

Evaluation of allergic rhinitis with nasal symptoms and nasal mucociliary clearance in patients with fibromyalgia syndrome

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Abstract.

BACKGROUND: The exact etiopathogenesis of fibromyalgia syndrome (FM) is still unclear but the pathogenesis of FM is associated with neurogenic inflammation. Allergic rhinitis (AR) is a common inflammatory and immunological disease of the nasal mucosa. As a result, it is known that neurogenic inflammation has a role in the pathophysiology of both FM and AR.

OBJECTIVE: The aim of this study was to evaluate AR and nasal allergic inflammation using nasal mucociliary clearance time (NMC) in FM patients.

METHODS: Forty-five FM patients and fifty healthy controls were included in the study. In both groups, AR was evaluated by total nasal symptom scoring (TNSS) and NMC was measured using saccharine transit time test (STT).

RESULTS: TNSS was positive in 9 patients (20%) in the FM group and no positivity in the control group. In FM group, the mean value of TNSS was higher than that of the control group ($p = 0.0001$). The average value of STT of FM patients was statistically significantly longer when compared to the control group ($p = 0.0001$).

CONCLUSION: The results we obtained suggest that there is a high possibility of coexistence of FM and AR. As a result, the coexistence of AR and FM cannot be denied but we believe that comprehensive clinical studies should be conducted on this subject.

Keywords: Fibromyalgia syndrome, allergic rhinitis, nasal mucociliary clearance time, saccharine, nasal symptom scoring

1. Introduction

Fibromyalgia syndrome (FM) is a rheumatological disease causing widespread musculoskeletal pain, sleep disorder, and easy fatigability. It overlaps with some other diseases such as autonomic dysregulation, neurological dysfunction, migraine, sensory hypersensitivity and rhinitis [1].

The interaction of immunological mechanisms with pain physiology has led to an identification of alterations in the levels of various cytokines in FM which is

not considered as an inflammatory disorder. Skin biopsies of patients with FM have revealed inflammatory cytokines such as interleukin (IL)-1 β , IL-6 and tumor necrosis factor alpha (TNF- α) [2]. In the study conducted by Uceyler et al., anti-inflammatory cytokines IL-4 and IL-10 levels were lower in FM patients compared to healthy controls [3].

The pathogenesis of FM is associated with neurogenic inflammation and autoimmune disorders where immunoregulatory abnormalities are seen [4]. In such disease, the immunologic signaling molecules such as ILs, cytokines, nerve growth factor (NGF), which is linked with rhinitis, TNF- α , and L-selectin are increased, which suggests that pathophysiology is related with the inflammatory response system. Possible mechanisms are reported to be the central nervous sys-

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tem cytokine activation through viral neurotropism and subsequent glial activation [5].

Allergic rhinitis (AR) is an immunological disease of the nasal mucosa. It is a common inflammatory condition resulting from seasonal or perennial responses to allergens [6]. The mechanism underlying the development of symptoms associated with AR are complex, including activation and infiltration of inflammatory cells, edema, increased and altered gland activity, nerve terminal activation, triggering of neurogenic inflammation and morphologically detectable remodeling processes in the mucous membrane [7,8]. Sneezing, rhinorrhea, nasal itching and nasal congestion are among the clinical symptoms. The mechanism underlying the symptoms are complex including edema, increases in altered gland activity, infiltration of inflammatory cells, nerve terminal activation, morphologically detectable remodeling processes in the mucous membrane and triggering of neurogenic inflammation [7]. The disease may be paired with various ambiguous and unrelated symptoms. Frieri and Arygiou [5] reported an association between allergic diseases, especially AR, non-AR and sinusitis.

Nasal mucociliary clearance time (NMC), which exists in many systems, is the first defensive mechanism of the human body [9]. Saccharine transit time test (STT) is one of the methods to measure NMC and is an inexpensive and simple technique [10]. As a result, it is known that neurogenic inflammation has a role in the pathophysiology of both FM and AR. In this study we aimed to evaluate the coexistence of FM and AR with nasal symptom scoring (NSS) and the effects of inflammatory changes in nasal physiology with STT in patients followed-up with FM diagnosis.

2. Materials and methods

2.1. Study design

This study was planned as a prospective case-control study at the Department of Physical Medicine and the Department of Rehabilitation and Otorhinolaryngology at Cumhuriyet University, Turkey and was carried out between March 2014 and August 2014. The number of patients and controls were assigned by statistical methods (using PASS 2008 Home-Power Analysis and Sample Size Program) where $\alpha = 0.01$, and the power of the test was found to be $P = 0.90438$.

The approval of the Human Ethics Committee at Cumhuriyet University was obtained (Decision no:

2014-03/25; Date: 18.03.2014) and the study was conducted in accordance with the Helsinki Declaration. A written consent from all the participants was obtained prior to the study.

2.2. Participants

Forty-five FM patients classified according to the criteria of the 1990 American College of Rheumatology (ACR) [11] and were recruited from the outpatient Physical Medicine and Rehabilitation Clinic. The control group was composed of 50 year-old and gender matched volunteered consecutive subjects from the hospital and university staff, who all declared to be healthy. Age, gender, history, physical examination and laboratory findings of all the cases included in the study were recorded on a standard FM follow-up form prepared in advance. The rhinoscopic examination of the participants was conducted by one physician (EEA). Participants who had a nasal pathology such as septum deviation, nasal polyps, concha bullosa or chronic infection such as chronic sinusitis, chronic otitis media were excluded in the study. Participants who used intranasal, inhaled or used systemic steroids within 2 months, an antihistamine within 2 to 7 days, a decongestant within 2 days, and other drugs having an effect on mucociliary activity, had an upper respiratory tract infection within one month and a positive history of nose bleeding in the last 48 hr or trauma, were current smokers, and/or underwent nasal surgery were excluded from the study. Patients who had additional inflammatory, metabolic-endocrine, any psychiatric diseases, and/or had used any (psychiatric) drugs for the treatment of FM were also excluded from the study.

2.3. Nasal symptom scoring (NSS)

The participants were examined in terms of symptomatology of AR. The NSS used in AR was modified and used to examine the symptoms of the participants. Nasal symptoms consisted of 4 symptoms: nasal discharge, nasal itching, sneezing, and nasal congestion. The severity of each symptom was scored 0 to 3 where 0 = none (no sign/symptom evident), 1 = mild (sign/symptom clearly present, but easily tolerated), 2 = moderate (definite awareness of sign/symptom, bothersome but tolerable), 3 = severe (sign/symptom hard to tolerate, interfere with activities of daily living and/or sleeping) with a maximum total score of 12 [12]. The sum of the individual scores gave the total symptoms score (TNSS). If TNSS is > 7 , it was con-

Table 1	
Nasal symptom scoring (NSS)	
Nasal discharge	
None	0
Causes sniffing or wiping 1–6 times a day	1
Causes sniffing or wiping 7–12 times a day	2
Continuous nasal discharge, very discomforting, nasal wings irritated	3
Nasal itching	
None	0
Sometimes in seizures	1
Continuous itching for half an hour or more	2
Prevents daily activity	3
Sneezing	
None	0
Sometimes in seizures	1
Continuous half an hour or more	2
Prevents daily activity	3
Nasal congestion	
None	0
Sometimes nasal congestion but not discomforting	1
One nostril or both nostrils are congested, generally inhalation from mouth but not discomforting	2
No breathing from nose and it is discomforting	3

Score: Max: 12, Min: 0; Generally > 7 is positive. 1, Little; 2, Middle; 3, A lot (more) [13].

sidered positive [13] (Table 1). The participants were also evaluated for other nasal symptoms, i.e. nasal bleeding, nasal dryness, nasal foreign material feeling, postnasal drip, anosmia, nasal voice, and headache history.

2.4. Determination of nasal mucociliary clearance time (NMC) with the saccharine time test (STT)

NMC was measured using STT and was recorded in minutes [14]. The subjects sat in a chair with their chin elevated 30 degrees and were asked to maintain normal ventilation and to swallow freely but to avoid deep breaths, talking, coughing, sneezing, sniffing or moving. Saccharine powder (20 mg) was deposited 2 cm inside the free airflow nostril and a timer was displayed when they returned their chin to the horizontal position. The time when the subjects reported the first perception of a sweet taste after saccharine deposition was written down [15].

2.5. Statistical analysis

In the statistical method, the data obtained in this study were studies using the SPSS 14.0 version (SPSSFW, SPSS Inc. Chicago, IL, USA). The normality of distribution of parameters was assessed by the Kolmogorov-Smirnov test. Differences between groups were compared using the students'-t test for

The results of total nasal symptom scoring (TNSS) and nasal mucociliary clearance time (NMC) by average saccharine transit test (STT) in healthy controls and patients with fibromyalgia syndrome (FM)

	FM group N = 45	Control group N = 50
TNSS [median (min-max)]	4 (0–12)*	0
STT (min) [mean ± SD]	7.8 ± 3.91*	4.33 ± 1.50

*p < 0.001. SD: Standard deviation.

normally distributed variables and the Mann-Whitney's U test for non-normally distributed variables. Differences between categorical variables were analyzed by the Chi-square test. A P-value less than 0.01 was considered significant.

3. Results

The mean age was 38.18 ± 10.98 in the FM group and 37.58 ± 10.57 in the control group. In terms of age, there was no statistically significant difference between the groups (p = 0.614). In this study, all participants were female.

When the cases in FM and control groups were examined in terms of nasal symptoms (nasal congestion, nasal discharge, nasal itching and sneezing), TNSS was positive in 9 patients (20%) in the FM group. In the FM group, the mean value of NSS was higher than that of the control group (Table 2).

When all participants were examined in terms of other nasal symptoms, in the FM group 20% (n = 9) had a nasal bleeding, 71.1% (n = 32) had a nasal dryness, 53.3% (n = 24) had a nasal foreign material feeling, 62.2% (n = 28) had a postnasal drip, 13.3% (n = 6) had an anosmia, 8.9% (n = 4) had a nasal voice, and 75.6% (n = 34) had a headache history. These symptoms were not observed in the control group. There was no positivity in the control group (p = 0.001).

The STT was carried out in all participants in this study and the STT results were compared between the groups. Average STT of the FM group was significantly longer than that of the control group (Table 2).

4. Discussion

In our study we aimed to evaluate the coexistence of FM and AR by NSS and the effects of inflammatory changes on nasal physiology by STT in FM patients. The NSS scores and STT results we obtained in our study suggested that FM and AR could be related

with nasal symptoms. The studies on this issue have been generally conducted on rhinitis patients. In contrary to these studies, we aimed at evaluating the underdiagnosed AR and nasal mucosal inflammation in FM patients.

Despite significant advances in the etiology of FM, the exact etiology is still unclear. Abnormal peripheral and/or central pain mechanisms or both, together with genetic factors, are known to play a role in generalized and chronic pain experienced by FM patients [16,17]. FM is considered to be a prototypical example of a central sensitization syndrome [17]. It is thought that increased release of neurotransmitters (serotonin, norepinephrine, norepinephrine reuptake inhibitors etc.) associated with various pain have a role in the pathophysiology of the disease as a result of the said central sensitization in FM patients. Multiple additional transmitters besides serotonin and norepinephrine also are involved in pain processing. This includes gamma-Aminobutyric acid (GABA), cannabinoid receptors, substance-P, nerve growth factor and opioid receptors [18]. These pain mediators may sensitize important nociceptor systems such as transient potential channel, vanilloid subfamily member 1 (TRPV1), acid sensing ion channel (ASIC) receptors and purinoceptors (P2X3). Afterwards, tissue inflammation mediators and nerve growth factors may stimulate these receptors and lead to fundamental changes in pain sensitivity [19]. The pathogenesis of FM is associated with autoimmune disorders where aberrant pain processing and immunoregulatory abnormalities are seen. In such disease, the immunologic signaling molecules such as ILs, cytokines, nerve growth factor (NGF), which is linked with rhinitis, TNF- α , and L-selectin are increased, which suggests that pathophysiology is related with the inflammatory response system [5].

It is thought that many neurotransmitters and immunologic molecule playing a role in the pathogenesis of FM may be playing a role in the pathogenesis of AR. For example, Ciprandi et al. [20] studies shows that serotonin serum concentrations were higher in AR patients out of pollen season than in control subjects; Khoo et al. [21] investigated the expression and function of acid-sensing ion channel-3 channels in AR. And they found that quantitative PCR on cDNA isolated from nasal biopsies from control and AR subjects demonstrated that acid-sensing ion channel-3 was significantly more highly expressed in AR ($P < 0.02$); König et al. [22] studies show that proinflammatory cytokines levels were elevated in AR patients.

Ciprandi et al. [20] reported that AR patients, when compared to the controls, had higher serotonin serum

concentrations out of pollen season, Khoo et al. [21] studied the expression and function of acid-sensing ion channel-3 channels in AR. They found that the quantitative PCR and cDNA isolated from nasal biopsies from control and AR subjects demonstrated that acid-sensing ion channel-3 was significantly more highly expressed in AR ($P < 0.02$). König et al. [22] reported that AR patients had an elevated proinflammatory cytokines levels.

FM overlaps with some other systemic diseases such as autonomic deregulation, neurological dysfunction, sensory hypersensitivity and rhinitis [23].

In a self-patients reports study, many allergic conditions such as AR, atopic dermatitis, asthma bronchiole, skin eruption due to drug or food were observed in FM patients [24]. In the study, AR was seen in 9.4 % of FM patients. In our study, the frequency of AR was found to be 20%. The reason for this high rate may be due to the use of a semi quantitative assessment scale.

Cleveland et al. [25] examined 47 cases having either seasonal or perennial AR or non-AR in a general allergy clinic. They administered a questionnaire for FM diagnosis and a performed physical examination for tender points. They found that 91% of the patients had a history of nasal congestion, 87% had nasal discharge and 83% had postnasal drip. Forty-nine percent of the patients had a history of chronic tiredness and pain for at least three months. Eighty-seven percent of the patients had a positive skin test but positive skin tests alone did not correlate with the number of tender points or criteria for FM. Cleveland et al. [25] stated that rhinitis could be an important underdiagnosed factor associated with FM.

Rhinitis symptoms are present in approximately 70% of subjects with FM and chronic fatigue syndrome. Because only 35% to 50% have positive allergy skin tests, nonallergic mechanisms may also play a role. In order to better understand the underlying mechanism, Baraniuk et al. [26] studied nasal lavage in patients having FM and chronic fatigue syndrome. They were found no differences in the basal secretion of these markers of vascular permeability, submucosal gland serous cell secretion, eosinophil and neutrophil degranulation in nonallergic FM/ chronic fatigue syndrome subjects. However, they drew attention to the fact that different studies were required to understand the underlying mechanisms.

In the literature, there are a limited number of clinical studies on the outcomes of surgical treatment in chronic rhinosinusitis and concomitant FM patients. Soler et al. studied patients having chronic rhinosi-

nusitis and concurrent FM experience an improvement in quality-of-life (QOL) following endoscopic sinus surgery (ESS) and whether such an improvement as similar to that observed in patients without FM. They found that those with chronic rhinosinusitis and comorbid FM had similar improvements in QOL after ESS when compare to those without FM [27].

Under the light of the new information on the pathophysiology of idiopathic non-AR, Baraniuk and Zheng [28] stated that the incidence of chronic fatigue syndrome and FM could be high in these patients and physicians should be alert for coexistence of these diseases.

In a study on the association between FM and rhinitis, Frieri and Argyriou [5] reported that clinicians should attach importance to multidisciplinary approach to increase treatment success in FM patients due to common points in the pathogenesis of FM and rhinitis.

As stated above, there are studies handling coexistence of FM and AR and/or rhinitis in different ways. However, we could not find any study reporting the underlying mechanism clearly. The results we obtained in our study indicated a possible association between AR and FM but are far from elucidating the underlying mechanism.

Some limitations of our study were: 1) the results presented are preliminary and the sample size was limited, 2) the absence of pathophysiological evaluation of nasal mucosa of the participants, 3) Evaluation of serum serotonin levels was not considered when the study was planned. Therefore serum serotonin levels were not studied. 4) the relative disadvantages of the STT, which depends on the sensation of taste and, therefore, individual differences in taste sensation could affect the results.

The strength of our study is the assessment of NMC and nasal symptom scoring in FM adult patients for the first time. Further studies are needed to clarify the exact mechanisms of the disturbing effect of FM on sinonasal mucosa in a larger cohort.

5. Conclusion

The results we obtained suggest that there is a high possibility of coexistence of FM and rhinitis as STT were longer and NSS were statistically longer in FM patients when compared to the health controls. It would not be proper to reach a final judgement since we had a limited number of patients and had no tissue samples

and histochemical studies. As a result, coexistence of AR and FM cannot be denied but we believe that comprehensive clinical studies should be conducted on this subject.

Conflict of interest

None to report.

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