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HASİBE ARTAÇ

HÜSAMETTİN VATANSEV

DERYA ÇİMEN

DERYA ARSLAN

FATMA KAYA

See next page for additional authors

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Authors

HASİBE ARTAÇ, HÜSAMETTİN VATANSEV, DERYA ÇİMEN, DERYA ARSLAN, FATMA KAYA, SEYİT ALİ KAYIŞ, and BÜLENT ORAN

N-terminal-pro brain natriuretic peptide levels in children with allergic rhinitis

Hasibe ARTAÇ^{1*}, Hüsamettin VATANSEV², Derya ÇİMEN³, Derya ARSLAN³, Fatma KAYA¹, Seyit Ali KAYIŞ⁴, Bülent ORAN³

¹Department of Pediatric Immunology and Allergy, Faculty of Medicine, Selçuk University, Konya, Turkey

²Department of Biochemistry, Faculty of Medicine, Selçuk University, Konya, Turkey

³Department of Pediatric Cardiology, Faculty of Medicine, Selçuk University, Konya, Turkey

⁴Department of Biostatistics, Faculty of Medicine, Karabük University, Karabük, Turkey

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Background/aim: Persistent upper airway obstruction may lead to increased pulmonary arterial pressure (PAP). The aim of this study was to evaluate N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations and PAP values in children with allergic rhinitis.

Materials and methods: Sixty-six patients with allergic rhinitis and 22 healthy children were prospectively enrolled in this study. Plasma NT-proBNP levels were measured at first admission and after treatment. Simultaneously, echocardiography was done to assess pulmonary arterial hypertension, and rhinitis symptom scores were recorded.

Results: The median age of the study group was 9.0 (5.0-17.0) years; 26 were female. PAP was found to be normal in all the patients. There was a negative correlation between age and NT-proBNP levels ($r = -0.452$, $P < 0.01$). Nasal blockage levels affected NT-proBNP levels mildly ($P = 0.067$). No significant difference between before and after nasal steroid treatment was observed in NT-proBNP levels.

Conclusion: These results suggest that NT-proBNP level and PAP may not be affected in children with allergic rhinitis, and primarily this influence may be associated with the severity of nasal obstruction.

Key words: Allergic rhinitis, pulmonary arterial pressure, N-terminal pro B-type natriuretic peptide, nasal obstruction, cardiac evaluation

1. Introduction

Allergic rhinitis (AR) is the most common chronic disease induced by an immunoglobulin E (IgE)-mediated reaction to environmental aeroallergens (1). Although this condition is not fatal, it is associated with many comorbidities, such as asthma, sinusitis, dermatitis, and conjunctivitis, which may accompany the disease at different ranges (2,3). In addition, allergic rhinitis is one of the frequent causes of persistent upper airway obstruction by nasal blockage in childhood. Persistent upper airway obstruction may lead to increased pulmonary arterial pressure (PAP). Previous studies have shown that obstruction of the upper airways is related to pulmonary arterial hypertension (PAH) in some patients with AR (4-6).

N-terminal pro brain natriuretic peptide (NT-proBNP) is a product of the cleavage of the cardiac prohormone pro B-type natriuretic peptide into its active form. It has proven to be a useful biomarker in children with cardiac disease (7). Studies have demonstrated significant correlations between BNP levels and mean PAP as well as pulmonary vascular resistance (8,9). Additionally, NT-proBNP has a

prognostic role, and it offers a noninvasive test that can be used to guide therapy in patients with PAH (8).

There is no clear evidence as to whether nasal obstruction in allergic rhinitis affects PAP and NT-proBNP levels or not. The aims of the present study were 1) to measure plasma NT-proBNP levels, 2) to evaluate pulmonary arterial pressure in children with AR, 3) to determine the correlation between these parameters and the severity of AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification, and 4) to assess varieties of posttreatment.

2. Material and methods

2.1. Study population and data collection

The study population included 66 patients diagnosed with allergic rhinitis. Twenty-two healthy children served as controls. Demographic characteristics (sex, age, height, and weight), family history of allergic disease, and the presence of other allergic diseases were evaluated. Rhinitis was classified according to the ARIA report (10). Children were considered to be suffering from AR if they had i)

* Correspondence: hasibeartac@yahoo.com

suggestive symptoms of rhinitis that should be related to skin prick test results and ii) at least 1 positive skin prick test and/or serum specific IgE to an allergen locally relevant. AR symptoms were assessed using the total 4 symptoms scores (T4SS) for nasal obstruction, rhinorrhea, nasal itching, and sneezing. Each nasal symptom was scored on a scale from 0 to 3 (0, no symptoms; 1, mild; 2, moderate; 3, severe), resulting in a T4SS ranging from 0 to 12. Severity was also assessed by the patient by means of a visual analogue scale (VAS), from 0 to 100. Patients who had received any treatment for their AR during a minimum 2-week period previously and who displayed the presence of other causes of upper airway obstruction, such as nasal polyp, sinusitis, and adenotonsillar hypertrophy, were excluded from this study. We also excluded children who had any comorbidities, including obesity and gastroesophageal reflux.

The diagnosis of asthma was based on medical history and physical examination as described in the Global Initiative for Asthma (GINA) consensus report (11). Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka (12). The study was approved by the local ethics committee of Selçuk University Medical Faculty. Informed consent was obtained from all the parents of the children before the study commenced.

2.2. Laboratory studies

Total serum IgE levels were measured by nephelometry, using commercially available kits (Date Behring Marburg GmbH, Marburg, Germany). Skin prick testing (SPT) was performed with 10 common aeroallergens, including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria*, *Cladosporium*, *Betulaceae*, a mixture of 5 trees (alder, elm, hazel, poplar, willow), a mixture of 4 cereals (oak, wheat, barley, rye), a mixture of 6 grasses (velvet grass, orchard grass, rye grass, timothy, blue grass, meadow fescue), *Salicaceae*, and latex (Allergopharma, Reinbek, Germany). A histamine solution (10 mg/mL) and saline served as positive and negative controls, respectively. The size of the wheal was measured after 15 min. A diameter of ≥ 3 mm was considered a positive reaction.

Venous blood samples were obtained at first admission and at the end of the first month after treatment in patients who had taken nasal corticosteroid therapy (mometasone furoate, 100 μ g per day, 1 puff in each nostril, in the evening for 4 weeks). Plasma samples were isolated within 2 h of collection from the patient and immediately stored at -80 °C. Plasma NT-proBNP levels were measured with ECLIA (electrochemiluminescence immunoassay) using Elecys ProBNP (Roche Diagnostics Inc.).

All patients were examined by pediatric cardiologists. A Toshiba system ultrasonic imager with a pediatric probe (3.5–7.5 MHz) was used for echocardiographic assessment.

The echocardiograms were obtained in the standard precordial positions, following the recommendations of the American Society of Echocardiography (13). Continuous wave Doppler echocardiography was used to estimate pulmonary arterial pressure and to measure right ventricular preejection period, ejection time, acceleration time, and correct acceleration time. In all the patients, mean pulmonary arterial pressure was estimated by measuring peak systolic acceleration time of the pulmonary artery described by Liu et al. (14) as: pulmonary arterial systolic pressure = $(55 \times \text{preejection period/acceleration time}) - 10.8$. A standard precordial short-axis view of the heart was used for echocardiographic examination. Pulmonary arterial hypertension in children was defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest (15).

2.3. Statistical analysis

All analyses were carried out using Minitab software (Release14)(16). The Anderson–Darling normality test was performed to obtain the distributional properties of data. Necessary response variables were log transformed and parametric tests were employed if the resultant variables were normally distributed; otherwise nonparametric tests were used. Pearson correlation was employed to study the relationship between variables. Pre- and posttreatment measurements were compared using the Wilcoxon signed-rank test. Covariance analysis was performed by fitting age as a covariate to evaluate the effects of explanatory factors on the response variables. $P < 0.05$ was accepted as statistically significant.

3. Results

3.1. Patients' characteristics

The median age of the study group was 9.0 (5.0–17.0) years, 26 of whom were female. No significant differences were observed between the study group and controls for age or sex ($P > 0.05$). The characteristics of the study population are summarized in Table 1.

According to the ARIA classification, the most frequent forms of AR were mild-persistent (33%) followed by moderate-severe persistent (32%), mild-intermittent (28%), and moderate-severe intermittent (6%) rhinitis. The 25 subjects with moderate-severe AR were treated with nasal steroid and leukotriene receptor antagonist (montelukast). Five subjects with severe nasal obstruction required only nasal steroid therapy. Pollen sensitivities were detected in the majority of patients (71%). Fifteen patients were polysensitized; the others had sensitivities to 3 molds and 1 mite.

Twenty-four patients suffered from asthma (36%). When patients were classified according to clinical features, half of them had mild-persistent asthma, followed by mild-intermittent (46%) and moderate-persistent (4%).

Table 1. Demographic and clinical characteristics of the study population.

Patients	Results
Age in years median (min.–max.)	9.0 (5.0-17.0)
Sex (male/female)	40/26
The median duration of symptoms (years)	2.0 (1.0-10.0)
Family history of allergic diseases	41 (62%)
The presence of asthma	24 (36%)
ARIA classification	
Mild-persistent	22 (33%)
Moderate-severe persistent	21 (32%)
Mild- intermittent	19 (28%)
Moderate-severe intermittent	4 (6%)
Skin prick test	
Pollen	47 (71%)
Polysensitized	15 (22%)
Mold	3 (4.5%)
Mite	1 (1.5%)

These subjects had taken a low-dose inhaler steroid (58%), moderate dose inhaler steroid (4%), and the others had symptomatically used an inhaler with short-acting B2 agonist (42%).

Significant differences were observed in pre- and posttreatment total 4 symptoms scores ($P < 0.001$, median (min.–max.) for: pre-T4SS: 7.00 (2.00–9.00) and post-T4SS: 5.00 (0.00–7.00). Visual analogue scores significantly

changed after treatment ($P < 0.001$, median (min.–max.) for pre: 80.0 (30.0–100), post: 40.0 (10.0–85.0). T4SS significantly correlated with VAS ($r = 0.71$, $P < 0.001$).

3.2. Pulmonary arterial pressure and NT-proBNP levels

Pulmonary arterial pressure was found to be normal in all the patients. Echocardiographic analysis showed that the subjects with AR who suffered from asthma had normal pulmonary arterial pressure.

No significant differences were detected in NT-proBNP levels between patients and controls at first evaluation (49.5 pg/mL in patients and 54.5 pg/mL in controls) (Table 2). There were also no significant differences in 30 patients who received nasal steroid therapy after treatment compared with pretreatment ($P = 0.45$). The Pearson correlation study indicated a negative relationship between age and NT-proBNP levels ($r = -0.452$, $P < 0.01$) (Figure). Covariance analysis showed that nasal obstruction was related to NT-proBNP levels. However, it was not statistically significant ($P = 0.067$). NT-proBNP levels did not vary significantly in patients with AR in the presence of asthma ($P = 0.64$).

4. Discussion

In this study, we observed that pulmonary arterial pressure and plasma NT-proBNP levels were normal in patients with allergic rhinitis compared with healthy controls. Our study population had no comorbidities such as obesity or other causes of upper airway obstruction, including adenotonsillar hypertrophy. These results suggest that NT-proBNP levels and PAP may not be affected in children with AR, and primarily this influence is associated with the presence of nasal obstruction.

Table 2. Hemodynamic and echocardiographic parameters in the patients with allergic rhinitis and controls.

Characteristics	Patients	Control	P ^a
	Median (min.–max.)	Median (min.–max.)	
NT-proBNP (pg/mL)	49.5 (5.0-318.0)	54.5 (5.0-229.5)	0.56
MPAP (mmHg) ^c	12.05 (7-21)	13.77 (12-17)	0.13
SPAP (mmHg) ^c	21.22 (14-30)	22.99 (21-27)	0.77
Nasal steroid therapy	Before treatment Median (min.–max.)	After treatment Median (min.–max.)	P ^b
NT-proBNP (pg/mL)	42 (9-176)	39.5 (7-128)	0.45
MPAP (mmHg) ^c	12.2 (9-2)	12.4 (9-13)	0.46
SPAP (mmHg) ^c	21.1 (12-27)	21.7 (17-27)	0.80

^a P values from the Mann–Whitney U test.

^b P values from the Wilcoxon signed-rank test.

^c MPAP, mean pulmonary arterial pressure; SPAP, systolic pulmonary arterial pressure.

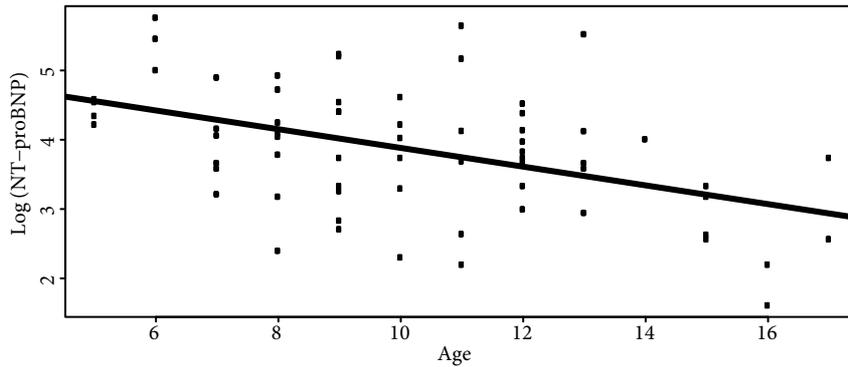


Figure. Correlation between NT-proBNP and age in the allergic rhinitis group. The Pearson correlation coefficient between NT-proBNP and age indicates a negative statistically significant relationship ($r = -0.452$, $P = 0.003$).

Elevation of PAP is the first step in findings leading to cor pulmonale and congestive heart failure. It has been reported that chronic upper airway obstruction, especially in children with obstructive sleep apnea, is related to an increase in PAP (17), that children with adenoid and/or tonsil hypertrophy had higher PAP levels when compared with healthy controls, and that their increased PAP decreased to normal levels after adenotonsillectomy (18,19). In the current literature, in limited studies featuring small numbers of patients, it has been reported that allergic rhinitis may lead to increased pulmonary arterial pressure in children, which could be reversed after medical treatment (4,5). In our study, pulmonary arterial pressure was found to be normal in children with symptomatic allergic rhinitis. The mean ages and symptom durations were similar in all studies. We speculate that allergic rhinitis might lead to increased PAP in severe upper airway obstruction at the late stage of the disease.

NT-proBNP levels have a diagnostic role in multiple conditions, including coronary artery disease, congestive heart failure, right ventricular dysfunction, and PAH (8). Although studies are lacking in children, data indicate that NT-proBNP can be used to monitor treatment effects and predict mortality in pediatric PAH (20). A study by Oran et al. (18) found that increased PAP and serum prohormone concentrations were reversible after surgery in 20 children with adenotonsillar hypertrophy. In our study, it was

detected that serum prohormone level is associated with the presence of nasal obstruction in patients with allergic rhinitis. Although the visual analogue scores and T4SS significantly decreased after 4 weeks of treatment, there was no change in NT-proBNP levels. These findings show that NT-proBNP levels correlate with the severity of upper airway obstruction, but prohormone levels are not affected in allergic rhinitis with mild obstruction.

Severe upper airway obstruction, such as adenoid hypertrophy, may lead to hypoxic pulmonary vasoconstriction and also elevated PAP with high pulmonary vascular resistance (21). Because of the absence of cardiovascular system-related symptoms in this period, it is not clear which patients should undergo a Doppler echocardiography examination. However, there have been a few clinical investigations supporting the increased PAP in allergic rhinitis. In light of these studies, Doppler echocardiography may be considered in selected patients with AR, especially for those who have severe nasal obstruction. NT-proBNP may be useful in order to determine the timing of cardiac evaluation.

NT-proBNP is a prognostic biomarker in diagnosing and managing right ventricular dysfunction and pulmonary hypertension. Further studies are needed to clarify the relationship between NT-proBNP levels and the severity of nasal obstruction in children with allergic rhinitis.

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