

RESEARCH ARTICLE

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Received: 10.09.2020
 Acceptance: 10.11.2020
 DOI: 10.18521/ktd.793301

Konuralp Medical Journal
 e-ISSN1309-3878
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Evaluation of Nasal Mucociliary Activity in Patients with Familial Mediterranean Fever

ABSTRACT

Objective: The aim of this study was to evaluate nasal airway resistance and nasal mucociliary activity in Familial Mediterranean Fever (FMF) patients using anterior rhinomanometry and saccharin clearance test.

Methods: 30 patients with FMF disease and 30 healthy individuals were included in this prospective, cross-sectional study. Nasal airway resistance was measured via active anterior rhinomanometry and saccharin test was carried out for the measurement of nasal mucociliary clearance (NMC) times of all participants.

Results: Mean values for NMC time in the FMF patient group and control group were found as 14.6 ± 4.7 (range, 8-30) min. and 9.7 ± 2.3 (range, 6-14) min. respectively. Nasal mucociliary clearance time in the FMF patients was significantly prolonged in comparison that of healthy controls ($p < 0.001$). We identified no significant correlation between the disease duration and NMC time ($p=0.921$, $r = 0.019$). When the mean nasal airway resistance values of both groups were compared, there was no significant difference was detected ($p = 0.371$).

Conclusions: The results of our study have revealed that NMC time was longer in patients with FMF than that healthy controls. However, there was no statistically significant correlation between nasal mucociliary clearance time and disease duration. Disruption of NMC increases the risk of infection in the upper and lower respiratory tract. Caution should be exercised against upper and lower respiratory infections in patients with FMF.

Keywords: Familial Mediterranean Fever, Mucociliary Clearance, Rhinomanometry

Ailesel Akdeniz Ateşi Olan Hastalarda Nazal Mukosilyer Aktivitenin Değerlendirilmesi

ÖZET

Amaç: Bu çalışmanın amacı Ailesel Akdeniz Ateşi (AAA) hastalarında anterior rinomanometre ve sakarin test kullanılarak nazal hava yolu direncini ve nazal mukosilyer aktiviteyi değerlendirmektir.

Gereç ve Yöntem: Bu prospektif, kesitsel çalışmaya AAA hastalığı olan 30 hasta ve 30 sağlıklı birey dahil edildi. Tüm katılımcılara nazal hava yolu direncini ölçmek için aktif anterior rinomanometre ve nazal mukosilyer klerens zamanını ölçmek için sakarin test uygulandı.

Bulgular: AAA hasta grubu ve kontrol gruplarında ortalama nazal mukosilyer klerens zamanı sırasıyla 14.6 ± 4.7 (aralık, 8-30) dk. ve $9,7 \pm 2,3$ (aralık, 6-14) dk. olarak saptandı. AAA hastalarında nazal mukosilyer klerens zamanı sağlıklı kontrollere göre anlamlı olarak uzundu ($p < 0.001$). Nazal mukosilyer klerens zamanı ile hastalık süresi arasında istatistiksel olarak anlamlı bir korelasyon tespit etmedik ($p < 0.001$, $r=0.019$). Her iki grubun ortalama nazal hava yolu direnci değerleri karşılaştırıldığında, anlamlı bir fark saptanmadı ($p=0.371$).

Sonuç: Çalışmamızın sonuçları, AAA hastalarında nazal mukosilyer klerens zamanının sağlıklı kontrollere göre daha uzun olduğunu ortaya koymuştur. Bununla birlikte, nazal mukosilyer klerens süresi ve hastalık süresi arasında istatistiksel olarak anlamlı bir korelasyon yoktu. Nazal mukosilyer klerensin bozulması, üst ve alt solunum yollarında enfeksiyon riskini artırır. AAA hastalarında üst ve alt solunum yolu enfeksiyonlarına karşı dikkatli olunmalıdır.

Anahtar Kelimeler: Ailesel Akdeniz Ateşi, Mukosilyer Temizlik, Rinomanometre

INTRODUCTION

Familial Mediterranean Fever (FMF) is an inherited monogenic autoinflammatory disease that occurs worldwide and mostly affecting people living in the Mediterranean region. Its incidence in Turkey has been reported as 0.1% (1). Proinflammatory cytokines particularly IL-1 beta and TNF alpha play a significant role in the pathogenesis of FMF (2). In FMF, a systemic inflammation affecting serosal tissues such as pleura, peritoneum, and sinovium is seen. FMF is characterized by recurrent self-limited attacks of fever associated with peritonitis, arthritis and pleuritis. The diagnosis of FMF is made according to Tel Hashomer criteria based on the clinical findings and can be supported by a genetic analysis (3,4). It has been demonstrated that, subclinical inflammation continues during treatment and even during the attack-free period (5).

Nasal mucociliary clearance (NMC) which is the initial defense system of the respiratory system is defined as the ability of the respiratory mucosa to eliminate inhaled particles and protect mucosal moisture. The time of removal of the inhaled molecules might be used to measure NMC time (6). Saccharin clearance test is an inexpensive, easily applicable and reliable method to measure NMC (6). Mucociliary dysfunction can be primary or secondary as a result of environmental, infectious and inflammatory stimuli that impair normal motility (7,8). Any discomfort in the NMC system can cause upper and lower respiratory tract infections (9). Mucociliary clearance activity can be affected by acute or chronic systemic inflammatory disease (7,8). The hypothesis of the present study is that chronic inflammatory processes in the FMF patients might have affected the nasal mucociliary activity.

The most common symptom seen in sinonasal diseases is nasal congestion. Rhinomanometry is an easily applicable method that objectively assessment nasal airway patency (10).

The aim of this study was to investigate whether there is a difference between patient with FMF and the healthy controls in terms of nasal airway resistance and nasal mucociliary activity by using anterior rhinomanometry and saccharin clearance test.

MATERIAL AND METHODS

In order to detect a difference between the groups with an anticipated effect size of $d=0.75$, we needed at least 29 participants in each group ($\alpha=0.05$ and $\text{power}=80\%$). Therefore, we included 60 patients in this prospective, cross-sectional study, which consisted of 30 FMF patients diagnosed according to Tel-Hashomer criteria and 30 age-matched healthy volunteers without rhinologic diseases.

All otorhinolaryngological physical examinations, including endoscopic examination of both patients and healthy volunteers were performed. Individuals with a history of nasal or paranasal operation, current respiratory tract infection, being smokers, and patients with nasal obstruction due to sinusitis, major septal deviation and nasal polyposis were excluded from the study. All FMF patients were using colchicine and all the measurements were carried out during the attack-free period.

The protocol of this study was approved by the local ethics committee in accordance with the Helsinki declaration (11.04. 2019 2019/105). Written and verbal informed consents were obtained from all participants in the study.

Saccharin test was carried out in order to measure the nasal mucociliary clearance time. Participants were rested for 30 minutes before the test. A sodium saccharin 1 mm in diameter was placed in the medial aspect of the inferior nasal concha when the patient sitting in an upright position. During the time of the saccharin test, the patients were asked to perform swallowing movements at 30-second intervals and to announce the time they felt the sweet taste. The time elapsing until first feeling of a sweet taste was accepted as NMC time.

Nasal airway resistance was objectively assessed by anterior rhinomanometry. In this study, measurement was carried out using SRE 2000 Rhinometer (RhinoMetrics, Lyngø, Denmark) device. Three normal breathings were required for each measurement. Left (RL) and right (RR) nasal resistance values were calculated according to Ohm's Law at a pressure of 150 Pa. (11) The formula $RL \times RR / RL + RR$ was used to calculate the total nasal airway resistance.

Statistical analysis: Numerical variables were compared using t-test and Mann -Whitney U test for independent groups according to the distribution of data. Dependent t-test for related groups was used to compare right and left nasal measurements. The examination of categorical variables was carried out by Pearson's chi-square analysis. Pairwise relations between numerical variables were analyzed by Pearson's correlation analysis. Data analysis was performed in SPSS 25.0 program and statistical tests were interpreted at $\alpha = 0.05$ significance level.

RESULTS

30 FMF patients (56.7 % female, 43.3 % male, mean age: 28.0 ± 12.4 years) and 30 healthy controls (63.3 % female, 36.7 % male, mean age: 29.2 ± 8.0 years) were included in the study. There was not any significant difference between the FMF patients and the healthy controls in terms of age and gender distribution ($p > 0.05$) (Table 1).

Table 1. Demographic data in FMF group and control groups

	FMF group (n=30)	Control group (n=30)	p	
Age (mean±SD; years) ^a	28.0±12.4	29.2±8.0	0.077	
Sex ^b	Male	13 (43.3)	11 (36.7)	0.598
	Female	17 (56.7)	19 (63.3)	

^aMann Whitney U test ^bPearson’s chi-square test SD = standard deviation FMF: Familial Mediterranean Fever

Mean values for NMC time in the FMF patient group and control group were found as 14.6 ± 4.7 (range, 8-30) min. and 9.7 ± 2.3 (range, 6-14) min. respectively (Table 2). Nasal mucociliary clearance time in the FMF patients was significantly prolonged in comparison that of healthy controls (p < 0.001) (Table 2). The average duration of FMF disease was 5.03 (range, 1-20) years. We identified no significant correlation between the disease duration and NMC time (p=0.921, r = 0.019) (Figure 1).

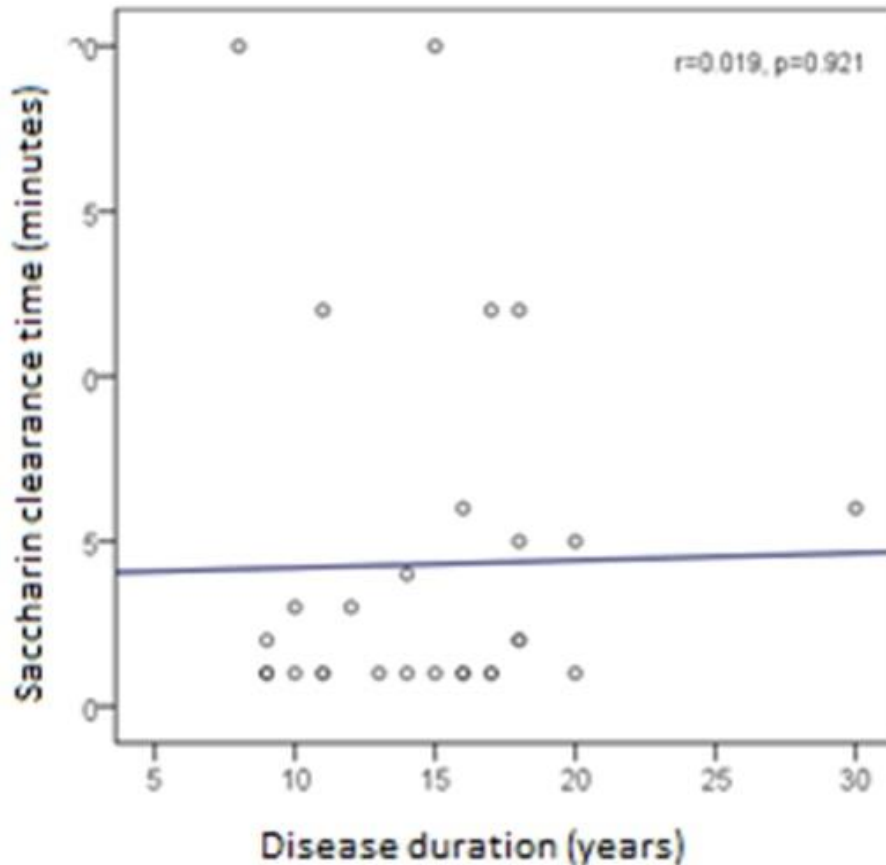


Figure 1. Correlation between the duration of FMF disease and nasal mucociliary clearance time.

The mean total nasal airway resistance in the FMF patient group and control group were found as 0.29 ± 0.11 (range, 0.18-0.60) Pa/mL/s and 0.27 ± 0.08 (range, 0.15-0.45) Pa/mL/s, respectively.

(Table 2) When the mean total nasal airway resistance values of both groups were compared, there was no significant difference was detected (p = 0.371). (Table 2).

Table 2. Comparison of nasal parameters between FMF group and control group.

	FMF group(n=30)	Control group (n=30)	P ^a - value
Right Nasal airway resistance (Pa*s/ml)	0.65±0.37	0.52±0.15	0.088
Left Nasal airway resistance (Pa*s/ml)	0.66±0.39	0.58±0.19	0.313
Total Nasal airway resistance (Pa*s/ml)	0.29±0.11	0.27±0.08	0.371
Nasal mucociliary clearance time (seconds)	14.6±4.7	9.7±2.3	<0.001

^aIndependent samples t-test
Data represent means ± standard deviations Pa*s/ml = Pascal second per milliliter
FMF Familial Mediterranean Fever

DISCUSSION

Our study has presented that nasal mucociliary clearance time is prolonged in the FMF patients with saccharin test results in the attack-free period. However, there was no significant difference was detected in nasal airway resistance. To the best of our knowledge, our study is the first study to investigate the effect of FMF disease on nasal functions or nasal mucociliary activity. Therefore, there is no other study available to be compared with our results.

FMF is an autoinflammatory multisystem disease with heterogeneous clinical symptoms, caused by inherited mutations in MEFV gene, which encodes pyrin (12). A mutated pyrin causes uncontrolled production of interleukin (IL)-1 β and IL-18 and consequently aberrant inflammation. These cytokines lead to increased TNF- α and IL-6. Increased serum levels of TNF- α , IL-1 β and IL-6 have been demonstrated during FMF attacks and attack-free period (13,14).

Nasal mucociliary clearance system is the primary defense mechanism of the respiratory airway. Proper mucus production and coordinated ciliary activity are required for effective mucociliary clearance. It has been shown in several studies that inflammatory cytokines are effective on NMC (15–17). In their study, Gonzalez et al. (16) have revealed that TNF α , a proinflammatory cytokine, inhibits viscosity-related ciliary activity in human respiratory cultures. Disruption of NMC increases the risk of infection in the upper and lower respiratory tract (9). Hypertonic saline improves mucociliary clearance by reducing mucus viscosity and may reduce the risk of respiratory tract infections in patients with NMC impairment.(18)

In a previous study, it was found that nasal methicillin-resistance bacterial colonization was more frequently seen in FMF patients compared to the healthy population (19). Birik et al. (20) reported that respiratory symptoms and signs were significantly more common during FMF attacks. Recently, Celiksoy et al. (21) stated that severe atopic disease and recurrent respiratory infections

are characteristic features of FMF disease. In the present study, it was found that there was longer NMC times in FMC patients compared to healthy controls. When the data were evaluated in the light of the literature respiratory symptoms in FMF patients may be associated with the disruption of the mucociliary clearance system.

The association of FMF with various systemic vasculitic disorders such as Henoch Schönlein Purpura, Behçet's disease and polyarteritis nodosa has previously been reported (22,23). The association between FMF and Behçet's disease has been demonstrated in various studies. It has been suggested that both conditions may have a common etiopathogenetic mechanism (24,25). Ozbay et al. (25) showed that NMC time was prolonged and positively correlated with disease duration in patients of Behçet's disease. In the present study, NMC time was found to be longer in the FMF patients compared to that of healthy controls. However, there was no correlation between nasal mucociliary clearance time and the disease duration.

Patients with nasal pathologies that may affect NMC and nasal airway resistance were excluded from the study and this was one of the strengths of our study. On the other hand, an important limitation of the present study was that one of these histology and electron microscopic examinations of the cilia and mucous structures was not performed. Another limitation of the present study was that our sample size was relatively small. Further studies should be conducted with greater number of patients using various methods to confirm the information obtained in this study, to reveal possible pathophysiological causes and to gather information about treatment approaches.

CONCLUSION

The results of our study have revealed that NMC time was longer in patients with FMF than that healthy controls. Disruption of NMC increases the risk of infection in the upper and lower respiratory tract. Caution should be exercised against upper and lower respiratory infections in patients.

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