From analgesic intolerance to analgesic induced asthma: are there some determinants?

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SUMMARY

Background: analgesic intolerance (AI) sometimes appear alone and sometimes with bronchial asthma affecting about 10% of asthmatics and sometimes before and the other times after asthma.

Objective: we investigated the possible clinical risk factors which might be affecting the transition from isolated AI to analgesic induced asthma (AIA).

Methods: a total of 344 patients admitted to Hacettepe University Hospital Adult Allergy Unit between January 1991 and March 1999 and diagnosed with AI were enrolled in this survey. Patients having AIA (group I) (n = 191) were compared with the patients having AI without asthma (group II) (n = 153). The diagnosis of AI and AIA were made by history and oral provocation tests. A standard questionnaire was filled-in for all the patients.

Results: the risk of AIA was increased with nasal polyp, and rhinosinusitis via OR's of 2.75 (95% CI: 1.09, 6.91), and 18.58 (95% CI: 9.86, 35.01), respectively. Having a pet, and ever smoking decreased the risk of AIA in the patients with AI via OR's of 0.53 (95% CI: 0.24, 1.17), and 0.37 (95% CI: 0.17, 0.80), respectively. The association of AIA and smoking was slightly modified by food intolerance (OR for ever smoked and food intolerance: 1.31, 95% CI: 0.40, 4.30).

Conclusion: there may be two different phenotypes of AI with different clinical features: one developing AIA (having nasal polyp and/or rhinosinusitis, and smoking if food allergy/ intolerance is present), and the other AI without asthma (having pet, and could smoke). Findings of this study should be confirmed by further investigations.

Key words: Analgesic induced asthma. Analgesic intolerance. Risk factors.

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INTRODUCTION

The prevalence of analgesic intolerance (AI) is less than 1% in general population and much more common in certain risk group of patients who have bronchial asthma, chronic urticaria and nasal polyps (1-5). The condition where AI and asthma are seen together is classically known as " Aspirin-Induced Asthma" or " Samter's Syndrome", and recently called as " Analgesic-Induced Asthma" (AIA) (6-9). In the classical description of this syndrome rhinitis starts first and nasal polyp, asthma and AI accompany rhinitis later. In some cases AI may be the first disorder appearing (6-9).

We do not have detailed knowledge about the etiology of AIA, which is known pathophysiologically as a leukotriene-driven disease (10-15). There are numerous surveys going on about the genetic basis of these patients who have increased amount of LTE_4 metabolites in their urine (16-18). Recent studies showed that there was an association between AIA and HLA-DQ, and DR antigens (19-22). It was also mentioned that additional trait of LTC_4S gene's allele C in asthmatics may facilitate the disease transition to its aspirin-sensitive variant and existence of a mechanism enhancing LTC_4S transcription in carriers of a common $_{444}C$ allele of this gene (22, 23). Various endocrine, metabolic, autoimmune and allergic diseases and conditions such as tyhroid diseases, obesity, acne, menstrual disturbances, autoimmune vasculitis, dermographism,

chronic urticaria; antibiotic, metal and food allergy might accompany AIA (25-28).

In this clinical survey we investigated the association between AIA and the patient characteristics and some of the allergic conditions in patients who had AI. The aim was to identify the possible risk factors, that could affect the transition from AI to AIA.

MATERIAL AND METHODS

A total of 344 patients admitted to Hacettepe University Hospital Adult Allergy Unit who were diagnosed with AI and followed between January 1991 and March 1999 were enrolled in this survey. Patients having AIA (n = 191) who were accepted as group I were compared with the patients having only AI (n = 153) who were accepted as group II for the possible risk factors playing a role in the transition from AI to AIA.

A standard questionnaire was filled in for all the patients. Data collected by this questionnaire included age, gender, age of diagnosis for asthma, rhinosinusitis, analgesic intolerance, nasal polyps; features of AI (responsible analgesic(s), latent period between the drug ingestion and the beginning of the symptoms, the reactions or the symptoms emerged, duration of the symptoms, cumulative analgesic consumption), other accompanying allergic diseases (antibiotic and food allergy/intolerance, metal allergy, dermographism, chronic urticaria), the atopic status of the patient and of his/her family and having pet animals at home. To evaluate the lifelong cumulative analgesic consumption the patients were asked the number of boxes of analgesics they had used until the appearance of AI (a regular medicine box in Turkey contains 20 pills).

Routine skin prick tests were performed to all the patients except for the patients, who were pregnant, or had chronic urticaria and/or dermographism or used antihistaminic drugs at the time of the test. Twelve standard antigen solutions (dermatophagoides pteronyssinus, phleum pratense, olea europa, artemisia vulgaris, parieteria officinalis, hazelnut, betula verrucosa, cat, dog, horse, altreneria alternata and cladosporium herbarum) were used which were prepared by ALK (Denmark) and Greer (USA) companies. Skin testing was performed as described by Österballe, et al (29). The standard antigen solutions were applied after pricking the skin of the volar aspect of the forearm with a special lancet having 1 mm tip. Histamine and saline were used as positive and negative controls, respectively. A wheal with perpendicular diameters of 3×3 mm or more was considered as positive reaction. Atopy was defined as a positive reaction to any one of the allergens. A positive familial history of atopy was considered when the patient reported a first-degree family member with the symptoms of asthma, allergic rhinitis and/or atopic dermatitis. Serum total IgE levels were measured in all the patients except for those who refused blood drawing or in whom blood could not be drawn for some reason. The diagnosis of bronchial asthma was made by history depending the international guidelines (30) or had been made in previous years in the same clinic.

The diagnosis of AI and AIA were made by history. Sufficient and reliable clinical history of at least 2 events was required for AI. The reaction should have occurred within 3 hours after the ingestion of the analgesic. If there was only one event, then confirmation by oral provocation test was required. Oral provocation tests are performed as described before (28).

Physical examination, chest radiography, pulmonary function testing was performed in all the patients. Bronchodilatation test, methacholine airway challenge, and serological test were also performed when indicated.

STATISTICAL ANALYSIS

SPSS statistical package (SPSS, 7.0-95 release) was used for the analysis of the data. Analgesic induced asthma patients were compared with AI patients without asthma. The means and the standard deviations for the numerical variables were calculated. Ten-based logarithm of the serum total IgE level was determined to obtain a normal distribution. Comparison of the continuous variables between the two groups was performed by student t test and by Mann-Whitney U tests for the ones with and without normal dispersion, respectively. Chi square test compared distribution of the categorical variables and was replaced by Fisher's exact test when the expected cell count was less than five. A p value of less than 0.05 was considered for statistical significance.

Independent associations of AIA with the patient characteristics and the other explanatory factors were investigated by multiple logistic regression analysis. Multiple logistic regression analysis generated odds ratios (OR) as the estimates of relative risks. Ninety-five percent confidence intervals (95% CI) were used to display the precision of the estimates. Hosmer Lemeshow statistics was used to assess the goodness of fit of the model. Interaction between the factors was investigated by

Table I

Comparison of demographic, clinical and laboratory characteristics of the analgesic induced asthma patients with the analgesic intolerance patients without asthma

	Analgesic induced asthma Group I (n = 191)	Analgesic intolerance without asthma Group II (n = 153)	P
Age	40.9 ± 12.3	39.5 ± 13.6	NS
Beginning age for analgesic intolerance	35.4 ± 12.0	34.2 ± 13.0	NS
Gender (Females)	140 (73.3%)	118 (77.1%)	NS
Rhinosinusitis	156 (81.7%)	6 (3.9%)	**
Nasal polyps	69 (36.1%)	8 (5.2%)	**
Familial history of atopy	115 (60.2%)	76 (49.7%)	*
Familial history of analgesic intolerance	14 (7.3%)	16 (10.5%)	NS
Skin prick test	161 (84.3%)	109 (71.2%)	**
Positive reaction among the patients tested	54 (34.2%)	23 (21.1%)	*
Mite sensitivity	34 (21.1%)	12 (11.0%)	*
Cat sensitivity	4 (2.1%)	1 (0.7%)	*
Dog sensitivity	1 (1.0%)	1 (0.7%)	NS
Total serum IgE (IU/mL)	8.01 ± 47.55	7.88 ± 36.36	NS
Log_{10} of total serum IgE†	1.89 ± 0.53	1.75 ± 0.60	NS
Cumulative analgesic consumption (boxes)	12.1 ± 15.1	9.2 ± 13.8	NS
Keeping pets	24 (12.6%)	32 (20.9%)	*
Smoking status (ever smoked)	48 (25.1%)	47 (30.7%)	NS
Chronic urticaria	14 (7.3%)	21 (13.7%)	*
Dermographism	24 (12.6%)	31 (20.3%)	*
Metal allergy	18 (9.4%)	27 (17.6%)	*
Antibiotic allergy	33 (17.3%)	42 (27.5%)	*
Food allergy/intolerance	46 (24.1%)	35 (22.9%)	NS

NS: nonsignificant ($p > 0.05$); *: $p < 0.05$; **: $p < 0.001$.
†: patients tested for the total serum IgE were 156, and 111 in the group with AIA, and the analgesic intolerance group without asthma, respectively.

trying every meaningful interaction into the model. When an interaction term was selected the condition was to keep the root terms in the model for a proper interpretation (33).

RESULTS

Comparison of demographic, clinical and laboratory characteristics of the two groups are given in table I. The mean age ± SD was 40.9 ± 12.3 for group I and 39.5 ± 13.6 for group II. The beginning age for AI was almost equal in groups I and II (35.4 ± 12.0 and 34.2 ± 13.0, respectively). There was a female predominance in both groups with 140 (73.3%) and 118 (77.1%) females in groups I and II, respectively. The prevalence of rhinosinusitis and nasal polyp were significantly higher in group I than group II (rhinosinusitis: 81.7% and 3.9%, nasal polyps: 36.1% and 5.2% in the two groups, respectively).

The familial history of atopy was significantly more common in group I (60.2%) compared to group II (49.7%). The frequency of the analgesic intolerance in the family was not significantly different in groups I and II (7.3 and 10.5%, respectively).

Skin prick testing was performed to determine the atopic status except for the 30 (15.7%) and 44 (28.8%) patients in groups I and II, respectively; due to the reasons mentioned in "Materials and Methods" section. Demographic and personal characteristics of the patients who did not have skin prick tests were not significantly different from those who had skin prick tests. The patients who did not have skin prick tests had a significantly higher frequency of antibiotic allergy, metal allergy, and chronic urticaria than the patients who had skin prick tests. However the prevalence of AIA was significantly lower in the patients who did not have skin prick tests (40.5%) as compared to the ones who had skin prick tests (59.6%).

Sensitivity to at least one allergen in group I (55, 28.3% of the tested) was significantly more common

Table II

Data about the analgesic intolerance

	Analgesic induced asthma Group I (n = 191)	Analgesic intolerance without asthma Group II (n = 153)	P
Aspirin intolerance:			
With clinical history	137 (71.7%)	81 (52.9%)	**
With provocation tests	2 (2.1%)	3 (3%)	NS
Paracetamol intolerance:			
With clinical history	36 (18.8%)	46 (30.1%)	*
With provocation tests	9 (9.4%)	3 (3%)	NS
Metamizol intolerance:			
With clinical history	101 (52%)	72 (47.1%)	NS
With provocation tests	2 (2.1%)	not performed	–
Naproxen intolerance:			
With clinical history	35 (18.3%)	34 (22.2%)	NS
Codein intolerance:			
With provocation tests	6 (6.6%)	8 (8%)	NS
Sodium salicylate intolerance:			
With provocation tests	4 (4.4%)	2 (2%)	NS
Nimesulide intolerance:			
With provocation tests	3 (3.3%)	5 (5%)	NS
Refractory period (from ingestion of the drug to the emergence of the reaction in minutes)	38.5 ± 42.8	36.8 ± 48.1	NS
Emergency room referrals in the last year due to analgesic intolerance	80 (41.9%)	81 (52.9%)	*
Type of reaction (with clinical history):			
Bronchospasm	130 (68.1%)	12 (7.8%)	**
Urticaria	51 (26.7%)	97 (63.4%)	**
Angioedema	49 (25.7%)	96 (62.7%)	**
Anaphylaxis	16 (8.4%)	20 (13.1%)	NS
Rhinitis	9 (4.7%)	6 (3.9%)	NS
Gastrointestinal symptoms	2 (1.0%)	4 (2.6%)	NS

NS: non significant ($p > 0.05$); *: $p < 0.05$; **: $p < 0.001$.

than in group II (23, 15.0% of the tested). Sensitivity was detected to mites in 34 (17.8%) and 12 (7.8%), to pollens in 21 (11.0%) and 14 (9.2%), to animals in 6 (3.1%) and 2 (1.3%) and to fungi in 4 (2.1%) and 0 (0) patients in groups I and II, respectively. Sensitivity to mite (21.1% vs 11.0%) and cat (2.1% vs 0.7%) was significantly more common in group I than in group II.

Serum total IgE level was not measured in 35 (18.3%) patients and 42 (27.5%) patients in groups I and II, respectively. The mean and ± standard deviation of the serum total IgE, and the ten based logarithm of serum total IgE level was 8.01 ± 47.55, and 1.89 ± 0.53 in group I, and 7.88 ± 36.36, and 1.75 ± 0.60 in group II, respectively. Cumulative analgesic consumption in boxes was not significantly different between the two groups (12.1 ± 15.1 and 9.2 ± 13.8 boxes, in groups I and II, respectively; $p > 0.05$).

Keeping pet animals at home was significantly more common in group II than in group I (20.9%, and 12.6%, respectively; $p < 0.05$). In group I, 11 patients had cage bird, 6 had dog, 4 had cat, 1 had both cat and dog, 2 had both cage bird and another animal. In group II 17 had cage bird, 12 had dog, 2 had cat, and 1 had rabbit. Smoking rate defined as ever smoked was not significantly different between the two groups (25.1 and 30.7%, in groups I and II, respectively; $p > 0.05$). Chronic urticaria, dermographism, metal and antibiotic allergies were significantly more common in group II than in group I (7.3% and 13.7% for chronic urticaria; 12.6% and 20.3% for dermographism; 9.4% and 17.6% for metal allergy, and 17.3% and 27.5% for antibiotic allergy, in the two groups respectively; $p <$

0.05 fol all). The prevalence of food allergy/intolerance was not significantly different between the two groups (24.1% and 22.9%, in groups I and II, respectively; $p > 0.05$).

One hundred fifty-one (79.1%) patients in group I and 100 (65.4%) patients in group II had been using analgesics to relieve headache, which was the most frequent reason for using analgesics. The data about AI is presented in table II. Among the responsible drugs reported in the clinical history of AI, aspirin was significantly more common (71.7% vs 52.9%) and paracetamol was significantly less common (18.8% vs 30.1%) in group I than in group II. Eighty (41.9%) patients in group I and 81 (52.9%) patients in group II had had to refer to the emergency room at least for once within the last year of admission to our department, with the reactions due to AI.

Among the reactions reported bronchospasm was significantly more common (68.1% vs 7.8%), whereas urticaria (26.7% vs 63.4%) and angioedema (25.7% vs 62.7%) were less common in group with I than group II. Controlled oral provocation test was performed in 96 (50.3%) patients in group I and in 100 (65.4%) patients in group II (table II).

Independent associations between AIA and patient characteristics among group II patients were investigated by multiple logistic regression analysis as presented in table IV. Age and gender were not associated with AIA in group II. Nasal polyp and rhinosinusitis increased the risk of AIA in group II patients by almost 3 and 18 times, respectively. Holding a pet decreased the risk of AIA, but the association did not reach statistical significance (OR: 0.53, 95% CI: 0.24, 2.54). Smoking decreased the risk of AIA in group II patients by almost 0.4 times. The association between AIA and food intolerance was not statistically significant (OR: 0.50 95% CI: 0.21, 1.16). The interaction between smoking and having food intolerance suggested an increased risk of AIA in group II who had ever smoked and reported food intolerance. The combined risk shown in table IV did not reach statistical significance (OR: 1.31, 95% CI: 0.40, 4.30).

Table III

Multiple logistic regression analysis findings comparing the independent associations of AIA and the personal factors with that of analgesic intolerance patients

Determinant	OR 95% CI
Age (1 year increase)	1.01 (0.98, 1.03)
Male gender	1.23 (0.60, 2.54)
Nasal polyp	2.75 (1.09, 6.91)
Rhinosinusitis	18.58 (9.86, 35.01)
Food intolerance	0.50 (0.21, 1.16)
Ever smoked	0.37 (0.17, 0.80)
Holding a pet	0.53 (0.24, 1.17)
Ever smoked and food intolerance	7.12 (1.51, 33.67)

DISCUSSION

The data about AI principally depends on clinical observations. As long as alternative analgesic/analgesics is/are found this condition does not cause a major health problem for the individual. However, it may play a role in determining the severity or moreover in precipitating a life threatening asthma attack in AIA, which is one of the most important diseases complicating AI (34, 35). Although, AI is usually the last component appearing in the clinical picture of AIA, it might occur earlier in some patients, and followed by the other components of AIA such as rhinosinusitis, asthma, and nasal polyp (6-9). It is reported that some endocrine, metabolic, autoimmune and allergic conditions may accompany AIA (25-28). This survey disclosed other risk factors for AIA in addition to the nasal polyp, which was a well-described risk factor for AIA (36).

The mean ages were similar and AI started in the middle age, and there was a female predominance both in group I and group II (table I). Female predominance in AI is in accordance with the literature suggesting that two thirds of the patients with AI are women (2, 6, 8, 37, 38). The prevalence of AI was reported in the ranges of 0.3-0.9% in the normal population, 14-22% in the patients with nasal polyps and 0.4-1.4% in the patients with perennial rhinitis (1, 4, 39). Although the combination of asthma, AI and nasal polyp is generally named " ASA triad" , some authors named it as a " quadrate" taking rhinosinusitis into consideration (40). The majority of the patients have only the two components of the syndrome ie, asthma and AI (4). The prevalence of nasal polyps in AI was found between 50% and 100% in various surveys (13, 30, 41-43). In this study both rhinosinusitis and nasal polyps were significantly more common in the group I than in group II (table I). When the multiple logistic regression analysis was used to take the other factors into account rhinosinusitis and nasal polyps were strongly associated with AIA in group II (table III).

Chronic urticaria, dermographism, metal and antibiotic allergy were significantly less common in group I than in group II (table I). Data exists for these conditions accompanying AIA (28, 36). To our knowledge there was not any study, which investigated the association between AIA and these factors.

Smoking and food allergy frequency were not significantly different between the two groups and they could be decreasing the risk of AIA in AI patients although statistically not significant, when they were found separately, but increasing the risk of AIA when they were found together (table IV). Although there are reports indicating the higher frequency of food allergy/intolerance in AIA (28, 36), there is not any data about the association between AIA and food allergy/intolerance according to the status of smoking. A plausible explanation for the negative association between AIA and smoking could be the "healthy smoker" effect, according to which, patients having atopy and/or airway hyperreactivity might be selecting not to smoke (44).

Atopy, defined by at least one positive skin prick test to a common allergen, is one of the main risk factors for asthma (44, 46). Various studies indicated the atopy rate in AIA between 3-65% and this wide range might at least partially be due to methodologic differences (2, 9, 37, 39, 40, 47-50). Group I was significantly more atopic and more mite sensitive than group II (table I). Although, keeping pets at home was significantly more common in group II than in group I, pet sensitivity as determined by skin prick testing was significantly more common in group I than in group II (table I). This might be explained by the higher prevalence of atopic status group I, which could have precluded them from keeping pets at home. Since it is believed that the fur of pet animals is a good reservoir for mites, mite sensitivity is expected to be more common among the individuals who have pets than the other individuals who do not have pet (51). However our findings did not confirm this proposition as mite sensitivity was not different in the groups having pet and not having pet. Indoor allergens and pets are well known risk factors for atopic asthma (43, 52, 53). Contrary to this, findings of the multiple logistic regression indicated that having a pet decreased the relative risk of AIA as compared to AI (table III). This might again be explained by a health selection factor, according to which patients with airway hyperreactivity would prefer not to have pets to avoid the asthmatic attacks due to allergens.

Atopy and asthma are frequently associated with a high serum total IgE level (55, 56), so a significantly higher level of total IgE might be expected in group I than in group II. The serum total IgE levels were similar in the two groups. Total IgE level might vary due to many conditions such as smoking cigarette, age, sex, race and life style (54, 57). Although the difference between the means of the two groups was not significant, this could be due to the selective referral of patients with atopy to the clinic.

Familial history of atopy was more frequent in group I than in group II, but there was not significant difference for the familial history of AI (table I). This could be expected as both groups have AI.

Emergency room referral due to AI, within the last year of admission to our department was more common in group II than in group I (table II). This might be due to the fact that asthmatics having a chronic disease do not have much anxiety when they have an attack after analgesic consumption and most of them know what to do when they have an acute attack. The cumulative analgesic consumption rate did not show statistically significant difference (table I) between the two groups. In another survey of ours cumulative analgesic consumption rate was higher in the asthmatics with AI than in the asthmatics without AI (28). Although this could support the causative role of analgesic consumption for AIA, this could be recall bias. Aspirin intolerance was significantly more frequent, and paracetamol intolerance was significantly less frequent in group I than in group II (table II). This might be a coincidence or might be resulting from the widely held belief among physicians that paracetamol is a relatively safe analgesic for the patients with analgesic intolerance. Bronchospasm was the most frequent reaction after analgesic ingestion for group I, whereas urticaria and angioedema were more frequent in group II than in group I (table II). This is in accordance with the literature where reactions are grouped as bronchospasm and nasal congestion; urticaria and/or angioedema; and mixed type. It is reported that bronchospasm is more frequent in asthmatics than the AI patients (4, 6, 37, 39, 47, 48).

A multiple logistic regression model among patients, who had AI, investigated association between AIA and the patient characteristics. As the prevalence of AIA was not low in the study population logistic regression analysis findings are overestimations of the relative risk of AIA due to the factors investigated. The major concern in the analysis was to identify the determinants, which could increase the risk of AIA in AI patients.

Table IV

Examples of the associations between AIA and smoking and food intolerance in analgesic intolerance patients

	OR 95% CI
Never smoked no food intolerance	1
Ever smoked no food intolerance	0.37 (0.17, 0.80)
Never smoked food intolerance	0.50 (0.21, 1.16)
Ever smoked and food intolerance	1.31 (0.40, 4.30)

Therefore findings of the analysis should not be interpreted as representing the association between AIA and the other factors on their own. Having a nasal polyp and rhinosinusitis were strongly associated with AIA. As the patients included in this study were from an allergy outpatient clinic, there would be a selective referral of patients with nasal polyp and or rhinosinusitis for the diagnosis of AIA. Therefore the relative risk estimate for rhinosinusitis and polyp could be underestimated. Modification of the association between AIA and smoking in the patients who had food intolerance could be related to a genetic susceptibility of the patients with food intolerance for developing AIA. Age and gender were added to the model as potential confounders and their presence did not change much the relative risk estimates of the other factors. Skin prick test positivity and total IgE level were used to define the atopic status. However none of these two factors were statistically significant in the multiple logistic regression model. Patients who did not have these measurements had a higher prevalence of AIA as compared to those who had these measurements. Thus, their exclusion from the model was preferred to build the model in an unbiased study population.

Further follow-up of these AI patients could clarify if the observed differences between AIA and AI are real or related to the course of the disease. We suggest that a clinician encountered with a patient having AI should keep in mind the possibility of these two distinct phenotypes that could develop. Frequency of emergency referral was higher in the AI patients without asthma than the AIA patients. Therefore discovering the safe analgesics with oral provocation tests has a high priority as a measure to prevent the analgesic intolerance patients from having emergencies. Suggestions of this study should be tested by further follow-up and laboratory investigations.

RESUMEN

Antecedentes: la intolerancia a analgésicos (IA) puede aparecer aislada o con asma bronquial. Afecta aproximadamente el 10% de las personas asmáticas y puede aparecer antes o después de un episodio de asma.

Objetivo: investigamos los posibles factores de riesgo clínico que pueden contribuir a la evolución de IA aislada a asma inducida por analgésicos (AIA).

Métodos: fueron incluidos en esta encuesta 344 pacientes ingresados en la Unidad de Alergia de Adultos del Hospital Universitario Hacettepe entre enero de 1991 y marzo de 1999 con el diagnóstico de IA. Los pacientes con AIA (grupo I) (n = 191) se compararon con los pacientes con IA sin asma (grupo II) (n = 153). Los diagnósticos de IA y AIA se establecieron por la historia y pruebas de provocación oral. Todos los pacientes completaron un cuestionario estándar.

Resultados: el riesgo de AIA aumentó en presencia de pólipo nasal y rinosinusitis, con OR de 2,75 (IC 95%: 0,24; 1,17) y 0,37 (IC 95%: 0,24; 1,17) y 0,37 (IC 95%: 0,17; 0,80), respectivamente. La asociación de AIA con tabaquismo se modificó ligeramente con la intolerancia a alimentos (OR de ser fumador e intolerancia a alimentos: 1,31, IC de 95%: 0,40; 4,30).

Conclusión: posiblemente existen dos fenotipos de IA cuyas características clínicas difieren: uno que evoluciona a AIA (con pólipo nasal y/o rinosinusitis, y hábito de fumar si existe una alergia/intolerancia a alimentos) y el otro de IA sin asma (presencia de un animal doméstico, posible fumador). Los resultados de este estudio deben ser confirmados por nuevas investigaciones.

Palabras clave: Asma inducida por analgésicos. Intolerancia a analgésicos. Factores de riesgo.

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