Respiratory Medicine (2008) **102**, 1011–1014

ELSEVIER

respiratoryMEDICINE

Childhood onset analgesic intolerance: A marker for bronchial asthma in adulthood?

Begüm Ergan Arsava*, Gül Karakaya, A. Fuat Kalyoncu

Hacettepe University Medical School, Department of Chest Diseases, Adult Allergy Unit, 06100 Sihhiye, Ankara, Turkey

Received 6 December 2006; accepted 4 February 2008
Available online 21 March 2008

KEYWORDS
Analgesic intolerance;
Children;
Analgesic-induced asthma

Summary
Analgesic intolerance (AI) which is classically known as a disease of the middle-aged adults, not uncommonly starts in childhood. In this study we sought to identify the characteristics of childhood onset AI and evaluated its association with the development of asthma. Among 729 analgesic intolerant patients followed in our institution between January 1991 and July 2004, 50 (16 male, 34 female, 6.8% of the total AI population) had history of AI starting before the age of 18. The prevalence of asthma was 24% in childhood and increased to 40% during adulthood. Atopy was more common in patients with bronchial asthma ($p<0.05$). The mean ($\pm$SD) age of onset for asthma (18.6 ± 9.7 years) was significantly greater than the onset of both rhinitis and AI (13.0 ± 6.5 and 13.2 ± 4.0 years, respectively). This finding is different than the chronology of events reported in the literature for adult onset AI patients, in which rhinitis and asthma usually precede the development of AI. The presence of such a difference in the sequence of disease patterns may be a clue for the pathophysiologic differences underlying childhood and adult onset AI. The role of childhood onset AI as a risk factor for developing for asthma in adulthood should be further assessed in prospective patient cohorts.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin (acetyl salicylic acid—ASA), are among the most frequently prescribed medications worldwide. Hypersensitivity to these agents is one of the most important allergic drug reactions, with an estimated prevalence of 1% in the general population and 10–20% in patients with asthma.[1–5] Analgesic intolerance (AI) has been widely studied in the adult population and to a lesser extent in children. The prevalence of NSAID-induced asthma in children is around 5% with oral provocation tests (OPTs), whereas decrease in pulmonary functions range up to 28% in asthmatic children.[6,7] Adults with AI usually have either severe asthma with chronic sinusitis or chronic urticaria and the first reaction to NSAIDs generally occurs several years after the

*Corresponding author. Tel.: +90 312 305 15 31; fax: +90 312 310 08 09.
E-mail addresses: erganb@hacettepe.edu.tr, arsavab@hotmail.com (B. Ergan Arsava).

0954-6111/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2008.02.003

onset of these diseases.[3,5,8] In the present study, our aim was to find out the characteristics of childhood onset AI and to evaluate whether it's a risk factor for adulthood asthma.

Methods

The records of patients diagnosed with AI in our adult allergy unit between 1 January 1991 and 31 July 2004 were analyzed retrospectively. AI was defined by the presence of clinical history for at least two episodes of any of the following reactions within 20–180 min after aspirin or NSAID ingestion: angioedema, acute urticaria, nasal obstruction, rhinitis, bronchospasm or anaphylaxis. Patients reporting the first episode of reaction to NSAIDs before the age of 18 were accepted as having childhood onset AI and included into the study. The following information was obtained for all patients: age, gender, smoking history, past medical history, the presence of asthma, rhinitis and nasal polyposis and the duration of these diseases, characteristics of AI (age of onset, causative analgesic/analgesics, reaction type), accompanying allergic diseases (atopy, antibiotic allergy, metal allergy, dermographism), emergency department visits due to AI reactions, and familial history for atopy, asthma and AI. Atopy, which was defined as at least one positive reaction to any of the 16 common aeroallergens (*Dermatophagoides pteronyssinus*, *Phleum pratense*, *Olea europaea*, *Artemisia vulgaris*, *Parietaria officinalis*, *Corylus avellana*, *Betula verrucosa*, cat, dog, horse, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, cockroach, *Apis mellifera*, *Vespula*) in skin prick tests (SPT; ALK-Denmark, Stallergens-France and Greer-USA), was assessed in 32 patients. SPT could not be performed in the remaining 18 patients due to the presence of dermographism, acute urticaria and/or the need for antihistaminic treatment at the time of evaluation. The study population was divided into two groups according to the presence or absence of ever diagnosis of bronchial asthma.

All numerical values in the text are expressed as mean ± standard deviation (SD). Mann–Whitney *U* test and Wilcoxon signed rank test were used for comparison of numeric variables. Differences between categorical variables were compared by chi square or Fisher's exact test. A p value of <0.05 was considered significant. Statistical analysis was done by SPSS version 10.0.

Results

Out of 729 patients with the diagnosis of AI, 50 (6.8%; 34 females–16 males; female/male ratio: 2.1) had childhood onset AI. The mean (±SD) age at the time of first admission to our clinic because of any allergic complaint was 25.0 ± 9.4 (range 16–56) years. Baseline patient characteristics are shown in Table 1.

Twenty-four patients (48%) had a diagnosis of rhinitis on admission among which 22 had rhinitis starting during childhood period. The mean age of onset for rhinitis was 13.0 ± 6.5 (range 2–31) years. The diagnosis of nasal polyposis, confirmed by an ear–nose–throat (ENT) specialist, was established in five patients and four of these patients underwent polypectomy procedures due to nasal obstruction.

Table 1 Characteristics of patients with childhood onset analgesic intolerance.

	Bronchial asthma (+) *n* (%)	Bronchial asthma (−) *n* (%)	Total *n* (%)
N	20	30	50
Male	6 (30.0)	10 (33.3)	16 (32.0)
Smoking history	2 (10.0)	11 (33.6)	13 (26.0)
Familial atopy history	5 (25.0)	5 (16.6)	10 (20.0)
Familial asthma history*	9 (45.0)	3 (10.0)	12 (24.0)
Familial AI history	9 (45.0)	8 (26.6)	17 (34.0)
Metal allergy	5 (25.0)	6 (20.0)	11 (22.0)
Antibiotic allergy	4 (20.0)	10 (33.3)	14 (28.0)
Dermographism	3 (15.0)	4 (13.4)	7 (14.0)
Atopy* (SPT positivity/SPT performed)	7/13 (53.8)	3/19 (15.7)	10/32 (31.2)
Rhinitis*	17 (85.0)	7 (23.3)	24 (48.0)
Nasal polyposis	4 (20.0)	1 (3.3)	5 (10.0)
AI			
Aspirin	15 (85.0)	19 (63.3)	34 (68.0)
Other NSAIDs	5 (15.0)	11 (36.6)	16 (32.0)
Reactions			
Respiratory			
Bronchospasm*	12 (60.0)	1 (3.3)	13 (26.0)
Nasal obstruction/rhinitis*	5 (25.0)	1 (3.3)	6 (12.0)
Dermatologic			
Acute urticaria*	8 (40.0)	22 (73.3)	30 (60.0)
Angioedema*	9 (45.0)	23 (76.7)	32 (64.0)

SPT: skin prick tests; AI: analgesic intolerance; NSAID: non-steroidal anti-inflammatory drug.
*$p<0.05$.

Seventy-one percent of the patients with rhinitis had also a diagnosis of asthma, whereas asthma was present in only 11% of the patients without rhinitis.

Overall 20 patients (40%) had a diagnosis of asthma. The diagnosis was established during childhood ($\leqslant$18 years of age) in 12 patients (24%) and during adulthood ($>$18 years of age) in eight patients (16%). The *incidence* of asthma was 21% during adulthood (8 out of 38 patients without prior diagnosis of asthma). There was no statistical difference regarding the incidence rates before (24%) and after 18 years (21%). The mean age of onset for asthma was 18.6 ± 9.7 (range 5–40) years; it was found to be lower in males than females (14.3 ± 9.5 and 20.5 ± 9.5 years, respectively, $p<0.05$). The mean age of onset for asthma was significantly later with respect to both the mean age of onsets for rhinitis and AI ($p<0.01$) (Figure 1). As expected, the frequency of rhinitis was higher in the asthmatic group (85% vs 23%, $p<0.01$). Among patients who were evaluated by SPT, atopy was more common in patients with bronchial asthma when compared to patients without asthma ($p<0.05$).

According to clinical history, 68% of patients were intolerant to aspirin and the remaining were intolerant to other NSAIDs (metamizole: 8%; paracetamol: 6%, more than one NSAID: 18%). The mean age of onset for AI was 13.2 ± 4.0 (range 3–18) years. The most common reported reactions triggered by NSAIDs were angioedema (64%) appearing as periorbital edema in 34% of patients; acute urticaria (60%), bronchospasm (26%), and nasal obstruction and rhinitis (12%). Bronchospasm and nasal obstruction/rhinitis were significantly more common in the asthmatic group ($p<0.01$ and $p<0.05$, respectively), whereas acute urticaria and angioedema were significantly more common ($p<0.05$ for both of the symptoms) in patients without asthma. Seventeen patients (34%) had to visit emergency department due to AI reaction; angioedema ($n=6$), acute urticaria ($n=2$), bronchospasm ($n=2$) and combinations of these symptoms ($n=7$).

OPT were performed in order to find out a safe alternative NSAID in 32 patients and due to presence of insufficient or suspicious history in two cases. Nine patients had positive reactions in OPT: two with ASA, five with meloxicam, one with nimesulid and one with piroxicam.

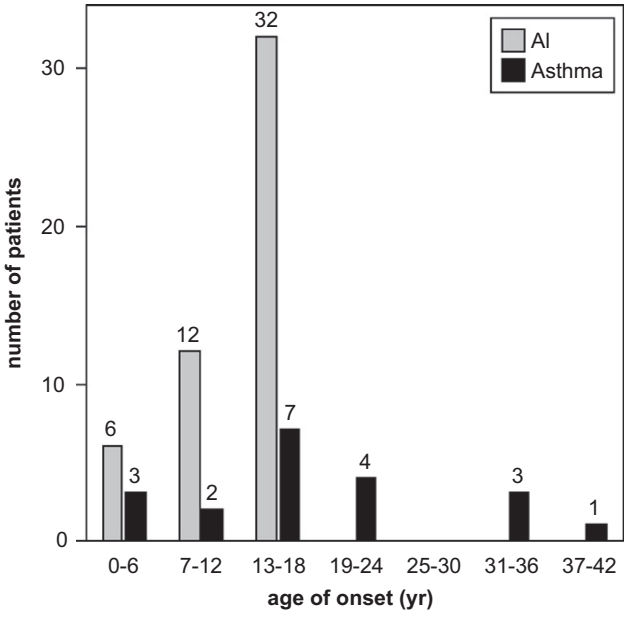

Figure 1 Age of onset of AI and asthma in childhood onset analgesic intolerance.

Discussion

NSAIDs are effective for the treatment of a wide spectrum of diseases and their widespread use contributes to the high incidence of AI. In a recent review, the prevalence of aspirin induced asthma determined by OPT was reported as 21% in adults and 5% in children.[6] Our study was undertaken to determine the characteristics of early onset AI by a retrospective analysis of patients diagnosed as analgesic intolerant in a tertiary adult allergy clinic. Among all the patients with AI, 6.8% had childhood onset AI and about two thirds of these patients were women, which was consistent with the reports in the previous literature.[2,5,8]

One of the most important results obtained from this study was the significant difference between the mean onset ages of AI, rhinitis and asthma. AI and rhinitis preceded the onset of asthma by approximately five years. This finding is different than the chronology of events reported in the literature for adult onset analgesic intolerant asthma (AIA), in which AI develops after rhinitis and asthma.[2,3,5,8] Whether this disparity in the chronology of events represents a difference in the underlying pathophysiology of adult and childhood onset AI is subject to further studies.

The mean age of onset for asthma was significantly lower in males compared to females. This finding may just be a reflection of the fact that childhood asthma occurs more commonly in males or may be secondary to different disease progression that may be observed between genders under the influence of female sex hormones.[5,9]

Although SPT was not performed in every patient, atopy was more common in patients with asthma. Atopy is a well-known risk factor for asthma. Previous studies have shown that rhinitis and asthma might manifest as AIA in earlier age in patients with atopy.[5] This interplay between atopy, asthma and AIA, might contribute to the predisposition of atopic AI patients to develop asthma earlier in life.

Studies about AI in children are limited in number and usually retrospective or cross-sectional in the literature. In our study due to retrospective analysis of cases, the diagnosis of AI was done primarily by clinical history. Based on the clinical features AI can be subdivided into two main groups: asthmatic and/or rhinitic (respiratory), urticaria/angioneurotic edema (dermatologic).[2] The most common reaction reported in our study group was dermatologic, mainly being periorbital edema. Respiratory symptoms were significantly more common in the asthmatic group, whereas dermatological symptoms were frequent in patients without asthma. This finding raises the question that whether AI presenting with respiratory symptoms in childhood could be a risk factor for developing asthma in the following years.

The prevalence of nasal polyposis in AI, which was found between 31% and 71% in various surveys,[2,5,10] was 10% in our patients. However, this result may be an underestimation of the actual figure, as not all of our patients had an ENT evaluation, which should ideally be done in every patient with AI.

A family history of AI was more common in our study population when compared with the previous reports in the literature (34% vs 4.5–6%).[8,11,12] This might be due to the long follow up of patients who were reassessed in every visit. The presence of a family history of atopy and asthma were 20% and 24%, respectively. The differences between the frequencies of familial history of each of these diseases might implicate that AI, atopy and asthma are disorders with different genetic basis.

Aspirin was the most common responsible agent for AI in adults. Despite the reports showing paracetamol as the most common consumed analgesic in Turkey,[13] and less frequent use of aspirin in pediatric age group after the demonstration of its relationship with Reye's syndrome, our study shows that, aspirin is still the most common responsible agent (68%) for AI in childhood. One of the basic characteristics of AI is cross-reaction. Therefore, the patients in our cohort reporting AI triggered by aspirin, are expected to develop allergic reactions with other NSAIDs. However, a formal challenge test with various NSAIDs has not been performed in most of the cases. Physicians usually hesitate performing OPT, especially in children, as a diagnostic test for AI because of the possibility of life threatening reactions. There is currently no in vitro test that has any diagnostic value in AI, and OPT, nasal or inhalation challenge are still the main tests recommended for the diagnosis of AI.[14]

In conclusion, AI which was once thought to be a disease of adulthood, can have childhood onset and children may have different sequence patterns of the disease. Despite being a retrospective study and being confounded by recall bias, with the diagnosis of AI depending on clinical history, the study shows that AI in childhood may be a risk factor for adult asthma. The pattern and pathophysiology of childhood onset AI and its role in the development of bronchial asthma must be evaluated in prospective, population-based epidemiological studies.

Conflict of interest statement

None of the co-authors has any direct or indirect conflicts of interest, financial or otherwise, related to the subject of this article.

References

1. Settipane RA, Constantine HP, Settipane GA. Aspirin intolerance and recurrent urticaria in normal adults and children: epidemiology and review. *Allergy* 1980;**35**:149–54.
2. Schiavino D, Nucera E, Milani A, et al. The aspirin disease. *Thorax* 2000;**55**(suppl 2):S66–9.
3. Babu KS, Salvi SS. Aspirin and asthma. *Chest* 2000;**118**:1470–6.
4. Settipane GA, Chafe FH, Klein DE. Aspirin intolerance. II: a prospective study in an atopic and normal population. *J Allergy Clin Immunol* 1974;**53**:200–4.
5. Szczeklik A, Nizankowska E, Duplaga M, On behalf of the AIANE Investigators. Natural history of aspirin-induced asthma. *Eur Respir J* 2000;**16**:432–6.
6. Jenkins C, Costello J, Hodge L. Systemic review of prevalence of aspirin-induced asthma and its complications for clinical practice. *Br Med J* 2004;**328**:434–7.
7. Rachelevsky GS, Coulson A, Siegel SC, Stiehm ER. Aspirin intolerance in chronic childhood asthma: detected by oral challenge. *Pediatrics* 1975;**56**:443–8.
8. Kalyoncu AF, Karakaya G, Şahin AA, Barış YI. Occurrence of allergic conditions in asthmatics with analgesic intolerance. *Allergy* 1999;**54**:428–35.
9. Forbes L. Asthma and atopy: endocrine or metabolic conditions? *Thorax* 2005;**60**:793–4.
10. Kowalski ML. Rhinosinusitis and nasal polyposis in aspirin sensitive and aspirin tolerant patients: are they different? *Thorax* 2000;**55**(suppl 2):S84–6.
11. Szczeklik A, Sanak M. Genetics of aspirin-induced asthma. *Thorax* 2000;**55**(suppl 2):S45–7.
12. Karakaya G, Demir AU, Kalyoncu AF. From analgesic intolerance to analgesic induced asthma: are there some determinants? *Allergol Immunopathol* 2000;**28**:229–37.
13. Kalyoncu AF. Acetaminophen hypersensitivity and other analgesics. *Ann Allergy* 1994;**72**:285.
14. Nizankowska-Mogilnicka E, Bochenek G, Mastelerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;**62**:1111–8.