorbidities and underlying emotional stress affect the quality of life in dermatological diseases. It is known that both rosacea and FMS are triggered by emotional stress, and psychiatric comorbidities such as anxiety and depression accompany both diseases.

Neuro-immuno-cutaneous inflammation occurs with the effect of various neuropeptides, cytokines, and neurotransmitters released by psychological stress[1,8,23,24]. We postulate that the so-called rosacea-FMS association might be related to the augmented emotional stress in cases and the underlying common pathophysiological mechanisms.

Limitations

The limitations of the present study were (i) the constitution of a single-center institute, (ii) not evaluating the levels of neuroinflammatory biomarkers, (iii) not assessing the psychological impact on a specific validated scale, and (iv) enrolling limited numeric values of the cases.

CONCLUSION

These data suggest that the FMS frequency and impact rate are augmented in cases with rosacea, independent of their disease severity. Dermatologic and disease-related quality of life is attenuated in rosacea with FMS and correlated with disability scores for FMS. To the best of our knowledge, this is the first study in English literature regarding FMS frequency in rosacea patients of both sexes and evaluating the relationship between the clinical severity of rosacea and FMS. Our preliminary findings from a single institute experience support the notion that rosacea with FMS has more restrictions in their daily routines than rosacea alone. Last but not least, physicians must be vigilant about this phenomenon, and further studies are required to reveal the mechanisms that explain the coexistence of rosacea and FMS.

AUTHORS' CONTRIBUTIONS

SK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **IDO:** Methodology, Project administration, Resources, Validation, Visualization. **IFS:** Methodology, Software, Project administration, Resources, Validation, Visualization. **FK:** Methodology, Project administration, Resources, Validation, Visualization. **IS:** Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **BA:** Methodology, Project administration, Resources, Validation, Visualization. **DS:** Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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