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Prevalence of Aspirin-Induced Asthma in Certain Group of Kosovo Population and its Presentation

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Abstract

Background. Aspirin-induced asthma (AIA) is characterized by onset of asthma attack 30 minutes to 3 hours after ingestion of aspirin or NSAIDs (Non steroid anti-inflammatory drugs). The typical reaction may be accompanied by intense rhinorhea, periorbital edema with conjunctival irritation and facial flushing. Often, at physical examination, nasal polyposis and serum eosinophilia are notable.

Aim: The aim of this study is to identify the behavior of aspirin induced asthma in a certain group of Kosovo population, in terms of age and its presentation.

Material and methods. At the University Hospital Centre in Prishtina, 172 adult patients with asthma were diagnosed, while 16 (9.3 %) of them were with aspirin-induced asthma (f/m=12/4).

Results. The average age was 40.2 years. Nine of them showed triad of symptoms (aspirin-intolerance, asthma, nasal polyposis) while 7 (43.7%) showed tetrad of symptoms (aspirin-intolerance, asthma, nasal polyposis, and sinusitis). Total IgE levels were increased only in 3 patients (18.8%), while eosinophilia was increased only in 8 (50%) of the patients. The skin prick test with standard set of inhalant allergens was positive only in 3 patients (18.8%). There was no correlation between in vitro and in vivo tests.

Conclusion. Since there is no reliable in vitro test for the diagnosis of aspirin sensitivity, definitive diagnosis requires an oral or nasal aspirin challenge, which needs to be performed in a hospital.

Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatments (1).

Asthma represents a major health problem. The cost paid for it exceeds 6 (Six) Billion US Dollars (2). Asthma is the most frequent chronic disease in child-

hood, and we can say that asthma and wheezing are the most frequent causes of visits of the pediatrician. The assessment of prevalence of minor age in USA ranges from 3.6 to 9.5%, depending on the definition/ questionnaires (3).

Aspirin-induced asthma (AIA) presents a syndrome, which in clinical aspect is similar to a persistent viral respiratory infection. This syndrome is manifested by triad of symptoms (rhinitis with or without nasal polyposis, asthma, and aspirin intolerance), or tetrad of symptoms (rhinitis with or without nasal polyps, asthma, sinusitis and aspirin intolerance) (4, 5). The asthmatic attack can appear when using a small dose of aspirin up to 80 mg and is manifested by the following symptoms: flowing from the nose, periorbital edema, conjunctival irritation, face reddening, stomach griping, and chest pains. A quarter of patients (25%) with asthma who required emergency mechanical ventilation were found to be aspirin intolerant (6). AIA is mostly present in middle age (the peak of incidence is the age of 35 years, although it can be identified even in adolescence). Female patients get ill more frequently than males (2.5 times).

The common feature of medications that trigger this reaction is their inhibition of the cyclo-oxygenase 1 (COX-1) enzyme (7). Other terms for aspirin-induced asthma are: aspirin-sensitive asthma, aspirin-intolerant asthma, and NSAID-induced rhinitis and asthma. The central characteristic of these patients is their sensitivity to medications that inhibit the COX-1 enzyme. The COX enzymes produce a range of mediators that are responsible for regulation of normal body functions (mainly COX-1) as well as inflammation, fever and pain (mainly COX-2). One of the mediators produced by COX-1 that regulates normal body function is prostaglandin E2. Evidence suggest that reduction of prostaglandin E2 levels by medications that inhibit COX allows activation of an enzyme pathway to produce increased amounts of inflammatory mediators called leukotrienes (7). The leukotrienes are responsible for many of the manifestations of an asthma attack, triggered in these patients by aspirin and NSAIDs (Fig. 1).

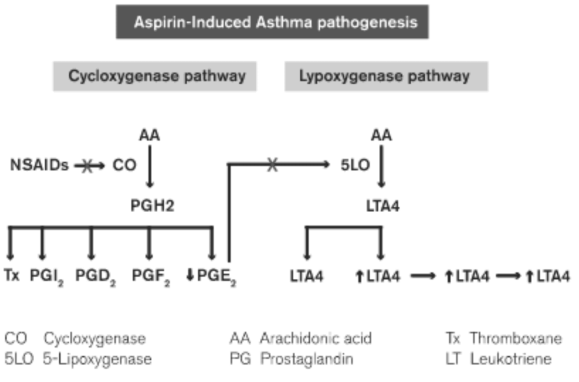

Figure 1: The mechanism of aspirin-induced asthma.

Based on the studies of challenge, AIA is a unique phenotype of asthma, which includes about 10-15% of asthmatic patients in several populations (3, 4). Only a few families have been described as presenting with "aspirin triad" (asthma, aspirin intolerance, and nasal polyposis). The Mennonite family reported by Locley and colleagues, 1973 (8) and the pair of sisters reported by Miller, 1973 (9), have much in common in that they conformed in large part to the classic description of aspirin-intolerant asthma. In contrast, the family presented by von Maur and coworkers, 1974 (10) included four of six affected individuals under 17 years of age at onset none had polyposis. A considerable discordance in clinical manifestation of the disease was noted in identical twin sisters, pointing to the influence of environmental factors (8, 11). In non-Mennonite family, studied by Locley and coworkers, 1973 (8), two siblings suffered from aspirin triad, while the third had intrinsic asthma that improved after ingestion of aspirin. The rare syndrome of asthma relieved by aspirin bears much clinical resemblance to aspirin-induced asthma, and in a sporadic patient one form may evolve into the other (12).

The airway of AIA patients show signs of persistent inflammation with marked eosinophilia, epithelial disruption, specific cytokine production, and up regulation of adhesion molecules (13). Eosinophils infiltration of airway tissue appears to be a central feature of AIA. The airway expression of interleukin 5 (IL-5), known to be involved in recruitment, activation, maturation and perpetuation of survival of eosinophils, is markedly increased in patients with AIA (14).

The objective of this study is to identify the behavior of aspirin-induced asthma in a certain group of Kosovo population, in terms of age and its presentation.

Material and methods

Adults presented by the Allergology and Clinical Immunology Department, with allergy of upper and lower respiratory tract (Asthma, Rhinoconjunctivits, Sinusitis, Nasal polyposis) as well as patients with history data of intolerance of aspirin and other non-steroid anti-inflammatory drugs, during the period from January 2003 to January 2004 were included in this study.

Parameters were set for all the patients: Erythrosedimentation rate (ESR), chemo gram, leukocyte formula, total IgE values, and Skin prick test with complete standards of Pneumoallergenes (Inhalant allergens). Standard methods have been used to identify the Erythrosedimentation, Chemo gram and Leukocyte formula. IRMA (Radioimmunoassay with monoclonal antibodies) method has been used to determine the level of total IgE in the serum (IMMUNOTECH Co., France). These analyses have been implemented at the Immunology Laboratory of the Institute of Physiology at the University Clinical Centre of Prishtina, Kosovo.

For the purpose of this study, the radioactivity has been measured in *gamma counter Type DPC,* and the calculation of results has been carried out by a computer program, adapted to calculate normal IgE values. In case of healthy persons, values of IgE grow easily from 0.2 kIU/L after birth, up to 20.0 kIU/L at the age of 15-20, with mayor individual variations (2-200 kIU/L).

The Skin prick test has been applied in the Allergology and Clinical Immunology Department of the University Clinical Centre of Prishtina, by using Reagent Test Kit G (Allergopharma Co., Hamburg, Germany). The edema over 3 mm, with the circled erythema was evaluated as a positive test.

Oral challenge with aspirin or acetylsalicylic acid (ASA) is the only definitive way to diagnose current aspirin sensitivity. Such a challenge can identify reactive patients with no previous history of drug sensitivity. Criteria to participate on this challenge was that subject must be symptoms free, while this test have been conducted in Department of Pathophysiology in Prishtina Hospital setting by experienced personnel equipped to treat anaphylactic or severe asthmatic reactions. During our study we have perform the protocol for 3-day oral aspirin challenge as per Stevenson(1), as follow: Day 1 - 8:00 a.m. – Placebo; 11:00 a.m. - Placebo; 2:00 p.m. – Placebo; Day 2 - 8:00 a.m. – ASA - 3 mg or 30 mg; 11:00 a.m. – ASA, 60 mg; 2:00 p.m. – ASA – 100 mg; Day 3 - 8:00 a.m. – ASA - 150 mg; 11:00 a.m. – ASA, 325 mg; 2:00 p.m. – ASA – 650 mg (25).

Results

In this cross-sectional epidemiological survey four hundred and ten patients (238 females and 172 males) have been treated at the Allergology and Clinical Immunology Department of the Prishtina University Clinic Centre. A considerable number of these patients have had more than one diagnosis. The most frequent disease is Asthma in 42% of cases (f/m=109/63), followed by Rhinoconjuctivitis with 32.9% (f/m=71/64). Other diseases were present with lower frequency, such as Rhinitis: 16.1%, Sinusitis 15.6%, Intolerance to aspirin 12.4% and the last, Obstructive rhinitis with Nasal polyposis: 7.1%. The significant distinction, by gender, has been noticed only in Asthma ($p < 0.01$), while for the rhinitis and aspirin intolerance, there has been no significant difference ($p > 0.05$) (Table 1).

Table 1: Patients treated in the Allergy-Immunology Department of University Hospital Center of Prishtina Clinic - cases by diagnosis and gender.

Diagnosis	Female		Male		Total		x^2 – test
	N	%	N	%	N	%	
Total patients	306	100.0	211	100.0	517	100.0	p<0.01
Rhinitis	41	13.4	25	11.8	66	12.8	p<0.05
Obstructive Rhinitis + Nasal polyposis	12	3.9	17	8.1	29	5.6	p>0.05
Rhinoconjuctivitis	71	23.2	64	30.3	135	26.1	p>0.05
Sinusitis	39	12.7	25	11.8	64	12.4	p>0.05
Asthma	109	35.6	63	29.9	172	33.3	p<0.01
Aspirin intolerance	34	11.1	17	8.1	51	9.9	p>0.05

Our patients were of different age, up to the age of 80. The majority of patients were 20-29 years of age (28.3%); 30-39 years of age 27.1%, and 40-49 years of age (17.6%), while up to 20 years were 8.9% of patients. The average age of patients was 35.9 years, with SD 14.1 (Fig.2).

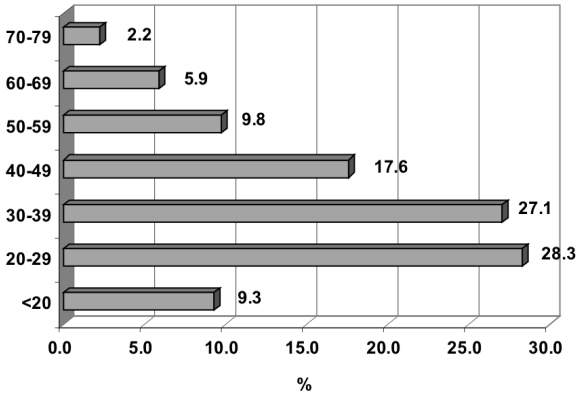

Figure 2: Patients with aspirin intolerance by age.

Out of total of 51 cases (f/m=22/13) with aspirin-intolerance, Asthma was found only in 16 cases or 31.4% (f/m=12/4). Aspirin-intolerance with asthma was recorded in 23.5% of males and 35.3% of females (Fig. 3).

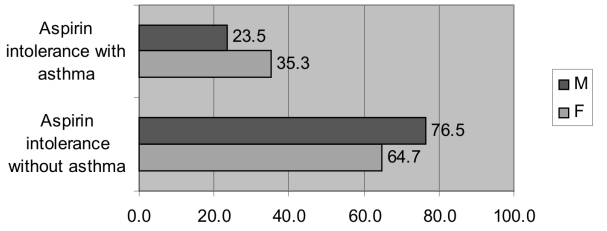

Figure 3: The structure of aspirin intolerance with or without asthma by gender.

The analysis of patients with aspirin-intolerance resulted into the inclusion of the largest group of 30-39 years of age (39.2%), and the group of 20-29 years of age (19.6%) of the average age of 36.7 years. For the two compared groups, (aspirin-intolerance with or without asthma) the age of 30-39 years 40% is predominant, at the aspirin-intolerance without asthma; and 37.5% for aspirin-intolerance with asthma. While the average age of patients with asthma was 40.3 years, and for those without asthma was 35.2 years (Table 2).

Table 2: Patients treated in the Allergy-Immunology Department of University Hospital Center of Prishtina Clinic - cases by diagnosis and gender.

Age Group	Aspirin Intolerance without Asthma		Aspirin Intolerance with Asthma		Total Aspirin Intolerance	
	N	%	N	%	N	%
<20	4	11.4	1	6.3	5	9.8
20-29	8	22.9	2	12.5	10	19.6
30-39	14	40.0	6	37.5	20	39.2
40-49	4	11.4	2	12.5	6	11.8
50-59	3	8.6	4	25.0	7	13.7
60-69	1	2.9	1	6.3	2	3.9
70-79	1	2.9	-	-	1	2.0
Total	**35**	**100.0**	**16**	**100.0**	**51**	**100.0**
X-bar (mean)	35.2		40.3		36.7 year	
SD	12.6		14.8		13.4	

Out of total of 410 patients examined in our Service, the most frequent disease is the Asthma, with 172 patients (42.2%), (f/m=109/63) (Table 1.). Among these patients, 156 (90.7%) are aspirin non induced asthma (f/m=97/59), and 16 patients (9.3%) are aspirin-induced asthma. The proportion f/m is 12/4. In the relation of f/m, a significant correlation was found for aspirin induced form ($p< 0.05$), while for the aspirin non induced form the gender was not significantly correlated ($p>0.05$) (Table 3).

Table 3: Patients treated in the Allergy-Immunology Department of University Hospital Center of Prishtina Clinic - cases by diagnosis and gender.

Diagnosis	Gender				Total		X^2-test
	Female		Male				
	N	%	N	%	N	%	
Aspirin-induced asthma	12	11.0	4	6.3	16	9.3	P>0.05
Non aspirin-induced asthma	97	89.0	59	93.7	156	90.7	P<0.01
Total Asthma	**109**	**100.0**	**63**	**100.0**	**172**	**100.0**	P<0.01

The analysis of total patients with asthma, by groups of age, shows that the most frequent are cases within the group age (30-39) 23.8%, and within the age (40-49) 22.7%.

Most of the patients with aspirin-induced asthma are in the group of 30-39 years of age (37.5%), and the group of 50 – 59 years of age – or 25% of our cases, while the highest prevalence of non aspirin-induced asthma is at the age of 40-49 years, or 23.7%. The average age of patients with Asthma is 39.1; those of aspirin-induced asthma 40.2 years, and those with non induced aspirin asthma 38.9 years. The difference in ages showed no significance ($p> 0.05$) (Table 4).

Table 4: Patients treated in the Allergy-Immunology Department of University Hospital Center of Prishtina Clinic - cases by diagnosis and gender.

Group of age	Aspirin-induced Asthma		Non Aspirin-induced Asthma		Total Asthma	
	N	%	N	%	N	%
<20	1	6.3	13	8.3	14	8.1
20-29	2	12.5	33	21.2	35	20.3
30-39	6	37.5	35	22.4	41	23.8
40-49	2	12.5	37	23.7	39	22.7
50-59	4	25.0	22	14.1	26	15.1
60-69	1	6.3	12	7.7	13	7.6
70-79	-	-	4	2.6	4	2.3
Total	**16**	**100.0**	**156**	**100.0**	**172**	**100.0**
X-bar (mean)	40.2 age		38.9 age		39.1 age	
SD	14.8		14.7		14.7	
t-test	p>0.05					

Patients with aspirin-induced asthma have presented by triad or tetrad of symptoms. Of total of 16 patients with aspirin-induced asthma, 9 (56.3%) had triad, and 7 (43.8%) had tetrad of symptoms. In aspirin-induced asthma, the majority of cases were recorded in the age group from 30-39 years (37.5%) followed by the group of 50 - 59 years old (25%). The average age of aspirin-induced asthma is 40.3, while for aspirin-induced asthma patients with triad of symptoms is 43.9 years and for those with tetrad of symptoms is

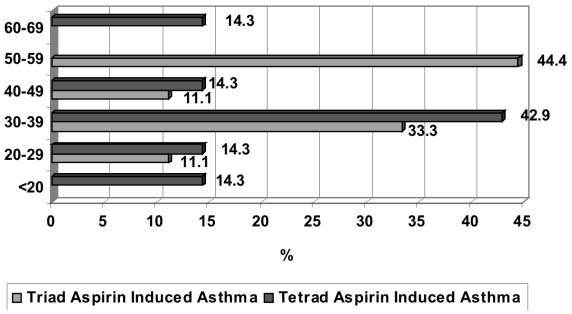

Figure 4: The age structure of patients with aspirin induced asthma triad and tetrad symptoms.

notably lower - 35.6 years. However, there is no significant distinction by ages (p >0.05) (Fig. 4).

The table 5 shows the relation between the skin prick test with pneumoallergenes, IgE and Eosinophililia in the peripheral blood of patients. Skin Prick test was positive in 3 (18.8%) patients; IgE has been identified as increased only in 3 patients, while increased eosinophilia was found in 8 cases (50%) of total patients (Table 5).

Table 5: Patients treated in the Allergy-Immunology Department of University Hospital Center of Prishtina Clinic - cases by diagnosis and gender.

	Skin test		IgE		Eosinophilia		
Diagnosis	Positive n (%)	Negative n (%)	Large n (%)	Normal n (%)	Large n (%)	Normal n (%)	Total n (%)
AIA triad	2 (22.2)	7 (77.8)	1 (11.1)	8 (88.9)	2 (22.2)	7 (77.8)	9 (100)
AIA tetrad	1 (14.3)	6 (85.7)	2 (28.6)	5 (71.4)	6 (85.7)	1 (14.3)	7 (100)
Total AIA	**3 (18.8)**	**13 (81.3)**	**3 (18.8)**	**13 (81.3)**	**8 (50.0)**	**8 (50.0)**	**16 (100)**

The analysis of the Fi coefficient shows that there is a weak statistic correlation between IgE, Skin test and eosinophililia in the blood of our patients (Table 6).

Table 6: Correlation between total IgE, Skin test and eosinophilia in the patients with aspirin-induced asthma.

Tests		Skin test		Total
		Positive	Negative	
Total IgE	Increased	0	3	3
	Normal	3	10	13
Total		3	13	16
Fi coefficient of correlation		0.23, low correlation		
Eosinophilia	Increased	2	6	8
	Normal	1	7	8
Total		3	13	16

The most interesting cases were introduced after the oral provocation test with aspirin. Reaction is seen after 30 minutes in whistling of the chest, skin efflorescence, nose blockage and gastrointestinal embarrassment (Fig. 5).

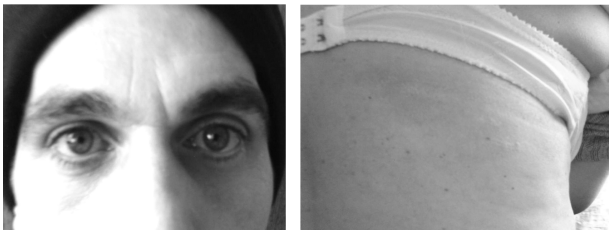

Figure 5: Oral provocation test with aspirin. Reaction is seen after 30 minutes in whistling of the chest, skin efflorescence (right), nose blockage, periorbital edema (left), and gastrointestinal embarrassment.

Discussion

The accompaniment of the allergic rhinitis and asthma is known as manifestation of atopy (15, 16). The World Health Organization has sponsored the development of ARIA Instruction (Allergic Rhinitis and Impact of Asthma) in 1999, as a basic document which addresses the relation between Asthma and allergic and non allergic Rhinitis (17). Many patients with allergic rhinitis have the accompaniment of asthma, and many asthmatic patients have allergic rhinitis too (18), often accompanied with sinus inflammation or rhino sinus (19). ARIA document recommends that the rhinitis patient should evolve for asthma and vice versa, because, the rhinitis is present in 75% of allergic asthmatics, and 80% of non allergic asthmatics. Rhinitis is the foregoing for later asthma in 64% of patients, as well as the same time appearing asthma and rhinitis happen in 21% of the cases. Nineteen to 38% of patients with rhinitis present asthma even clinically, i.e. many of the patients with rhinitis demonstrate bronchial non specific hyper reactivity against metacholine and histamine (20).

Patients with allergic rhinitis without asthma demonstrate higher bronchial hyper reactivity primarily during the pollen season (21). Bronchial hyper reactivity is more significant with perennial allergic rhinitis against home dust and against cats, more than seasonal allergic rhinitis against pollen (22). Subjects with allergic and non allergic rhinitis risk three times more to develop asthma (23, 24). Furthermore, patients with rhinitis and sinusitis have much more chances to develop asthma than patients with rhinitis alone (24).

Patients for our study had more than one diagnosis. Out of 410 patients treated in the Department of

Allergy with clinical Immunology, the most frequent disease was Bronchial Asthma in 42% of cases. Rhino conjunctivitis was present in 32.9%; Rhinitis - 15.6%, while aspirin intolerance: in 12.4% of our cases. Out of 172 patients with bronchial asthma, sensitive forms were presented only in 16 cases (0.93%) that correspond with the prevalence of this disease.

In our study, we did not find any correlation between total IgE, eosinophils and Prick test with pneumo-allergenes. Thus, the test for oral and nasal challenge still remains the preferred diagnostic method for this disease.

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