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ARAŞTIRMA RESEARCH ARTICLE

Levels of soluble intercellular adhesion molecule-1 and tumor necrosis factor-α in the sera of young children with persistent or recurrent wheeze

Sürekli veya tekrarlayan vizingi olan küçük çocuklarda serum solubl interselüler adezyon molekülü-1 ve tümör nekroz faktörü-alfa düzeyleri

Mahmut ÇAKIR[1], Feyzullah ÇETİNKAYA[2]

[1] **Samsun Women and Children Training and Research Hospital, Samsun, Turkey**
Samsun Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Samsun, Türkiye

[2] **Division of Pediatrics Allergy, Children Health and Diseases, Faculty of Medicine, Maltepe University, Istanbul, Turkey**
Maltepe Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Allerji Bölümü, Istanbul, Türkiye

ABSTRACT

Objective: Intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-alfa (TNF-α) are important inflammatory mediators in asthma and other allergic diseases. But their role is not clear in young children with wheezing. This study analyzed plasma levels of soluble ICAM-1 (sICAM-1) and TNF-α in young children with persistent or recurrent wheeze.

Materials and Methods: Thirty children (aged 4-24 months) with acute wheezing were recruited from pediatric outpatients of our hospital. The diagnosis of acute wheezing episodes was based on symptoms and the children with known causes of wheezing were excluded from the study. The study also consisted of 30 age-matched controls who admitted for anemia or mild trauma but had never wheezed before.

ÖZET

Giriş: İnterselüler adezyon molekülü-1 (ICAM-1) ve tümör nekroz faktörü-alfa (TNF-α) astımda ve diğer allerjik hastalıklarda yer alan önemli inflamasyon mediyatörleridir. Fakat bunların vizingi olan küçük çocuklardaki rolü tam olarak belli değildir. Bu çalışmada sürekli veya tekrarlayan vizingi olan küçük çocuklarda solübül ICAM-1 (sICAM-1) ve TNF-α'nın rolü araştırılmıştır.

Gereç ve Yöntem: Çalışmaya hastanemizin çocuk polikliniğine başvuran ve akut vizingi olan 30 çocuk (yaşları 4-24 ay) alınmıştır. Akut vizing ataklarının tanısı semptomlara göre konulmuş olup, başka bir sebeple vizingi olan çocuklar çalışmadan çıkarılmıştır. Çalışmaya ayrıca hastaneye anemi veya küçük travma sebebiyle başvurmuş olan ama daha önce hiç vizing geçirmeyen benzer yaş grubundan 30 çocuk da kontrol grubu olarak alınmıştır.

Yazışma Adresi/Address for Correspondence
Prof. Dr. Feyzullah ÇETİNKAYA
Maltepe Üniversitesi Tıp Fakültesi Hastanesi, Atatürk Caddesi Çam Sokak No: 3 34843 Maltepe-İstanbul, Türkiye
e-posta: feyzulkaya@mynet.com

Results: In wheezy patients soluble ICAM-1 and TNF-α levels were significantly higher (815 ± 296 ng/mL and 253 ± 207 pg/mL respectively) during symptomatic period than symptom-free period (609 ± 280 ng/mL and 100 ± 86 pg/mL respectively) and both of first and second levels of these markers were higher in patients than in controls.

Conclusion: These results show that sICAM-1 and TNF-α levels increase in sera of children with wheezing and measurement of these molecules may be useful to show the presence and activation of airway inflammation in young wheezy children.

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Key words: Wheezing, intercellular adhesion molecule-1, tumor necrosis factor-alpha, asthma

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Bulgular: Vizingi olan çocuklarda sICAM-1 ve TNF-α seviyeleri semptomatik dönemde (sırasıyla 815 ± 296 ng/mL ve 253 ± 207 pg/mL) semptomsuz döneme göre (sırasıyla 609 ± 280 ng/mL ve 100 ± 86 pg/mL) ve her iki dönemde de kontrol grubuna göre daha yüksek bulunmuştur.

Sonuç: Bu sonuçlar sICAM-1 ve TNF-α seviyelerinin vizingli çocukların serumlarında yüksek olduğunu ve bu moleküllerin seviyelerinin ölçülmesinin küçük çocuklarda hava yolu inflamasyonunun varlığını ve aktivasyonunu göstermede yardımcı olabileceğini göstermektedir.

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Anahtar kelimeler: Vizing, interselüler adezyon molekülü-1, tümör nekroz faktörü-alfa, astım

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INTRODUCTION

Wheezing is very common in infancy; 20% of all children suffer from wheezing in early childhood[1,2]. Although not all children who wheeze can be accepted as asthma some of these children are at an increased risk of development of asthma in later childhood[1,3]. Wheezing is principally a result of the inflammation of the airways and occurs in different phenotypes in infants and children[3,4]. The inflammation lying beneath the wheezing is mediated via some cytokines and adhesions molecules, which are triggered by some factors such as viral infections[5,6]. Because of the difficulty of tissue sampling by bronchoscopy in daily practice, some indirect methods have been tried to develop to evaluate the severity of the airway inflammation in asthmatic children. Measurement of serum levels of some eosinophil products such as eosinophil cationic protein (ECP) and eosinophil protein X (EPX) contributed limitedly to the clinical practice[7,8]. Intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin superfamily of the adhesion proteins and it is expressed by a variety blood cells and endothelial, fibroblastic and epithelial cells. Many studies have shown that it is involved in the pathogenesis of asthma[9,10]. Tumor necrosis factor-α (TNF-α) is a multifunctional cytokine and plays an important role in the pathophysiology of many diseases including allergies[11]. In this study serum levels of ICAM-1 and TNF-α were measured in young children during activation and remission periods of wheezing and compared with age-matched controls.

MATERIALS and METHODS

This study comprised 30 young children aged 4-24 months (mean 7.1 ± 4.7 months) with acute wheezing that occurred after a viral upper respiratory tract infection admitted to Ondokuz Mayis University Hospital's pediatric outpatients (Samsun, Turkey). The diagnosis of acute wheezing episodes was based on symptoms (tachypnoea, dyspnoea, prolonged expiration and wheezing)[12]. Children with known causes of wheezing such as pneumonia, laryngomalacia/tracheomalacia, congenital heart diseases, cystic fibrosis and gastroesophageal reflux were excluded from the study. None of the children had ever received any kind of glucocorticoids before or antihistamines in the last 15 days. The study also consisted of 30 age-matched controls who admitted to the hospital for no infection or allergy but for some other reasons such as minor trauma or anemia. The

control group had never wheezed in their life before. Informed consents were obtained from all parents (including controls) for both study and treatment.

At the beginning of the study routine biochemical measurements and radiographs were taken from all of the patients in addition to serum total immunoglobulin E (IgE) levels. Twice sera samples were obtained from all subjects (at the beginning and 16 weeks thereafter) and stored at -40°C until measurement. Both soluble ICAM-1 (sICAM-1) and TNF-α levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) method in accordance with the manufacturers' instructions (Cell Diagnostic and Cytoscreen respectively). The patients with intermittent symptoms were treated with nebulized salbutamol as required during 16 weeks follow-up. In those children with persistent wheezing nebulized budesonide and salbutamol were used until the symptoms were taken under control.

Statistical Analysis

Statistical analysis were performed with SPSS software program. Statistical significance was assessed by chi-square test, Kruskal-Wallis one-way analysis of variance, Mann-Whitney U test and paired-t test. A p value of less than 0.05 was considered significant.

RESULTS

The wheezing time among patients had ranged between 5 days-12 months (mean 4.3 ± 2.6 months). Fifteen patients gave personal or familial atopy history. In eight of these patients personel atopic dermatitis, in three paternal asthma and in four maternal asthma were reported. Eight of the patients had had another wheezing attack before.

The first sICAM (815 ± 296 ng/mL vs. 609 ± 280 ng/mL) and TNF-α (253 ± 207 pg/mL vs. 100 ± 86 pg/mL) levels were significantly higher than the second levels in patients ($p< 0.001$ for each) (Table 1). The first and second sICAM-1 levels of patients correlated with first TNF-α levels ($r= 0.78$; $p= 0.012$). Both the first and second values of sICAM-1 and TNF-α were significantly higher than the controls' values ($p< 0.001$ for both). On the other hand, IgE, sICAM-1 and TNF-α levels were significantly higher in atopic wheezy children than non-atopics. In eleven children -five of whom were atopic- wheezing was still present when the second blood samples were taken.

DISCUSSION

Several cytokines have been shown to be present in urine, serum and bronchoalveolar lavage fluid from asthmatics as markers of airway inflammation[7,8]. But, most of these studies have been performed in adults in comparison to a few studies in children[13-15]. Some previous stuides have shown inconsistent results between the symptoms of asthmatic patients and sICAM-1 levels[9,15]. In our study sICAM-1 levels were correlated with the symptoms of the patients and were higher than the controls' even in the symptom-free period.

Many investigations have pointed to a key role of the proinflammatory, pleiotropic cytokine TNF-α in host defense and inflammatory processes, including asthma[16]. Increased levels of TNF-α have been detected in sputa,

Table 1. sICAM-1, TNF-α and total IgE levels of the patients and controls

	Patients			Controls		
	First	Second	p	First	Second	p
sICAM-(ng/mL)	815 ± 296	609 ± 280	< 0.001	248 ± 123	238 ± 130	> 0.05
TNF-α (pg/mL)	253 ± 207	100 ± 86	< 0.001	69 ± 47	58 ± 43	> 0.05
IgE (IU/mL)	209 ± 37	96 ± 19	< 0.001	32 ± 14	30 ± 13	> 0.05

bronchoalveolar lavage fluid and sera in patients with wheezing just after viral infection and antigen challenge[17,18]. In our study, TNF-α levels have been found higher in acute period than symptom-free period and controls in wheezy infants. Ying et al. have reported higher secretory TNF-α levels in atopic patients than non-atopics following allergen challenge[19].

It is well known that airway inflammation persists in wheezy patients in spite of absence of symptoms[20]. This has been observed in our patients with high levels of inflammation markers in their symptom-free periods. In addition, any kind of viral infection or allergen exposure might have contributed to high levels of markers[20,21]. In our study wheezing persisted in six of eight atopic patients during 16 weeks follow-up period, which may support the idea that these patients are more inclined to develop asthma in later years[1,3]. But we were not able to follow the patients for years because of distance of their homes from our center. We think sICAM-1 and TNF-α levels can be used as a marker of airway inflammation in wheezy infants and young children. Higher levels of these molecules both in symptomatic and asymptomatic periods may be an early sign of long-term wheezing and such children should be followed closely.

In our study, significant differences were found between first and second IgE levels of the patients. This may be due to viral infections as a cause of wheezing in our children, because many studies have shown that serum IgE values in acute phase of respiratory tract infections caused by viruses increase in comparison to improvement phase of the patients or healthy controls[22,23].

In conclusion; serum sICAM-1 and TNF-α levels might be used for the evaluation of clinical activity and follow-up of the wheezy infants, but we need long-term studies with more subjects.

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