CORRELATIONS BETWEEN DEMOGRAPHIC FACTORS, SPIROMETRY, EXHALED NITRIC OXIDE AND SEVERITY LEVEL IN CHILDREN WITH ASTHMA AND/OR RECURRENT WHEEZING

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Keywords: *asthma, demographic, spirometry, nitric oxide*

Abstract: *The purpose of this paper is to demonstrate the existence of correlations between demographic factors (age, gender, origin environment), family history, forced expiratory volume per second (FEV), concentration of exhaled nitric oxide (FENO) and asthma severity. There were included in the study 90 children diagnosed with asthma in different stages of severity or with recurrent wheezing. As findings, the following were revealed: one cannot say that there is an association between the type of asthma and gender ($p = 0.423$), origin environment ($p = 0.678$), existence of prior family medical history ($p = 0.254$), normalized or increased values of nitric oxide in exhaled air at 3 months after initiation of background therapy ($p = 0.078$) or between the type of asthma and normalization or decrease of FEV after 3 months of background treatment initiation ($p = 0.276$), but it can be said that there is an association between asthma type and age ($p = 0.001$), thus in the age group ≤ 10 years, recurrent wheezing is predominating (55.6% of cases) and in the age group > 14 years intermittent bronchial asthma is prevalent (56.3% of cases).*

INTRODUCTION

Asthma is a "chronic inflammatory airway abnormality", occurring in many cells, including mast cells and eosinophils; in individuals prone to this inflammation, it generates symptoms that are usually associated with extended obstruction of airways, although variable that is often reversible either spontaneously or with treatment, which increases the reactivity of the airways to various stimuli" (Bethesda International Consensus 1992).(1)

Special attention is paid to the imbalance between T helper 1 lymphocytes (LyTh1) and T helper 2 lymphocytes (LyTh2) and type of cytokines released by these cells (IL-4, IL-17, ITF-γ etc.).(2)

Classification of asthma according to etiology mentions the following categories:

- *Persistent or recurrent wheezing* is a state preceding the development of asthma, representing 40% of all patients with wheezing, starting under the age of 3 and persisting over the age of 6. It may be allergic (in this case, patients have elevated total IgE and eosinophils) or viral after infections (case in which intra/postinfectious bronchial hyperresponsiveness occurs);
- *Viral/intrinsic induced asthma* (patients have usually normal levels of total IgE and eosinophils);
- *Allergic/extrinsic asthma* (patients have usually elevated total IgE and eosinophils);
- *Effort asthma* that occurs in some patients during physical exercise; these patients being able to associate some predisposing factors, namely allergy/infections.(3,4)

Classification of asthma by severity is made clinically by evaluating the frequency of symptoms day and night, impaired daily activities and sleep and by evaluating the frequency of exacerbations and the need to use "attack" medication (bronchodilators) and paraclinically, by the influence on the ventilation parameters determined by spirometry. Based on these criteria, the following categories are being described:

- *Intermittent asthma;*
- *Mild persistent asthma;*
- *Moderate persistent asthma;*
- *Severe persistent asthma.(3,4)*

In terms of clinical manifestations, asthma is characterized by recurrent episodes of expiratory dyspnea, coughing and wheezing that occur predominantly at night (due to the predominant activity of the cholinergic system during this period), but also during exposure to various allergens or viral infections or to effort.(3,4)

Lung function investigations in asthma refers to determining the ventilation parameters allowing the assessment of lung function damage and of obstruction degree of small airways by using spirometry, and other functional exploration methods (peakflowmetry, body pletismography etc.). Respiratory functional explorations are useful in patients over the age of 6, as they require good cooperation for conducting the tests, below this age, their importance is questionable.

In this study, we have considered FEV or FEV1, which is expiratory volume per second (this is expressed as a percentage and it is related to an ideal value corresponding to the anthropometric indices). FEV is the volume expired in the first second of a maximal expiration following a maximal inspiration and provides information about how quickly the lungs can be emptied. This parameter has the normal value> 80% and it drops below this value in asthma.(5)

Dosing the fraction of nitric oxide in exhaled air (FENO), another useful parameter for quantifying the severity of asthmatic disease, assesses the inflammatory process of the airways, in direct proportion to the degree of inflammation. This parameter is expressed in parts per billion or ppb. FENO represents the concentration of nitric oxide in exhaled air. Its

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Article received on 11.05.2016 and accepted for publication on 03.06.2016
ACTA MEDICA TRANSILVANICA June 2016;21(2):50-53

normal levels are < 20 ppb (parts per billion) and increases in asthma, but it may also increase in acute infections of the airways after consumption of beverages with nitrates, smoking etc. FENO values over 35 ppb suggests an eosinophilic inflammation present in the airways. Values between 20-35 ppb must be interpreted according to the Asthma Control Test (ACT). FENO levels increase by 20% compared to the previous determination in patients with initial FENO> 35 ppb means an incomplete response to background therapy. Decrease of FENO levels by 20% compared to the previous determination in patients with initial FENO> 35 ppb means a good response to the background therapy.(6)

PURPOSE

1. Establishing some correlations between patient gender and stage of disease severity.
2. Establishing some correlations between age and stage of disease severity.
3. Establishing certain correlations between the origin environment (rural or urban) and stage of disease severity.
4. Establishing certain correlations between the presence of positive family history of atopy and severity level of asthma.
5. Correlation between FENO fluctuations under the background therapy and asthma severity stage.
6. Correlation between FEV fluctuations under the background therapy and asthma severity stage.

MATERIALS AND METHODS

The study was conducted on 90 patients with asthma/recurrent wheezing in the evidence of the "Centre for Laboratory, Clinical and Paraclinical Research in the field of Paediatric Respiratory Medicine CCMRP" within Pediatrics Clinic of Sibiu during 2013-2014.

It was a case-control study including: a group of patients taking inhaled corticosteroids as background therapy and a treatment group taking inhaled corticosteroids associated with leukotriene inhibitors.

There were included in the study children previously diagnosed with asthma (classified in different stages of severity) or recurrent wheezing, aged more than three years and under 18 years, non-smokers, under treatment with inhaled corticosteroids or with inhaled corticosteroids and inhibitors of leukotrienes (with or without antihistaminic treatment) with background therapy of approximately 3 months, with proper management of inhaled corticosteroids or leukotriene inhibitors, patients in disease stable stage, able to perform forced expiratory manoeuvres.

There were excluded from the study patients with acute or chronic respiratory pathology other than asthma, patients in asthma crisis at the inclusion in the study, patients who could not correctly perform spirometry or in whom FENO could not be performed.

Spirometry was performed with the spirometer belonging to the Pediatrics Clinic of Sibiu.

Regarding NO dosage, this was done with NObreath® portable device, belonging to the "Centre for Laboratory, Clinical and Paraclinical Research in the field of Paediatric Respiratory Medicine CCMRP" within Pediatrics Clinic of Sibiu during 2013-2014.

Statistical analysis was performed with the help of SPSS software.

The study was conducted on male and female children, aged 6-18 years (divided into three age groups: 6-10 years or during prepubertal or pubertal period, 10-14 years or during puberty, 14-18 years or postpuberty or adolescence), coming from rural or urban areas, with or without positive family history of allergies (allergic rhinitis, asthma, atopic dermatitis etc.).

These children were included in some stages of severity of asthma/wheezing depending on the severity of clinical manifestations and modification of ventilation parameters. Depending on the severity stage, there was set a background regimen (a class of drugs or association between several classes of drugs) and then, they were re-evaluated at 3 months and 6 months after initiation of therapy.

Table no. 1. Distribution by type of asthma and gender

Gender	Asthma			Recurrent wheezing	Total	p test Likelihood ratio
	Moderate	Mild	Intermittent			
Boys	9	13	14	24	60	0,423
	15.0%	21.7%	23.3%	40.0%	100.0%	
Girls	3	10	9	8	30	
	10.0%	33.3%	30.0%	26.7%	100.0%	
Total	12	23	23	32	90	
	13.3%	25.6%	25.6%	35.6%	100.0%	

Figure no. 1. Repartition by type of asthma and gender

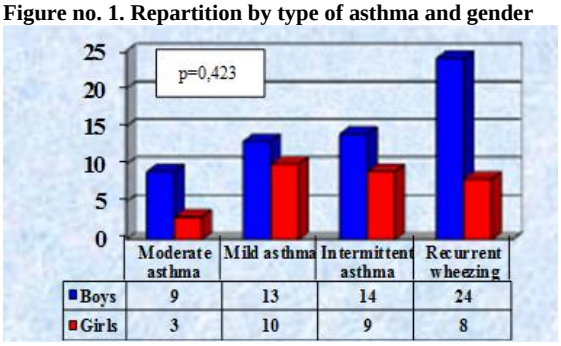

Table no. 2. Distribution by type of asthma and age group

Age group	Asthma			Recurrent wheezing	Total	p test Likelihood ratio
	Moderate	Mild	Intermittent			
≤ 10	-	6	6	15	27	0,001**
		22.2%	22.2%	55.6%	100.0%	
11 ÷ 14	9	13	8	17	47	
	19.1%	27.7%	17.0%	36.2%	100.0%	
> 14	3	4	9	-	16	
	18.8%	25.0%	56.3%		100.0%	
Total	12	23	23	32	90	
	13.3%	25.6%	25.6%	35.6%	100.0%	

Figure no. 2. Repartition by type of asthma and age group

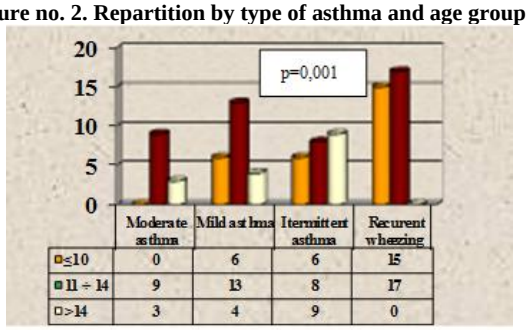

Table no. 3. Repartition by asthma and origin environment

Origin environment	Asthma			Recurrent wheezing	Total	p test Likelihood ratio
	Moderate	Mild	Intermittent			
Rural	4	7	4	8	23	0,678
	17.4%	30.4%	17.4%	34.8%	100.0%	
Urban	8	16	19	24	67	
	11.9%	23.9%	28.4%	35.8%	100.0%	
Total	12	23	23	32	90	
	13.3%	25.6%	25.6%	35.6%	100.0%	

Figure no. 3. Repartition by type of asthma and origin environment

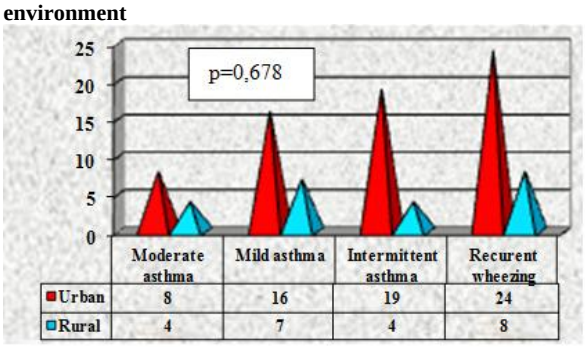

Table no. 4. Repartition by type of asthma and existence of family medical history (FMH)

FMH	Asthma			Recurrent wheezing	Total	p test Likelihood ratio
	Moderate	Mild	Intermittent			
Da	3	10	7	6	26	0,254
	11.5%	38.5%	26.9%	23.1%	100.0%	
Nu	9	13	16	26	64	
	14.1%	20.3%	25.0%	40.6%	100.0%	
Total	12	23	23	32	90	
	13.3%	25.6%	25.6%	35.6%	100.0%	

Figure no. 4. Repartition by asthma type and family medical history

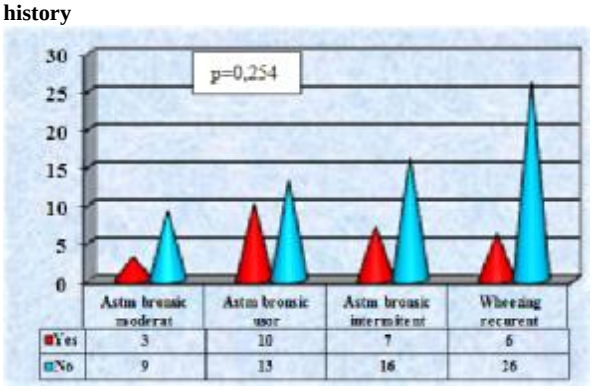

Table no. 5. Distribution by type of asthma and exhaled nitric oxide fluctuations 3 months after initiation of background therapy

FENO	Asthma			Recurrent wheezing	Total	p test Likelihood ratio
	Moderate	Mild	Intermittent			
Crescut	8	7	9	8	32	0,078
	25.0%	21.9%	28.1%	25.0%	100.0%	
Normal	4	16	14	24	58	
	6.9%	27.6%	24.1%	41.4%	100.0%	
Total	12	23	23	32	90	
	13.3%	25.6%	25.6%	35.6%	100.0%	

Table no. 6. Distribution by type of asthma and FEV fluctuations 3 months after initiation of background therapy background

FEV	Asthma			Recurrent wheezing	Total	p test Likelihood ratio
	Moderate	Mild	Intermittent			
Normal	8	18	18	29	73	0,276
	11.0%	24.7%	24.7%	39.7%	100.0%	
Low	4	5	5	3	17	
	23.5%	29.4%	29.4%	17.6%	100.0%	
Total	12	23	23	32	90	
	13.3%	25.6%	25.6%	35.6%	100.0%	

DISCUSSIONS

Asthma is a disease of the modern world, a disease that is the subject of numerous studies. Literature data bring complex information regarding the correlations between this condition and genetic, demographic factors etc., as well as with the progress recorded on the investigational area, progress that aimed mainly at early diagnosis and adequate control of the disease.

According to the literature, it can be said that there is a close link between patients' gender and severity of asthma. Thus, there is a prevalence of approximately 10.5% higher of asthma in females compared to males. Also, asthma is more frequently and more severely encountered in boys in prepuberty and in girls during postpuberty.(7)

Also, numerous studies have shown that exposure to air pollutants, most common in children living in industrialized cities, predisposes to the occurrence of asthma, as there has been also found an increased incidence of asthma in children living in rural areas, exposed to contact with farm animals.(8)

Most studies show that there is a minimal difference between the prevalence of asthma in patients from rural areas as compared to those from urban areas, but that, however, the urban area is the prototype that leads to asthma susceptibility development.(9)

Regarding the association between asthma severity and family history positive for atopy, studies have shown that family history of asthma or other allergic diseases is a key factor in developing the disease in children, but the severity of events is closely linked to the exposure to certain environmental factors and not just to "genetics".(10)

Studies in the literature on the correlation of asthma severity and the response to treatment, response objectified by fluctuations in the concentration of nitric oxide in exhaled air, state that FENO is a true biomarker of eosinophilic inflammation in mild and moderate forms of the disease. In severe forms, resistant to conventional therapies, usefulness of NO dosing in regular evaluations in order to modulate the therapy according to FENO values is questionable. In patients with mild or moderate asthma, there are recorded high values of FENO, which decrease after the background therapy with inhaled corticosteroids (ICS), while in severe forms, these values are not significantly influenced.(11,12)

Numerous studies on the effectiveness of the ICS on the chronic inflammatory process of asthma, demonstrated positive effects in different stages of severity, effects objectified by elevated FEV values.(13)

After analyzing the two groups proposed in this study, according to the objectives set, the following assumptions have been made, which coincided with data or studies in the literature:

1. One cannot say that there is an association between asthma type and gender (p = 0.423 - Likelihood ratio test) (see table no. 1, figure no. 1).
2. It can be said that there is an association between asthma type and age group (p = 0.001 - Likelihood ratio test) (see table no. 2, figure no. 2). For the age group ≤ 10 years recurrent wheezing is predominating (55.6% of cases) and for the age group > 14 years, intermittent asthma is predominating (56.3% of cases).
3. One cannot say that there is an association between asthma type and origin environment (p = 0.678) (see table no. 3, figure no. 3).
4. One cannot say that there is an association between asthma type and the existence of family medical history (p = 0.254-test Likelihood ratio) (see table no. 4, figure no. 4).
5. One cannot say that there is an association between asthma type and normal or increased levels of nitric oxide in exhaled air at 3 months after initiation of background therapy (p = 0.078-test Likelihood ratio) (see table no. 5).

6. One cannot say that there is an association between asthma type and normalisation or decrease in FEV, 3 months after initiation of background therapy (p = 0.276-test Likelihood ratio) (see table no. 6).

CONCLUSIONS

Despite the fact that numerous studies in the literature have proven the important contribution in monitoring inflammation at airways level in asthma as a result of dosing the fraction of nitric oxide in exhaled air (not only the invasive methods such as bronchoscopy with bronchoalveolar lavage and biopsy), this method relatively inexpensive, non-invasive, safe, has not been fall included in the diagnostic guidelines of this chronic condition.(14,15)

In the present study, the correlation between this method relatively newly introduced in medical practice and spirometry (old, consecrated method) revealed the following aspect linked to fluctuations in FEV and FENO 3 months after initiation of background therapy: it appears that within the same stage of severity, a higher percentage of patients still show elevated levels of FENO equivalent to persistence in the bronchial tree of the eosinophilic inflammation, while FEV shows a clear improvement, especially in the group of patients with recurrent wheezing, evidenced by lower percentage of patients who still presented lower values of FEV. Therefore, FEV remains as the first indicator of improving pulmonary function, at least after only 3 months of treatment with inhaled corticosteroids or association between this therapy and leukotriene inhibitor.

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