International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 6 Issue 4 ǁ April 2017 ǁ PP. 10-16

Exhaled Nitric Oxide among Bulgarian Children with Asthma Exacerbation

[1]Dr. Rada M. Markova, M.D, PhD ,
[2]Assoc. Prof. Dr. Milka Markova, M.D, PhD
[1]MC" First Pediatric Consultative Clinic – Sofia, Bulgaria
[2]Clinical Laboratory - University Hospital for Pulmonary diseases "St. Sophia" , MC "First pediatric consultative clinic" – Sofia

Resume: *Bronchial asthma is the most common chronic disease of childhood. Exhaled nitric oxide (FeNO) is an important method to measure airway inflammation non-invasively. We propose that FeNO should be used as an additional tool for asthma diagnosis and treatment plan.*
Keywords: *bronchial asthma, children, FeNO*

I. Introduction

Bronchial asthma is the most common chronic disease of childhood. Asthma severity can be monitored by clinical symptoms, questionnaires and pulmonary function tests (spirometry). Exhaled nitric oxide (FeNO) is a proposed method to measure airway inflammation non-invasively. FeNO is proved to be a very important molecule in evaluation of allergic inflammation of the lungs. Traditional asthma treatments are typically adjusted in asthmatic children using symptoms and spirometry. Treatments tailored in accordance to inflammatory markers, such as fraction of exhaled nitric oxide or sputum eosinophils, are increasing in use. We propose that FeNO should be used as an additional monitoring tool for asthma diagnosis and treatment plan.
The aim of our study is to investigate FeNO values among 126 patients with bronchial asthma and asthma exacerbation for one year period, 10 healthy controls and 15 controls with cystic fibrosis. To evaluate some clinical, laboratory, and functional parameters and their correlation with FeNO. To follow up asthmatics in a 3 month period in a condition of a clinical remission.

II. Methods

FeNO was measured by a single breath on-line measurement with "Nioxmino" device (Aerocrine) with normal values for children: 5-15 (20 ppb). The performed lab tests include: Leukocyte count (WBS), erythrocyte sedimentation rate (ESR), CRP, total IgE levels (ELISA). For all asthmatics and control groups pulmonary function tests (PFT) were performed. Blood and sputum eosinophils (nasal smear eosinophils) were investigated trough a light microscopy. Some of the etiology agents of asthma exacerbation were determined including: respiratory viruses – RSV, Parainfluenzavirus, Influenzavirus, Adenovirus, Mycoplasma pneumonia and Chlamydia pneumonia (ELISA method).

III. Results of the study

Our results regarding the patient's age demonstrate that all 151 patients (126 asthmatics and 25 controls) are distributed between 5 and 23 years, with mean age of 10.38 years. Distribution of patients according to the patient's gender show a domination of males with 62.91%, on opposite : 37.09% are females (fig.1)

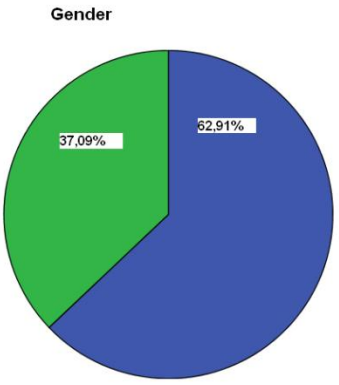

Fig.1 – Gender distribution

Family history for asthma and allergic diseases is observed in 58.94% of asthmatic patients (fig. 2)

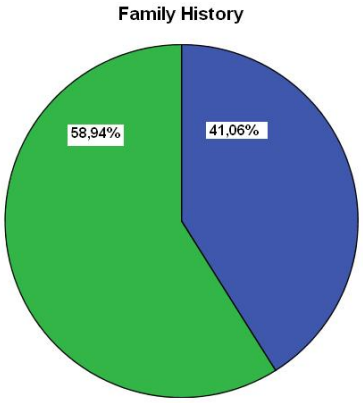

Fig.2 – Family history for asthma and allergic diseases

Asthma duration is determined as an interval from asthma diagnosis regarding ERS/ATS criteria , to FeNO measurement . The asthmatic patients can be divided into 3 groups:
- group "0": up to 6 months from the diagnosis (18.2% of all patients)
- group"1": 31% of the asthmatics – asthma duration 6 months up to 5 years
- group"2": 50.8% of the asthma patients – asthma diagnosis more than 5 years (fig. 3)

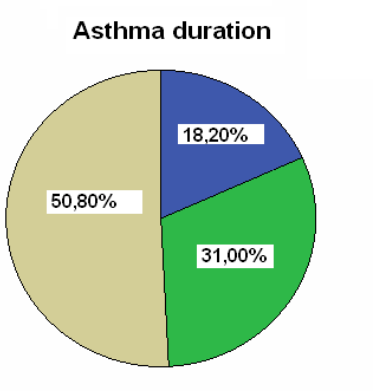

Fig. 3 – Asthma duration

In our study most of the patients, hospitalized due to asthma exacerbation (82.54% of the cases) did not receive steroid .For the rest 17.46% a systemic steroid was given (fig. 4).

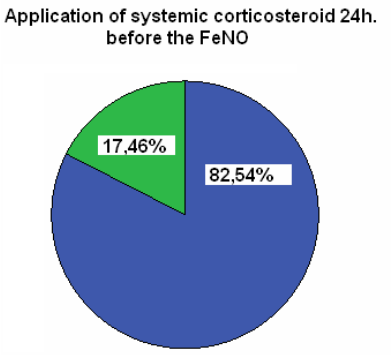

Fig. 4 – Application of corticosteroid before FeNO measurement

Before the hospital admission asthma control medication appear in the followed configuration:
- Group "0" – without control medication
- Group "1" – leukotriene modifier :Montelukast
- Group "2" – inhaled corticosteroid (ICS)
- Group "3" – ICS+ long acting beta $_2$ – agonists (LABA)
- Group "4": ICS+ Montelukast

Regarding our results , 41.27% of hospitalized asthmatic children have no asthma control medication prior to the FeNO measurement (fig.5).

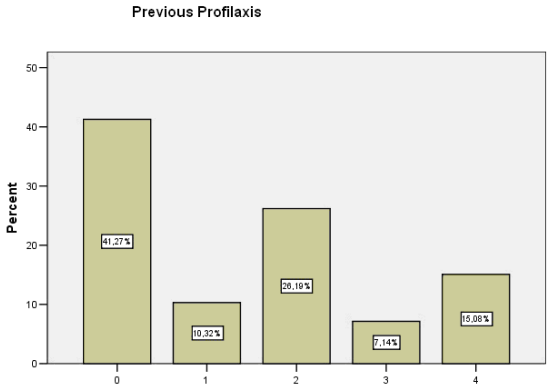

Fig. 5 – Asthma control medication before the hospital admission

There is a strong correlation between asthma duration and asthma control medication: (Fisher‘s exact test: p<0.001): longer asthma duration corresponds with more children that are receiving asthma control medications. We find an association of asthma and allergic rhino sinusitis : 45.24% of the children with asthma also have an allergic rhino sinusitis (fig.6)

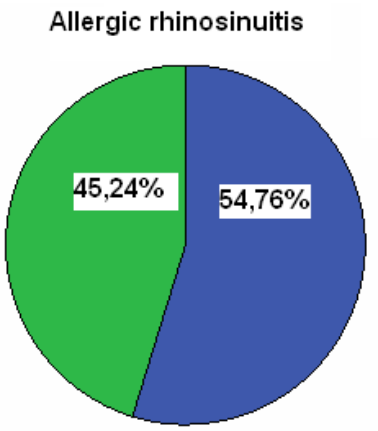

Fig. 6 – Allergic rhinosinuitis and asthma

Blood eosinophils are also a part of allergic inflammation. We found that this parameter has a broad variety and is less specific for an allergic inflammation. Our results shown mean eosinophil count 3.71%, median 2.00% with very high standard deviation 4.081(fig.7).

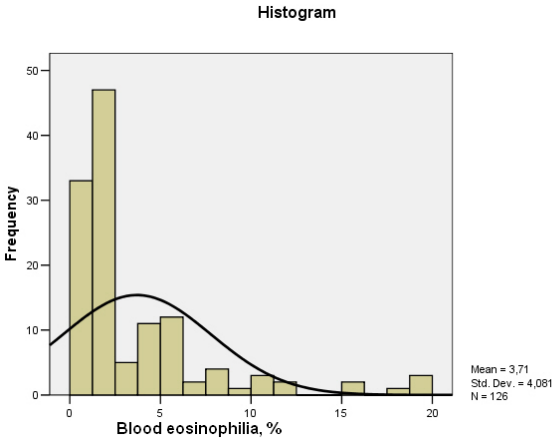

Fig. 7 – Distribution of blood eosinophilia

Local tissue inflammation is assessed by sputum or nasal eosinophilia. 15.1% of asthmatics are able to deliver a sputum, for other 84.9% – a nasal swab from the middle nasal channel for eosinophils is taken. Mean value for nasal swab eosinophils is 4,66%, for sputum eosinophils: 2,26% (fig.8).

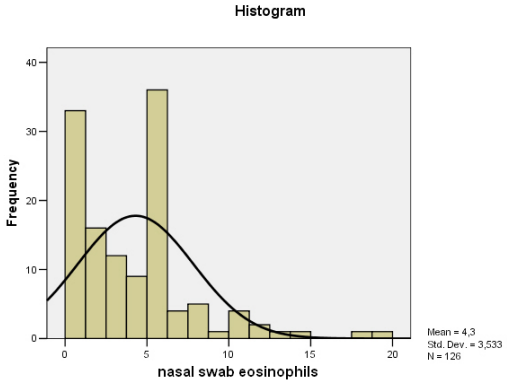

Fig. 8 – Distribution of nasal eosinophilia

For all patients with bronchial asthma leukocyte count, erythrocyte sedimentation rate (ESR), and C – reactive protein (CRP) are investigated. All CRPs are negative, mean leukocyte count is 9,49x10 ^{9}, mean ESR:11,89 mm (Panchenko).
For 91 children of all 123 patients with asthma a total IgE levels are investigated (with normal values up to 100 IU/ml).Mean value for total IgE is 252.69 U/ml – elevated for asthmatics with standard deviation 250.34 U/ml(fig.9).

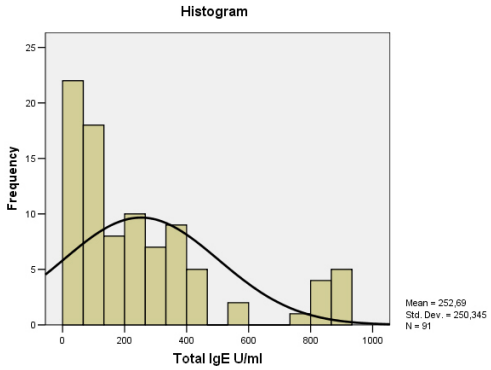

Fig. 9 –Histogram distribution and statistical data for total IgE

Three groups of patients are included in the clinical study:
"0" – healthy controls,"1" – asthmatics; "2" – cystic fibrosis patients (fig.10)

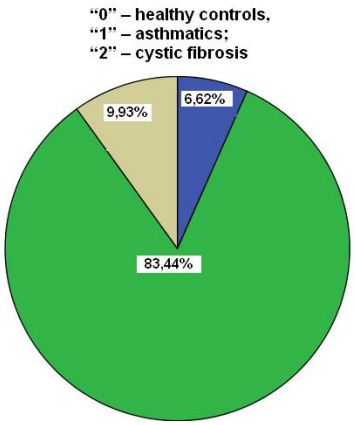

Fig.10 - Distribution of tree groups in the study

The mean values of FeNO in the three groups are completely different:8.30 ppв in healthy controls, 31.67 ppb in asthmatics and 7.07 ppв for the cystic fibrosis group .Statistically significant difference is found between groups "0" and "1" (P < 0.0001) and "1" and "2", but no such difference between groups "0" and "2". No significant difference between healthy controls and patients with cystic fibrosis.
In 151 patients (asthmatics and control groups) FeNO is measured by a single breath on-line method. In a 3-month period FeNO is repeated for asthmatic group in status of clinical and PFT remission (fig.11) .

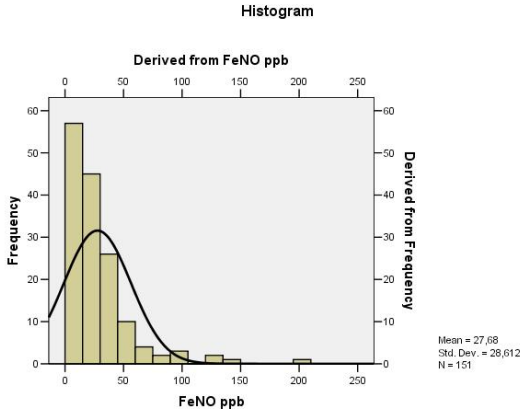

Fig. 11 –Histogram distribution for FeNO

FeNO , followed up in a 3 month interval show a decrease of the mean values from 27.68 ppb to 17.21 ppв (Wilcoxon test :a statistically significant difference).
We find out a correlation between the age in years and FeNO values with statistical coefficient r=0.319. There is a positive and strong linear correlation between the age and FeNO values (p<0.0001, r=0.319) .

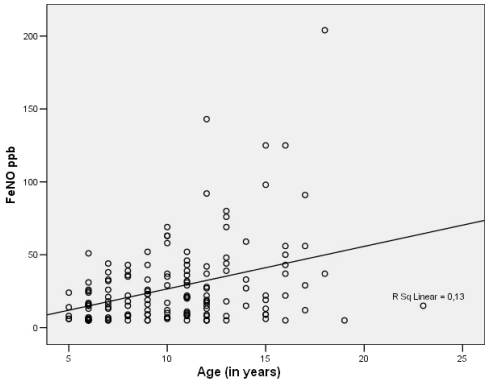

Fig. 12 – FeNO and age correlation

Also we find out a positive linear correlation between nasal eosinophils and FeNO values with r=0.396 (fig.13).

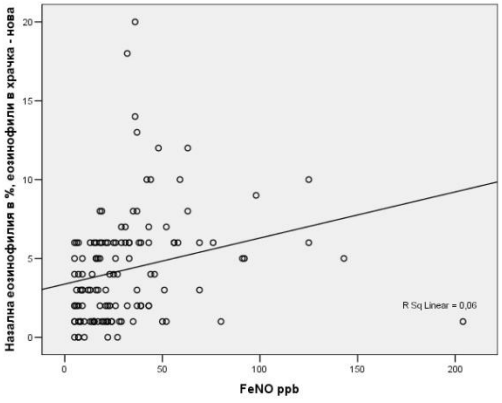

Fig. 13 – FeNO and nasal eosinophils

The structure and distribution of asthma control medication is different after the hospital discharge of the patients: the part of non-treated asthmatics decrease, the part of ICS group and Montelukast group increase (fig.14).

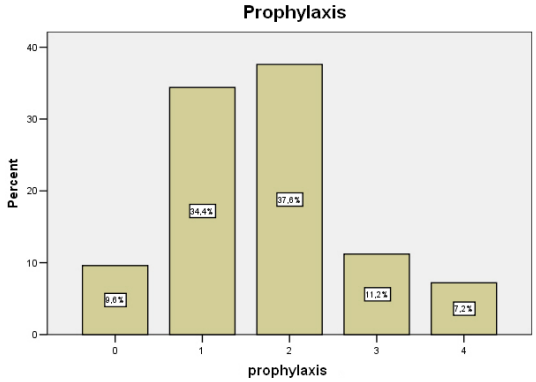

Fig. 14 – Distribution of asthma control medication after the hospital discharge

In order to find out the etiology of asthma exacerbations some serological tests (ELISA) are performed for: RSV, Adenovirus, Chlamydia pneumoniae, Mycoplasma pneumoniae, Influenzavirus and Parainfluenzavirus: IgM and IgG antibodies.

In 9.52% of asthmatics an acute RSV infection is found (/+/ IgM) and almost ½ have positive IgG antibodies (42.1%) for RSV. No acute Adenovirus infection is found, positive /+/ IgG in 22.2%. Positive /+/ IgG for Chlamydia pneumoniae in 4%of cases, M.pneumoniae: /+/ IgM in 0.8%, /+/IgG in 3.2% , Influenzavirus :/+/IgG in 1.6% and Parainfluenzavirus: /+/IgG in 19.8%.

PFTs (spirometry) is performed before hospital admission and in a 3-month interval in a condition of a clinical remission : a statistically significant reverse correlation is found between FeNO values and FEF25/75, and positive between PEF and FEF25/75, and FEV1 and FEF25/75.

IV. Conclusion

We receive some data regarding FeNO values for bulgarian asthmatics and their follow up in a 3 month period . FeNO is significantly higher in the asthmatic group compared with the control groups. There is a positive linear correlation between age and FeNO values. Male gender is dominating among asthmatics. Positive family history is observed in over ½ of the asthmatic patients . Upper respiratory airways are involved in 46.24% of asthmatics with allergic rhino sinusitis. Lots of the asthmatics have a long duration of bronchial asthma (more than 5 years). Mean values of IgE total are increased in the group of asthmatics . The FeNO ‘s mean values are 27.68 ppв . The 3 month follow up shows significantly decrease of the mean FeNO values from 27.68 to 17.21 ppв in asthmatic group. The serological tests for viruses show the leading role of a passed RSV infection , followed by Adenovirus and Parainfluenzavirus. FeNO is an important marker of allergic inflammation. Asthma diagnosis is mainly a clinical one and it is based on a complex assessment, clinical, laboratory data and physical examination.

References

[1]. Генкова Н., Бошева М. Измерване на азотния оксид в издишания въздух при деца – неинвазивен маркер на възпалението на дихателните пътища, 2015 г, Наука пулмология, кн. 3, стр. 25-30

[2]. Генкова Н. Роля на нивата на азотния оксид в издишания въздух за диагнозата на някои белодробни заболявания във възрастта 5-18 години – Дисертационен труд – 2016 г – МУ – Пловдив

[3]. Люцканова Ц., М. Бошева, Н. Генкова. Промени в нивото на IgE у деца с бронхиална астма, Българска медицина, том III, бр. 1–2, стр 28–30. 5

[4]. Милева Ж, Попов Т, Станева М.,”Честота и характеристика на алергичните болести в България”, Алергия и астма, 2000, прил. 1;3-32.

[5]. Alving K, Janson C, Nordvall L. Performance of a new hand – held device for exhaled nitric oxide measurement in adults and children, Respir Res 2006; 7:67

[6]. Baraldi E, Azzolin NM, Cracco A, Zacchello F. Reference values of exhaled nitric oxide in healthy children 6-15 years old. Pediatr Pulmonol 1999; 27:54-58

[7]. Culotta E, Koshland DE: NO news is good news,Science“ 1992; 258:1862-1865.

[8]. ERS Handbook Paediatric Respiratory Medicine. Chapter: Exhaled nitric oxide, induced sputum and exhaled breath analysis.

[9]. Franklin PJ, Taplin R, Stick SM. A community study of exhaled nitric oxide in healthy children. Am J Respir Crit Care Med 1999; 159:69-73
[10]. Genkova N, M. Todorova, B. Marinov et al. Exhaled nitric oxid is associated with pseudomonas aeruginosa infection and peripheral airway obstruction in cystic fibrosis, J of Cystic Fibrosis, 2013 (Supp.1), ISSN1569-1993
[11]. Kharitonov SA, Gonio F, Kelly C, et al. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. Eur Respir J 2003; 21:433-438
[12]. Pijnenburg MW, Bakker EM, Hop WC, et al. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial.Am J Respir Crit Care Med 2005; 172:831-836
[13]. Pizzichini E, Pizzichini MM, Efthimiadis A, et al. Measuring airway inflammation in asthma; eosinophils and eosinophilic cationic protein in induced sputum compared with peripheral blood. J Allergy Clin Immunol 1997; 99:539-544