

Leukotriene E4 and Endothelin-1 Levels, Their Response to the Therapy, Potential Relationship with Gastroesophageal Reflux and Developing of Infantile Asthma in Wheezy Infants

Hışıltılı Çocuklarda Lökotrien E4 ve Endotelin-1 Düzeyleri, Tedaviye Yanıt, Gastroösefageal Reflü ve Süt Çocuğu Astımı Gelişmesi ile Potansiyel İlişkileri

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ABSTRACT Objective: Wheezing is a common symptom among children and is proposed to be associated with inflammatory cell infiltration, cytokines production, and with some risk factors such as gastro esophageal reflux (GER). The aim of the present study was to investigate endothelin-1 (ET-1) and leukotriene-E4 (LTE-4) levels, their response to steroid and β 2-agonist therapy, and to establish if these parameters can be used as a diagnostic tool for infantile asthma and assess their relation with GER during acute attack of wheezy infants (WI). **Material and Methods:** Thirty WI and 12 healthy infants were enrolled in the present study. Serum IgE, ET-1, urine LTE-4 levels, and eosinophil percentage were measured prior to and 5 days after the treatment (systemic or inhaled steroid therapy and inhaled β 2-agonist) in children with WI. In addition, esophageal pH was monitored for 24 hours. **Results:** Serum IgE, ET-1, and urine LTE-4 levels were significantly higher in the patients compared to the controls before and five days after the treatment ($p=0.009$; $p=0.039$, $p=0.032$; $p=0.014$, $p=0.017$, respectively). The serum IgE and urine LTE-4 levels prior to and 5 days after the treatment were higher in the patients with GER when compared to the controls ($p=0.021$, $p=0.016$ and $p=0.039$). Moreover, the systemic or inhaled steroid therapy did not influence the serum ET-1 and urine LTE-4 levels. We found that the serum IgE and ET-1 levels on 5th day of the treatment and LTE-4 levels at the beginning and 5th day of the treatment were notably different in patients with higher likelihood for developing infantile asthma when compared to the controls. Finally, increased serum IgE levels were present in patients with good response to inhaled β 2-agonist with regard to those with poor response to inhaled β 2-agonist ($p=0.031$). **Conclusion:** The present study indicated that IgE, ET-1 and LTE-4 levels were related to airway inflammation in WI while LTE-4 and IgE levels were associated with GER. LTE-4 and IgE levels could be novel parameters for determining the risk factor for developing asthma in child with WI. Inhaled β 2-agonist therapy seemed to be beneficial only in patients with high serum IgE levels.

Key Words: Gastroesophageal reflux; leukotriene e4; endothelin-1; asthma

ÖZET Amaç: Hışıltı, çocuklarda yaygın bir semptomdur ve inflamatuvar hücre infiltrasyonu, sitokinler ve gastro ösefageal reflü (GER) gibi bazı risk faktörleri hışıltı gelişmesini açıklamak için önerilmiştir. Bu çalışmanın amacı, hışıltılı çocuk (HÇ) tanılı hastaların akut atakları sırasında endotelin-1 (ET-1) ve lökotrien-E4'ün (LTE-4) düzeylerini, bu düzeylerin steroid ve β 2-agonist tedavisine yanıtlarını, GER ile ilişkisini ve astım gelişmesini saptamak için yeni parametreler olup olmadıklarını araştırmaktır. **Gereç ve Yöntemler:** Yirmi HÇ ve 12 sağlıklı çocuk çalışmaya alındı. HÇ hastalarında serum IgE, ET-1 ve idrar LTE-4 düzeyleri, eozinofil yüzdeleri tedavi (sistemik ya da inhale steroid ve inhale β 2-agonist) öncesi ve tedavi sonunda (5. gün) ölçüldü. Hastalara 24 saatlik özeofagus pH monitörizasyonu yapıldı. **Bulgular:** Hastaların başlangıçta ve 5. günde ölçülen serum IgE, ET-1 ve idrar LTE-4 düzeyleri kontrol grubuna göre yüksek bulundu (sırasıyla $p=0.009$; $p=0.039$, $p=0.032$; $p=0.014$, $p=0.017$). Tedavi öncesi ve tedavinin beşinci günü ölçülen serum IgE ve idrar LTE-4 düzeyleri GER olan hastalarda kontrol grubuna göre daha yüksek bulundu ($p=0.021$, $p=0.016$ ve $p=0.039$). Serum ET-1 ve idrar LTE-4 düzeylerini (başlangıç ve 5. gün) astım için risk skoru yüksek olan hastalarda kontrol grubuna göre yüksek bulduk. Yüksek IgE düzeyleri inhale β 2-agonistlere cevap iyi cevap veren grupta vermeyenlere göre daha yüksekti ($p=0.031$). **Sonuç:** IgE, ET-1 ve LTE-4 düzeyleri HÇ'deki havayolu inflamasyonu ile ilişkili bulunurken IgE ve LTE-4 GER ile ilişkiliydi. LTE-4 ve IgE, HÇ astım gelişmesini belirlemek için yeni parametreler olabilir. İn hale β 2-agonistler yalnızca IgE düzeyi yüksek HÇ' da yararlı gibi gözükmektedir.

Anahtar Kelimeler: Gastroözofageal reflü; lökotrien e4; endotelin-1; astım

Wheezing is a common symptom among infants with varying prevalence between 4%-32%.¹ Most of the risk factors for wheezing are due to the obstruction and infection of small airways. The etiology of wheezing during infancy might contain multiple factors, including inflammation (asthma, cystic fibrosis, bronchopulmonary dysplasia), infection, gastro esophageal reflux (GER) with or without aspiration, congenital malformations, extrinsic or intrinsic compression and extra-thoracic disease. It is not clear why some infants are wheezy during viral upper respiratory tract infections while others are not. It is possible that WI have a tendency to mount an exaggerated inflammatory response leading to production of mediators such as interleukins, leukotriens (LTE), endothelins (ET) and histamine.²⁻⁴ However, the effects of ET-1 and LTE are not well known in wheezy infants. Therefore, we hypothesized that (i) systemic or inhaled glucocorticoids treatment would decrease concurrently urine concentration of LTE-4, blood levels of ET-1 and IgE and absolute eosinophil counts, (ii) whether LTE-4, ET-1, and IgE levels can be new risk factors for wheezy infant who might develop infantile asthma in the future, and (iii) whether the presence of GER would elevate LTE-4 and ET-1 levels in WI. Therefore, we measured the urine concentration of LTE-4, blood levels of ET-1 and IgE and absolute eosinophil counts before (day 0) and five days after (day 5) the steroids treatment in wheezy patients with or without GER.

MATERIAL AND METHODS

PATIENTS AND CONTROL SUBJECTS

We randomly selected 30 patients diagnosed as WI in the Department of Pediatric Allergy, Medical School of Eskisehir Osmangazi University, Eskisehir, Turkey. The WI group consisted of 22 boys and 8 girls with a mean age of 12.2 ± 4.8 , ranging from 6 to 24 months. The control group of the current study consisted of 12 healthy normal children (7 boys, 5 girls with mean age of 13.6 ± 5.9 , ranging from 6-24 months). The WI patients were enrolled to the study during acute bronchiolitis. The bronchiolitis was defined according to following crite-

ria: episode of dyspnea occurring immediately after an episode of nasopharyngitis and combining coughing, expiratory impairment, and/or obstructive dyspnea, that is, tachypnea, inspiratory retraction, hyperinflation of lungs, wheezing (audible or on auscultation), crackles, or, in the most serious cases no signs at all.⁵ Patients younger than three months of age with respiratory rate higher than 70 breaths per minute, lethargic in appearance, with wheezing and respiratory distress associated with oxygen saturation below 92 percent on room air, showing hypercarbia and atelectasis or consolidation on chest radiography were treated in the hospital.^{6,7} The patients were determined as high or low risk for infantile asthma according to criteria described previously by Martinez.⁸ According to these criteria, the patients having parents with atopic diseases such as asthma, eczema, allergic rhinitis and suffering more than three wheezy attacks were determined as having high risk for development infantile asthma. The patients with bronchopulmonary dysplasia, history of prematurity, cystic fibrosis, neurological or cardiovascular disease, urinary tract infection and bacterial pneumonia, and those receiving previous steroid treatment, β_2 -agonist and/or immunosuppressive drugs were excluded from this study. The WI group were treated with prednisolone (1-2 mg/kg/day, maximum 40 mg/day) or inhaled budesonide (125-250 μ g/dose for 5 days), or inhaled β_2 -agonist.⁵⁻⁷ The patients were divided into two groups according to their response to the inhaled β_2 -agonist: Good responder group (Group 1), showing no wheezing and tachypnea following to the treatment of inhaled β_2 -agonist, and poor responder group (Group 2), demonstrating little improvement in their symptoms on 3rd day of the treatment with the inhaled β_2 -agonist.

The presence of GER in WI patients was determined according to the modified criteria's of Vandenasplas et al.⁹

STUDY PROTOCOL

All the patients were hospitalized and checked for the presence of GER (including regurgitation, eructation nausea, vomiting, excessive salivation, cough,

and dyspnea), exposure to smoking (antenatal or postnatal) and atopy history in siblings or parents. The complete blood count, erythrocyte sedimentation rate, C-reactive protein, urine analysis and culture, sweat chloride test, specific IgE tests as radioallergo sorbent test (RAST) were performed. In addition, 24 hours esophageal pH monitorization and chest X-ray were done in the WI group. At the beginning of the study (day 0) and 5 days after the steroid treatment, urine and peripheral venous blood samples were obtained from the patients and the controls to assess the urine LTE-4/creatinin, ET-1, IgE, and the absolute eosinophil counts.

The levels of IgE were measured using chemiluminescence methods (Roche Diagnostics GmbH Hitachi E170, Germany). Specific IgE for mite, cacao, egg and cow milk were also determined by RAST (UNICAP 100, Pharmacia, Sweden). The results were expressed in standard units ($\text{SU}\cdot\text{mL}^{-1}$) and they were classified into conventional allergy classes (0-5). The high sensitivity protocol was used, with a cut-off value of $0.5 \text{ SU}\cdot\text{mL}^{-1}$. A positive test was considered when the values were $>0.5 \text{ SU}\cdot\text{mL}^{-1}$ (0-1 class).

Moreover, serum ET-1 levels were measured with a commercial kit (ACE™ Endothelin-1 EIA kit; Cayman Chemicals, Michigan USA, Catalog No. 583151). Assays were done using solid phase, enzyme-labeled chemiluminescent immunometric method. Urine LTE-4 levels were measured by competitive enzyme-labeled assay methods (ACE™ LTE-4 EIA kit; Cayman Chemicals, Michigan USA, Catalog No. 520411). Urine LTE-4/creatinin levels were measured via spectrophotometric methods (AEROSSET™ Abbott USA).

STATISTICAL ANALYSIS

Data were analyzed using the SPSS 16.0 for Windows package. The Shapiro-Wilk test was performed for testing normality. Parametric tests were used for normally distributed variables and non-parametric tests were used for variables that were not normally distributed. Mann Whitney U test, Chi-square test and Spearman's rank correlation coefficient were used. When abnormally distributed variables belonged to multiple groups, Kruskal

Wallis test was employed and Mann Whitney U test was performed to compare intergroup differences. Results were expressed as mean \pm SD and p value <0.05 was considered statistically significant.

ETHICS

The protocol of the present study was approved by the Research Ethics Committee of Eskisehir Osmangazi University. Informed consent was obtained from the parents or guardians of all the participants in WI and control groups.

RESULTS

There was no statistically significant difference between the control and study groups for their age, sex and body weights ($p=0.46$, $p=0.96$, $p=0.071$ respectively). The present results demonstrated that 20 (66.6%) patients showed good clinical response to the inhaled β_2 -agonist treatment; however, 10 (33.3%) patients developed poor response to the same treatment. Using the criteria established earlier by Martinez,⁸ for estimating the risk for developing asthma in infants, we found that 8 (26.7%) patients had high risk and 22 (73.3%) patients had low risk for mounting infantile asthma.

Egg and cow milk specific IgE were detected in 1 and 5 patients, respectively. These six patients were also suffered from GER. The serum ET-1 and IgE, and urine LTE-4 levels at the beginning and fifth day of the treatment were significantly higher in the WI group than the controls (Table 1 and 2). Unexpectedly, systemic steroid therapy failed to decrease these levels.

Furthermore, the serum ET-1 levels on 5th day of the treatment were significantly elevated ($p=0.038$) in patients treated with inhaled steroids with respect the controls (Table 3). Urine LTE-4 levels on 0 and 5th days of the treatment were also notably increased ($p=0.02$ and $p=0.044$) in patients treated with inhaled steroid in comparison to the controls (Table 3). The serum ET-1 and urine LTE-4 levels were considerably amplified in patients treated with systemic steroids on 0 ($p=0.033$ and $p=0.005$) and 5th days of the treatment ($p=0.05$ and $p=0.009$). The effect of the systemic and inhaled steroid treatment on serum ET-1 and urine LTE-4 le-

TABLE 1: Level of hemoglobin, leucocyte, and IgE eosinophil count in study and control groups (mean \pm SD).

	Study group	Control subjects	p
	(n=30)	(n=12)	
Hemoglobin (g/dl)	10.1 \pm 1.6	10.1 \pm 1.1	0.643
Leucocyte (mm ³)	11403 \pm 4762	10225 \pm 3120	0.432
Eosinophil counts (%)	1.5 \pm 1.5	1.3 \pm 1.1 (0.2-3.2)	0.530
IgE (ng/ml)	37.4 \pm 56.4	7.7 \pm 8.7	0.009

TABLE 2: Level of serum ET-1 and urine LTE4 on day 0 and day 5 in study and control groups (mean \pm SD).

	Study group	Control subjects	p
	(n=30)	(n=12)	
ET-1 (pg/ml) (Day 0)	4.2 \pm 2.7	2.8 \pm 0.7	0.039
ET-1 (pg/ml) (Day 5)	4.4 \pm 2.7		0.032
LTE-4 (pg/ml) (Day 0)	1063.4 \pm 453.7	758.7 \pm 280.9	0.014
LTE-4 (pg/ml) (Day 5)	1023.2 \pm 398.7		0.017

vels was found to be similar (Table 3), indicating that the delivery way of the steroid did not make a difference.

Moreover, a negative correlation existed between serum ET-1 and urine LTE-4 levels at the beginning ($r = -0.566$, $p = 0.008$; Figure 1). No relation was found between ET-1, LTE-4 levels and eosinophil counts, on 0 and 5th days of the treatment

with regard to the gender, age, presence of GER, atopy of parents, smoke exposure, systemic steroid therapy and breast feeding ($p = 0.345$, $p = 1.000$, $p = 0.657$, $p = 0.419$, $p = 1.000$, $p = 1.000$ and $p = 0.0854$).

We further found that the eosinophil counts, serum IgE and ET-1 levels before the treatment and LTE-4 levels on 0 and 5th days of the treatment were markedly higher in patients with high risk for developing infantile asthma when compared to the controls (2.7 \pm 1.5 vs. 1.3 \pm 1.1, $p = 0.017$; 53 \pm 65 vs. 7.7 \pm 8.7, $p = 0.002$; 3.7 \pm 0.8 vs. 2.8 \pm 0.8, $p = 0.04$; 1343.2 \pm 394.8 vs. 758.7 \pm 280.9, $p = 0.003$; 1123.6 \pm 395.1 vs. 758.7 \pm 280.9 $p = 0.049$). Only eosinophil counts and the serum IgE levels were higher in the high risk group (8 patients) for infantile asthma when compared to the low risk group (22 patients) for infantile asthma ($p = 0.006$ and $p = 0.05$). Our observations revealed that the gender, age, GER, smoke exposure and breast feeding were not related to the development of infantile asthma ($p = 1,000$, $p = 0.488$, $p = 1,000$, $p = 0.384$ and $p = 0.689$, respectively).

The GER was determined in 7 (23.3%) patients with wheezing, and 6 of 7 patients (85.7%) had specific IgE against cow milk and egg. Eosinophil counts and serum ET-1 levels on day 0 and 5 were not statistically different in wheezing children with GER than the controls (Table 4). In addition, the

TABLE 3: Level of serum ET-1 and urine LTE-4 levels according to treatment modality.

	Steroid treatment		Control (n=12)	p
	Inhaled (n=14)	Systemic (n=16)		
ET-1 (pg/ml) (Day 0)	3.6 \pm 1.1	4.7 \pm 3.8		P1= 0.049*
			2.8 \pm 0.7	P2= 0.033**
ET-1 (pg/ml) (Day 5)	4.8 \pm 3.3	4.4 \pm 2.7		P3= 0.408***
				P4= 0.038*
				P5= 0.05**
				P6= 0.981***
LTE-4 (pg. mg-1 creatinine) (Day 0)	969.8 \pm 482.8	1092.6 \pm 406.5		P7= 0.02*
			758.7 \pm 280.9	P8= 0.005**
LTE-4 (pg. mg-1 creatinine) (Day 5)	985.6 \pm 511.7	1092.3 \pm 298.7		P9= 0.325***
				P10= 0.044*
				P11= 0.009**
				P12= 0.865***

*Inhaled vs control; **systemic vs control and *** Inhaled vs systemic

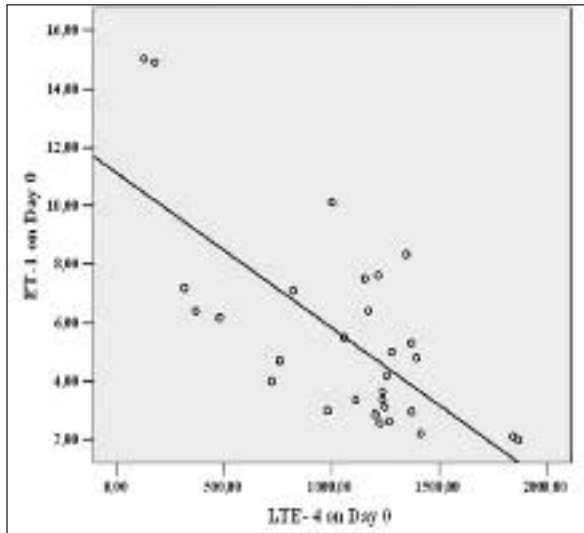


FIGURE 1: Negative correlation between serum ET-1 and urine LTE-4 levels in patients.

levels of serum IgE and urine LTE-4 on day 0 and 5th days of the treatment were augmented in WI with GER with respect to the controls (Table 4). Low body weight was strongly correlated with WI having GER ($p= 0.007$, Table 4).

Eosinophil counts, serum IgE on day 0 and ET-1 levels were also not statistically different in WI with GER than wheezing without GER on day 0 and 5th day of the treatment ($p= 0.522$, $p= 0.540$, $p= 0.619$ and $p= 0.598$, respectively).

High serum IgE levels were statistically significantly associated to inhaled β_2 -agonist in patients with good response when compared the ones with poor response to inhaled β_2 -agonist ($p= 0.031$).

DISCUSSION

The pathogenesis of wheezing episodes are intricate and not well understood. Even though it is not well established, one of the mechanisms regarding wheezing episodes is believed to be IgE mediated reactions. Our present data suggest that there is a relation between high levels of IgE and wheezing occurring between 6-24 months of age. Possible mechanisms for IgE mediated reactions might include sensitization with aeroallergens during the first year of life predisposing infants to produce large quantities of IgE in response to a variety of antigens. In the present study, six patients (20%) generated specific IgE; however, we did not observe any relation between the presence of specific IgE and wheezing in our patients. Although some studies showed that specific IgE was related with wheezing, we did not find a correlation between RAST specific IgE and wheezing. This finding may be explained with the development of sensitization to a set of various specific allergens changing with age, feeding and genetic predisposition.

ET-1 is a potent bronchoconstrictor agent in lung tissue, exerting its effect via releasing secondary spasmogenic mediators and augmenting cholinergic neurotransmission.¹⁰⁻¹² Similar to IgE, the role of ET-1 in the development of wheezing episodes is not well defined. We found higher plasma ET-1 levels in our patients at the beginning (0 day) and 5th day of the treatment. The present findings indicated that ET-1 may play a role in the pathogenesis of WI. In addition, even though ET-1 lev-

TABLE 4: Age, body weight and height, eosinophil counts, level of serum ET-1 and IgE, urine LTE-4 in gastroesophageal reflux (GER) with wheeze and control groups (mean \pm SD).

	GER with Wheeze	Control subjects	p
Age (month)	11 \pm 5.4	13.6 \pm 5.9	0.112
Body weight (kg)	7.7 \pm 1.9	10.3 \pm 1.5	0.007
Body height (cm)	70 \pm 11.3	76.7 \pm 5.7	0.196
Eosinophil counts (%)	1.3 \pm 1.6	1.3 \pm 1.1	0.946
IgE (ng/ml)	41.7 \pm 70.2	7.7 \pm 8.7	0.021
ET-1 (pg/ml) (Day 0)	5.4 \pm 4.5	2.8 \pm 0.7	0.138
ET-1 (pg/ml) (Day 5)	4.7 \pm 4.1		0.249
LTE-4 (pg. mg-1 creatinine) (Day 0)	792.9 \pm 545.3	758.7 \pm 280.9	0.016
LTE-4 (pg. mg-1 creatinine) (Day 5)	955.9 \pm 457		0.039

els were higher on 5th day of the treatment with regard to day 0, this increase was not statistically significant (Table 2). This condition can be explained with the effect of other cytokines such as interleukin-1 and tumor necrosis factor alpha that might stimulate the production of ET-1 on the fifth day. In addition, we observed steadily increasing levels of ET-1 during the treatment; a finding might be stimulated by other cytokines such as interleukin-1 and tumor necrosis factor alpha. The high serum ET-1 levels did not change with inhaled or systemic steroid therapy (Table 3). Therefore, anti ET-1 therapy may be useful in WI.

Leukotrienes (LTs) consist of 20-carbon unsaturated fatty acids released from membrane phospholipids via the arachidonic acid cascade. The LTE-4 is a potent bronchoconstricting cysteinyl leukotriene and is the end product of cysteinyl leukotriene metabolism.¹³ The role of LTs is controversial in pathogenesis of wheezing infants.^{2,3} Our data here suggests that cysteinyl LTs but not IgE may play a role in the pathogenesis of wheezy infants through induction of smooth-muscle contraction, modulation of vascular permeability and vasoconstriction in addition to the enhancement of mucous secretion and immune modulation. Similar to ET-1, systemic or inhaled steroid therapy did not reduce the urinary levels of LTE-4 in our study (Table 3). The existence of constant levels of Cys-LTs in patients treated with corticosteroids can be explained with the presence of other mediators such as interleukin 3, which may modulate susceptibility to corticosteroids.¹⁴ Taken together, our study indicate that inhaled or systemic steroid treatments do not appear to be useful for reducing levels of LTs in wheezy infants. Therefore, development of selective antagonists is required in these patients.

Although ET-1 possesses similar potency and efficacy on LTs, we found a negative correlation between serum ET-1 and urine LTE-4 levels in our patients on day 0 (Figure 1). This is the first report about relationship between ET-1 and LTE-4 levels in wheezy infants. This evidence also supports the notion that elevated LTE-4 levels do not arise in consequence of elevated ET-1 in WI.

The present study showed that increased serum IgE levels were present in patients generating a good response to inhaled β_2 -agonist with regard to those developing poor a response to inhaled β_2 -agonist ($p= 0.031$). Therefore, we claim that inhaled β_2 -agonist therapy could be beneficial in patients with high serum IgE levels and this can be a guide for individualization of the therapy.

GER is a potential trigger of WI.^{15,16} The possible mechanisms include a vagally mediated reflex, a direct axonal reflex, increased bronchial reactivity with neuropeptides including substance P, neurokinin A and micro aspiration. However, our study showed that high ET-1 levels were not found in patients with GER in comparison to patients without GER and controls. Therefore, ET-1 was not related to inflammations of GER. However, the high levels of serum IgE and urine LTE-4 were associated with GER in our patients. This is the first report on relationship of GER with LTE-4 in children. Elevated IgE levels might be due to exposure to some allergens including food allergens present in the aspirated content. We think that specific IgE should be investigated in WI with GER, especially in hyper-reactivity to food allergens. On the other hand, high urine LTE-4 levels in WI patients with GER can be explained with the presence of neuropeptides that can stimulate leukotriens.¹⁷

It is important to identify children at risk for developing asthma, and to distinguish these from those in whom early wheezing is likely to be transient. The history of parental asthma, presence of eczema in the childhood, allergic rhinitis, >3 wheezing attacks, and eosinophilia might be an indication of infantile asthma development in WI.¹⁸ To date, no diagnostic tools are available that can firmly distinguish transient wheezing from persistent wheezing at an early stage. The present study is the first one showing that high serum IgE levels are as important as high eosinophil counts for determination of developing asthma in patients with wheezing. In addition, we, for the first time, showed that high urine LTE-4 levels may be an important risk factor determinant for development of infantile asthma in WI. Further studies are needed to prove this.

In conclusion, IgE, ET-1 and LTs levels are related to the airway inflammation in WI and only IgE and LTE-4 are related to GER. Steroid therapy does not reduce levels of ET-1 and LTE-4. The serum IgE and urine LTE-4 levels may be useful as new markers for the determination of developing asthma. In-

haled β_2 -agonist (salbutamol), anti-leukotriene and anti-ET-1 therapy seemed to be beneficial in WI.

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REFERENCES

- Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC) Eur Respir J 1998;12(2):315-35.
- Balfour-Lynn IM, Valman HB, Wellings R, Webster AD, Taylor GW, Silverman M. Tumour necrosis factor-alpha and leukotriene E4 production in wheezy infants. Clin Exp Allergy 1994;24(2):121-6.
- Oommen A, Grigg J. Urinary leukotriene E4 in preschool children with acute clinical viral wheeze. Eur Respir J 2003;21(1):149-54.
- Samransamruajkit R, Moonviriyakit K, Vanapongtipagorn P, Prapphal N, Deerojanawong J, Poovorawan Y. Plasma endothelin-1 in infants and young children with acute bronchiolitis and viral pneumonia. Asian Pac J Allergy Immunol 2002;20(4):229-34.
- Halna M, Leblond P, Aissi E, Dumonceaux A, Delepouille F, El Kohen R, et al. [Impact of the consensus conference on the ambulatory treatment of bronchiolitis in infants]. Presse Med 2005;34(4):277-81.
- Perlstein PH, Kotagal UR, Bolling C, Steele R, Schoettker PJ, Atherton HD, et al. Evaluation of an evidence-based guideline for bronchiolitis. Pediatrics 1999;104(6):1334-41.
- Steiner RW. Treating acute bronchiolitis associated with RSV. Am Fam Physician 2004;69(2):325-30.
- Martinez FD. Recognizing early asthma. Allergy 1999;54(Suppl 49):24-8.
- Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics 1991;88(4):834-40.
- Battistini B, Dussault P. Biosynthesis, distribution and metabolism of endothelins in the pulmonary system. Pulm Pharmacol Ther 1998;11(2-3):79-88.
- Hay DW, Henry PJ, Goldie RG. Endothelin and the respiratory system. Trends Pharmacol Sci 1993;14(1):29-32.
- El-Gamal Y, Hossny E, Awwad K, Mabrouk R, Boseila N. Plasma endothelin-1 immunoreactivity in asthmatic children. Ann Allergy Asthma Immunol 2002;88(4):370-3.
- Kumlin M. Measurements of leukotrienes in the urine: strategies and applications. Allergy 1997;52(2):124-35.
- Sebaldt RJ, Sheller JR, Oates JA, Roberts LJ 2nd, FitzGerald GA. Inhibition of eicosanoid biosynthesis by glucocorticoids in humans. Proc Natl Acad Sci U S A 1990;87(18):6974-8.
- Aral YZ, Bahar A. [Gastroesophageal reflux disease in children: four cases admitted with chronic or recurrent respiratory symptoms]. Turkiye Klinikleri J Pediatr 1999;8(1):31-4.
- Sipahi T, Teziç T, İpekçioğlu H, Uzel, G. [Recurrent or persistent lower respiratory tract infections in infancy: a study of 99 cases]. Turkiye Klinikleri J Pediatr 1994;3(3):99-103.
- Stein MR. Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness. Am J Med 2003;115 (Suppl 3A):55S-59S.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133-8.