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ORIGINAL ARTICLE

Receptor of advanced glycation end products in childhood asthma exacerbation

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KEYWORDS

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Abstract *Background:* Receptor of advanced glycation end products (RAGE) is a new marker of inflammation in different inflammatory disorders. Bronchial asthma as an inflammatory disease is associated with increased levels of many markers of inflammation which are used to evaluate the severity of childhood asthma, and may be the targets of new therapeutic options aiming at improving the management of such diseases.

Aim: To evaluate serum levels of RAGE in acute asthma exacerbation in children, and also to correlate their levels with peak expiratory flow rate (PEFR) and number of exacerbations during the last 6 months.

Methods: One hundred asthmatic children, aged 6–12 years, with acute exacerbation were evaluated during their visit to ER unit for serum RAGE (measured by ELISA) and PEFR before receiving any treatment. They were 53 males and 47 females. Fifty subjects were taken as controls for serum RAGE.

Results: Serum RAGE was significantly higher in asthmatic children compared to control group. It was higher in asthmatic children who had poor response to initial therapy at emergency room. Serum RAGE showed significant negative correlation with PEFR and significant positive correlation with a number of asthma exacerbations during the last 6 months.

Conclusion: Serum RAGE is elevated during acute asthma exacerbation in children. High levels above 1733.5 pg/mL can expect poor response to initial therapy at emergency room and need for hospitalization with sensitivity and specificity and a specificity of 90.5% and 83.35% respectively.

Introduction

Bronchial asthma is by far the most common chronic disease of childhood and it is considered to be the leading cause of childhood morbidity caused by chronic diseases leading to

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absence from school, emergency department (ER) visits and hospitalization [1].

Asthma exacerbation is a well known factor that can increase the risk of asthma mortality [2].

As an inflammatory disease, pediatric asthma was associated with high levels of many inflammatory markers [3,4].

The receptor for advanced glycation end products (RAGE), a member of the immunoglobulin superfamily of cell surface molecules, is involved in the signal transduction from pathogen substrates to cell activation during the onset and continuation of inflammation [5].

Its involvement in inflammation has been suggested, that RAGE is upregulated in all inflammatory lesions studied, including rheumatoid arthritis, inflammatory kidney disease, arteriosclerosis, inflammatory bowel disease and others [6].

RAGE was first identified in lung tissue, it is located on the basolateral membranes of alveolar epithelial type I cells but RAGE mRNA has also been found in alveolar epithelial type II cells [7].

The aim of this study was to evaluate the serum levels of RAGE in asthmatic children during exacerbation compared to control subjects and find a relationship between these levels and outcome of asthma exacerbation.

Subjects and methods

This study was carried out in Pediatric Department, Tanta University Hospital, Egypt between June 2013 and December 2013.

We examined 100 children attending the emergency room of Pediatric Department with asthma exacerbations. A control group consisting of fifty age and sex matched children was included in our study.

Written informed consents were obtained from parents of all children.

Inclusion criteria of patients:

- Age was ranging from 6 to 12 years.
- Diagnosis of bronchial asthma according to GINA guideline and National Asthma Education and Prevention Program, 2007.
- Patients were coming to emergency room due to exacerbation of their asthma.

Exclusion criteria:

- Patients with other pulmonary disorders as bronchiectasis and cystic fibrosis.
- Children below 6 years or above 12 years of age.
- Children of control group had no chest troubles and negative history of steroid use in last 6 months. All of them had negative personal and family history of wheezy chest, asthma or nebulizer use before.

All subjects had detailed history taking, and thorough clinical examination. Peak expiratory flow rate (PEFR) was measured in all of them.

Blood samples were taken from all patients in the ER unit during acute asthma exacerbation before any rescue medication was given to them.

Patients were given standard treatment of asthma exacerbation and then re-assessed after 1 h for response to initial therapy. Children with good response are who did not need admission and with no return of exacerbation for 1 week. Children with poor response are who needed admission to the hospital or returned back within 1 week with another exacerbation.

Determination of RAGE serum level: estimation of RAGE in the serum pg/mL by enzyme immunoassay supplied by RayBiotech, Inc.

The RayBio® Human RAGE ELISA (Enzyme-Linked Immunosorbent Assay) kit is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human RAGE in serum. This assay employs an antibody specific for human RAGE coated on a 96-well plate. Standards and samples are pipetted into the wells and RAGE present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated anti-human RAGE antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and color develops in proportion to the amount of RAGE bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm.

Results

One hundred children with asthma exacerbation and fifty control children were included in our study. The demographic data and peak expiratory flow rate (PEFR) of both patients and control are demonstrated in Table 1.

Mean RAGE serum levels were 1770.1 ± 423.3 pg/mL in children with asthma exacerbation, and 745 ± 224.6 pg/mL in control children (Table 2).

Serum RAGE levels showed significant negative correlation with PEFR and significant positive correlation with a number of asthma exacerbations during the last 6 months before inclusion in the study (Table 3).

After initial therapy in the emergency room, 55 patients showed good response and 45 patients showed poor response.

Table 1 Demographic data and peak expiratory flow rate (PEFR) of the studied subjects.

	Control (No = 50)	Asthmatic (No = 100)	*t*	*p*
Age in years	8.1 ± 1.8	8.2 ± 2.1	1.1	0.28
BMI in kg/m^2	20.8 ± 3.8	21.3 ± 4.2	1.2	0.25
Male/female	24/26	53/47	χ^2 = 1.6	0.48
Age at time of diagnosis	–	3.2 ± 1.6		
Associated nasal allergy	–	55%		
Immediate family history of asthma	6%	58%		
Blood eosinophils %	2.1 ± 0.3	7.1 ± 2.4	5.6	0.009*
PEFR (% of predicted)	93.1 ± 8.3	48.2 ± 6.4	6.3	0.008*

* Significant.