ORIGINAL ARTICLE

Incidence of aspirin hypersensitivity in patients with chronic rhinosinusitis and diagnostic value of urinary leukotriene E_4

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KEY WORDS

aspirin hypersensitivity, asthma, chronic sinusitis, leukotriene E_4

ABSTRACT

INTRODUCTION Chronic rhinosinusitis (CRS) with nasal polyposis (NP) may be associated with hypersensitivity to nonsteroidal anti-inflammatory drugs, representing a syndrome of aspirin-exacerbated respiratory disease (AERD).

OBJECTIVES The aim of the study was to validate a simple measurement of urinary leukotriene E_4 ($uLTE_4$) excretion for the diagnosis of AERD in patients with CRS and indication for surgery.

PATIENTS AND METHODS Subjects requiring functional endoscopic sinus surgery (FESS) were recruited from the Department of Otolaryngology ($n = 24$). Before surgery, a standard oral placebo-controlled aspirin challenge was performed to diagnose aspirin hypersensitivity. Urine samples were collected on the placebo day and both before and within 2 to 4 hours after aspirin challenge for $uLTE_4$ measurement.

RESULTS All patients with CRS had sinusitis confirmed by computed tomography. Previous ear, nose, and throat surgery was performed in 70% of the patients, NP was present in 86%, and asthma was diagnosed in 62.5%. AERD was diagnosed in 8 subjects (7 women and 1 man). Five of those patients had bronchoconstriction. At baseline, median $uLTE_4$ was 7.5-times higher in AERD subjects than in the remaining patients. It increased almost 6-fold following the challenge, while remained unchanged in patients without aspirin hypersensitivity. Pretest $uLTE_4$ had a sensitivity of 87.5% and specificity of 93.75% to diagnose aspirin hypersensitivity in patients with CRS. After the challenge, the values improved to 100% sensitivity and 93% specificity.

CONCLUSIONS Among CRS subjects requiring FESS, as many as 33.3% may have AERD and respond to a small provocative dose of aspirin with bronchoconstriction and/or mucosal and skin edema. A simple and inexpensive measurement of $uLTE_4$ can help diagnose AERD in patients with CRS with sensitivity of 87.5%, but its specificity is limited and depends on the arbitrary threshold of $uLTE_4$.

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Received: May 27, 2012.
Revision accepted: July 10, 2012.
Published online: July 19, 2012.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012; 122 (9): 422-427

INTRODUCTION Chronic rhinosinusitis (CRS) with nasal polyposis (NP) can be associated with aspirin hypersensitivity, representing a syndrome of aspirin-exacerbated respiratory disease (AERD). While the pathophysiology of allergic respiratory diseases has been well studied, our understanding of nonallergic CRS and its impact on asthma is still a matter of debate.[1] There is a gap in clinical and pathophysiological knowledge on the effect of upper airway diseases, especially of CRS with NP, on asthma. Nasal endoscopy, computed tomography (CT) imaging, and clinical symptoms are all helpful in establishing the diagnosis,[2] but provide no information about the etiology and lower airway comorbidity of CRS with NP.

The medical management of CRS is currently focused on the control of inflammation that aggravates nasal obstruction. Surgical interventions

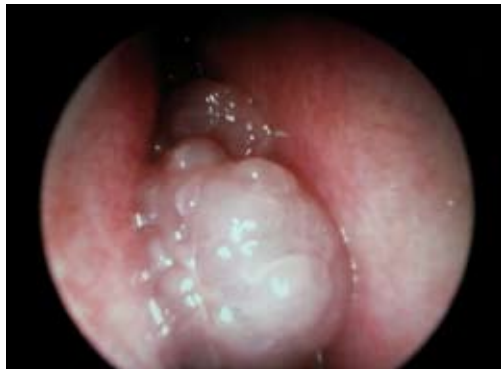

FIGURE 1 Endoscopic image of nasal polyps

aim to restore patency of the ostiomeatal complex but relapses are common. We wondered about the unbiased estimate of AERD frequency among patients with CRS with or without NP, since most patients are usually diagnosed following asthma exacerbations. The hallmark of AERD is the overproduction of cysteinyl leukotrienes, which have been known for over 20 years. Leukotriene E_4 (LTE_4) is excreted in urine and could be used as one of the markers of AERD. [3] However, $uLTE_4$ may decrease after sinus surgery.[4] In this study, we screened patients with CRS and NP for AERD; patients were recruited from the ear, nose, and throat (ENT) clinic before surgery. We also aimed to estimate the diagnostic value of simple $uLTE_4$ measurements.

PATIENTS AND METHODS

Patients Consecutive patients were recruited at the Department of Otolaryngology, Jagiellonian University Medical College, Kraków, Poland. The inclusion criterion was CRS with or without NP requiring functional endoscopic sinus surgery (FESS). A standard oral placebo-controlled aspirin challenge was performed at the Department of Pulmonology to diagnose AERD.[5] All study subjects were in clinically stable condition and had a negative history of respiratory tract infection or asthma exacerbation within the preceding 6 weeks.

The diagnosis of asthma was based on patient's history, physical examination, histamine bronchial challenge test, or bronchial obstruction reversibility when indicated.

All subjects with AERD had a history of the disease which developed following a typical sequence of symptoms starting with persistent rhinitis, then accompanied by asthma, aspirin sensitivity, and NP.[6] They had a past history of at least 1 asthmatic attack triggered by an ingestion of aspirin or other nonsteroidal anti-inflammatory drug (NSAID).

All study subjects gave informed consent to participate in the study, and the protocol was approved by the Jagiellonian University Bioethical Committee (KBET/49/B/2012).

Aspirin challenge test Before oral aspirin challenge, a standard modification of the current therapy was requested. Long-acting β-mimetics were withheld for 48 hours, short-acting β-mimetics for 6 hours, and antihistamines for 7 days preceding the test. No patient received cysteinyl-leukotriene-modifying drugs (receptor antagonists or inhibitor of biosynthesis) or systemic corticosteroids. Disease-controlling treatment with inhaled corticosteroids was maintained. In all asthmatic subjects, a standard spirometry and assessment of disease control using the Asthma Control Test was done before aspirin challenge.[7] The test contains 5 questions with a 5-point scale and reflects the level of asthma control in the previous 4 weeks. The maximum score of 25 means well-controlled asthma, a score between 20 and 24 is partly controlled asthma, and a score less than 20 characterizes poorly controlled disease. Only subjects with well and partially controlled asthma and with forced expiratory volume in 1 second (FEV_1) exceeding 70% were scheduled for the challenge test.

Urine collection and urinary leukotriene E_4 measurements The measurement of $uLTE_4$ estimates the systemic production of cysteinyl leukotrienes. Urine samples were collected on the placebo day and then before and within 2 to 4 hours after oral aspirin challenge. $uLTE_4$ was measured using the LTE_4 ELISA kit (Cayman Chemical Co., Ann Arbor, Michigan, United States) following 1:10 to 1:30 dilution of crude samples with phosphate-buffered saline.[8] The results were adjusted for urinary creatinine concentration and were presented in picograms per milligram of creatinine. The diagnostic value of $uLTE_4$ was estimated using the receiver-operator characteristic curve (ROC; GraphPad Prism Software 4, La Jolla, California, United States) with the oral aspirin challenge test as gold standard. In this analysis, diagnostic performance of $uLTE_4$ was assessed across the range of the measured values. The area under the ROC curve characterizes the overall discrimination between aspirin-tolerant and -hypersensitive subjects, while sensitivity and specificity was calculated for the arbitrally chosen $uLTE_4$, which provided the best stratification of the study subjects.

RESULTS

Characteristics of the subjects with chronic rhinosinusitis Thirty subjects with CRS and NP were recruited to the study, but only 24 fulfilled the entry criteria. Five patients had poorly controlled asthma and/or FEV_1 below 70%. One patient could not undergo spirometry due to laryngeal nerve injury after thyreoidectomy. In all patients, sinusitis was confirmed by CT imaging. Nasal polyps were diagnosed on laryngological examination (FIGURE 1). The median of CRS history was 9 years (1–50 years). As many as 83.3% of the patients experienced previous ENT surgery; 58.3% either presented NP on examination or had a history of NP. Physicians diagnosed asthma in 66.7% of the recruited subjects; all subjects with AERD had a history of asthma (P <0.01). Neither age, duration of CRS, or the frequency of nasal polyp surgery differentiated patients with AERD from aspirin-tolerant subjects.

TABLE 1 Clinical characteristics of the study subjects

	Subjects with CRS (n = 24)	Aspirin-hypersensitive subjects (n = 8)	Aspirin-tolerant subjects (n = 16)
male/female, n	6/18	1/7	5/9
age, y	45.8 ±16.1	41 ±15.8	48.2 ±16.9
duration of CRS, y	9 (1–50)*	7 (1–50)*	17 (1–51)*
history of nasal polyps, n (%)	14 (58.3)	7 (87.5)[a]	7 (43.8)
previous ENT surgery, n (%)	17 (70.8)	5 (62.5)	12 (75)
asthma, n (%)	16 (66.7)	8 (100)[b]	8 (50)
atopy, n (%)	8 (33.3)	1 (12.5)	7 (43.8)
allergic rhinitis, n (%)	5 (20.8)	0 (0)	5 (31.3)
total serum IgE, IU/ml	57.1 (20.3–139)	67 (22.5–163)	51.2 (20.3–94.1)
peripheral blood eosinophil count, IU/mm^3	424.5 (251.8–516.5)	420 (284–1216)	428.5 (251.8–480)

Data are presented as mean ± SD, number (percentage), median (min–max)*, or median (25th–75th percentile).

a $P = 0.014$ for the comparison between aspirin-hypersensitive and aspirin-tolerant subjects (Fisher's exact test)
b $P = 0.04$ for the comparison between aspirin-hypersensitive and aspirin-tolerant subjects (Fisher's exact test)

Abbreviations: CRS – chronic rhinosinusitis, ENT – ear, nose, and throat, IgE – immunoglobulin E, SD – standard deviation

TABLE 2 Oral aspirin challenge test results

	Subjects with CRS (n = 24)	Aspirin-hypersensitive subjects (n = 8)	Aspirin-tolerant subjects (n = 16)
pretest FEV_1, % predicted	94.7 ±15.9	86.6 ±13.3[a]	98.8 ±15.9
ΔFEV_1	NA	20.6 ±15.5	0.3 ±3.55
bronchoconstriction: decrease in FEV_1 >20%, n	NA	5	0
pretest LTE_4, pg/mg creatinine	373.5 (173.3–1110)	2371 (1012.3–10,284)[b]	316.5 (118.5–392.8)
LTE_4 after aspirin challenge, pg/mg creatinine	464 (248–8728)	16,996.5 (3808–26,026)[c]	262 (157–429)
other clinical manifestation of hypersensitivity (mucosal and facial skin edema, rhinitis, conjunctivitis), n	NA	3	0

Data are presented as mean ± SD or median (25th–75th percentile).

a $P = 0.04$ for the comparison between aspirin-hypersensitive and aspirin-tolerant subjects (analysis of variance)
b $P = 0.002$ for the comparison between aspirin-hypersensitive and aspirin-tolerant subjects (Mann-Whitney *U* test)
c $P = 0.0007$ the comparison between aspirin-hypersensitive and aspirin-tolerant subjects (Mann-Whitney *U* test)

Abbreviations: FEV_1 – forced expiratory volume in 1 second, LTE_4 – leukotriene E_4, NA – not applicable, others – see TABLE 1

Frequency of atopy, defined as a documented positive skin prick test reaction to common allergens, the presence of allergen-specific immunoglobulin E (IgE) at a concentration exceeding 35 IU/ml, or both, did not differ between the groups. Moreover, the groups did not differ in peripheral blood eosinophil counts and total serum IgE levels. The characteristics of the study subjects are summarized in TABLE 1.

Aspirin challenge test Aspirin challenge test revealed aspirin hypersensitivity in 8 subjects (7 women, 1 man). Five of them experienced bronchoconstriction during the challenge (average FEV_1 decrease by 30.4%; 1 severe asthmatic attack following 45 mg of aspirin). In this group, the mean provocative dose was 111 mg of aspirin. In 3 remaining subjects with AERD, mucosal and facial skin angioedema developed during the challenge with the cumulative 312 mg dose of aspirin. In aspirin-tolerant subjects, we observed both a decrease and an increase of FEV_1 after aspirin challenge test; however, these changes did not exceed 10% (TABLE 2).

Differences in urinary leukotriene E_4 concentrations $uLTE_4$ was significantly higher in patients with AERD than in aspirin-tolerant patients. There was a satisfactory correlation between the 2 measurements of $uLTE_4$ performed on the placebo day and before aspirin challenge (Spearman's rho = 0.856; $P < 0.0001$; FIGURE 2). Median $uLTE_4$ concentration at baseline was 7.5-times higher in AERD subjects compared with aspirin-tolerant patients (2371 vs. 316 pg/mg creatinine; FIGURE 3). It increased almost 6-fold following aspirin challenge, while remained unchanged in aspirin-tolerant subjects with CRS (16,696 vs. 262

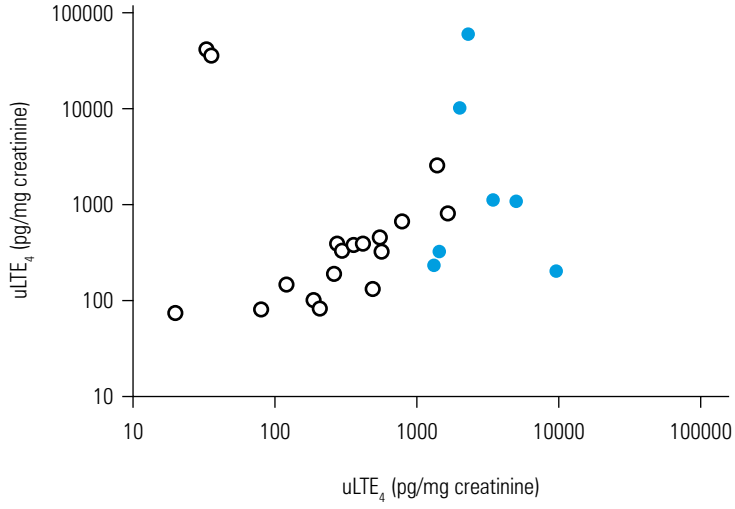

FIGURE 2 Urinary leukotriene E_4 ($uLTE_4$) levels were measured twice: on the placebo day and before aspirin administration; individual $uLTE_4$ levels were intercorrelated (Spearman's rho = 0.856); white circles denote aspirin tolerance, blue circles denote aspirin-exacerbated respiratory disease

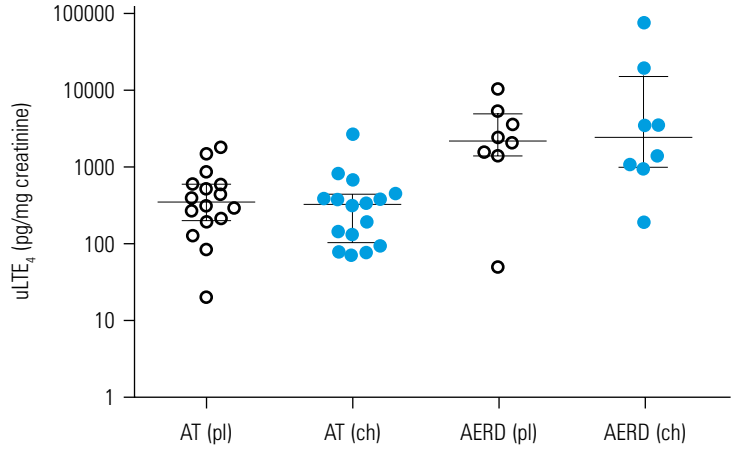

FIGURE 3 Urinary leukotriene E_4 ($uLTE_4$) levels on the placebo day (pl) and before aspirin administration (ch); median and interquartile range (25%–75%); white circles denote aspirin tolerance (AT), blue circles denote aspirin-exacerbated respiratory disease (AERD)

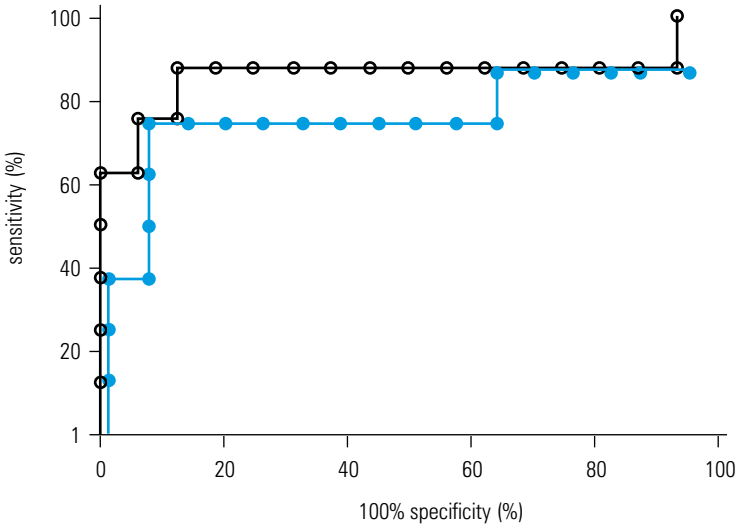

FIGURE 4 Receiver operator characteristics for the placebo day (white circles) and pretest urinary leukotriene E_4 ($uLTE_4$; blue circles); sensitivity and specificity for diagnosis of aspirin--exacerbated respiratory disease is shown over the full range of $uLTE_4$ concentrations

pg/mg creatinine). These differences were statistically significant ($P = 0.0002$ for baseline $uLTE_4$ excretion and $P = 0.0007$ for post-challenge increase; Mann-Whitney U test). However, pretest $uLTE_4$ had a limited sensitivity of 87.5%. For $uLTE_4$ values within the range from 184 to 859 pg/mg creatinine, we observed increasing specificity of discrimination from 37.5% to 93.75% between AERD and aspirin-tolerant patients with CRS (area under the ROC curve = 0.859 on the placebo day and 0.898 before aspirin challenge; $P < 0.01$ for both; FIGURE 4). Thus, the threshold $uLTE_4$ value of 859 pg/mg creatinine could be assumed as the best diagnostic value. By comparison, post-challenge $uLTE_4$ improved discrimination to 100% sensitivity and 93.75% specificity (area under the ROC curve = 0.954) at the cut-off value of 940 pg/mg creatinine.

DISCUSSION

In our pilot study, among CRS subjects requiring FESS, as many as 33.3% had AERD and responded to a small provocative dose of aspirin with bronchoconstriction and/or mucosal and skin edema. AERD remains widely underdiagnosed both in patients with asthma and with CRS. There are numerous reasons for this including failure to recognize NSAID-induced reactions in some patients, deliberate avoidance of NSAIDs in fear of adverse reactions among allergic patients, and self-administration of rescue medication in asthmatics who mistake the drug reaction for asthma exacerbation. Limited awareness of AERD among health care professionals is an additional factor contributing to a low diagnosis rate.[9] Thus, a differential diagnosis of aspirin hypersensitivity should be made in all patients with CRS/NP admitted to the ENT department. Even more importantly, it seems that the ENT department could play a pivotal role in diagnosing aspirin hypersensitivity, because CRS symptoms in most cases strongly affect patients' activity and force them to seek medical treatment. Whereas severe asthmatic attack or a life-threatening anaphylactoid reaction following NSAID ingestion is observed incidentally,[10] subjects with CRS have both higher incidence of AERD and better chance of establishing the correct diagnosis. Our study also shows that the measurement of $uLTE_4$ is a simple and inexpensive laboratory method for diagnosing AERD, which can correctly identify 87.5% aspirin-sensitive subjects with CRS but has limited specificity. Further studies are required to confirm the effect of FESS on $uLTE_4$, as it can decrease the urinary excretion and worsen the diagnostic performance of this biomarker.

Acknowledgments The study was supported by PSPB-072/2010 – a grant from Switzerland through the Swiss Contribution to the enlarged European Union.

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Występowanie nadwrażliwości na aspirynę u chorych na przewlekły nieżyt nosa i zapalenie zatok przynosowych oraz wartość diagnostyczna pomiaru leukotrienu E_4 w moczu

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SŁOWA KLUCZOWE

astma, leukotrien E_4, nadwrażliwość na aspirynę, przewlekłe zapalenie zatok

STRESZCZENIE

WPROWADZENIE Przewlekły nieżyt nosa i zatok (*chronic rhinosinusitis* – CRS) wraz z polipami nosa może wiązać się z nadwrażliwością na niesteroidowe leki przeciwzapalne jako choroba dróg oddechowych zaostrzona przez aspirynę (*aspirin-exacerbated respiratory disease* – AERD).

CELE Celem pracy było sprawdzenie przydatności prostego pomiaru stężenia leukotrienu E_4 (LTE_4) w moczu (*urinary* LTE_4 – $uLTE_4$) w diagnostyce AERD u chorych na CRS ze wskazaniem do leczenia operacyjnego.

PACJENCI I METODY Chorych wymagających czynnościowej endoskopowej operacji zatok (*functional endoscopic sinuses surgery* – FESS) rekrutowano w Klinice Otolaryngologii (n = 24). W okresie poprzedzającym zabieg wykonano u nich standardową doustną próbę aspirynową w celu wykrycia nadwrażliwości na aspirynę. W dniu próby z placebo oraz próby właściwej, bezpośrednio przed prowokacją oraz 2–4 godziny po jej zakończeniu zebrano próbki moczu do oznaczenia $uLTE_4$.

WYNIKI U wszystkich chorych na CRS potwierdzono zapalenie zatok za pomocą tomografii komputerowej. Wcześniejsze zabiegi laryngologiczne przeprowadzano u 70% chorych, u 86% występowały polipy nosa, a u 62,5% rozpoznano astmę. U 8 chorych (7 kobiet i 1 mężczyzny) stwierdzono nadwrażliwość na aspirynę. U 5 z tych chorych w czasie próby obserwowano skurcz oskrzeli. Przed próbą mediana $uLTE_4$ w grupie z nadwrażliwością na aspirynę była 7,5 razy większa niż u pozostałych osób. Różnica ta wzrosła 6-krotnie po próbie prowokacyjnej, podczas gdy w grupie bez nadwrażliwości na aspirynę stężenie $uLTE_4$ się nie zmieniło. Diagnostyka nadwrażliwości na aspirynę u chorych na CRS na podstawie pomiaru $uLTE_4$ przed próbą prowokacyjną wykazała 87,5% czułość i swoistość sięgającą 93,75%. Wartości te po próbie prowokacyjnej osiągnęły 100% czułość i 93% swoistość.

WNIOSKI Wśród chorych na CRS wymagających FESS do 33,3% może mieć AERD i reagować na prowokacyjną dawkę aspiryny dusznością i/lub obrzękiem błony śluzowej i skóry. Prosty i niedrogi pomiar stężenia $uLTE_4$ może z czułością 87,5% pozwolić na rozpoznanie nadwrażliwości na aspirynę u chorych na CRS, lecz swoistość tego parametru jest ograniczona i zależy od przyjętego progowego stężenia $uLTE_4$.

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Praca wpłynęła: 27.05.2012.
Przyjęta do druku: 10.07.2012.
Publikacja *online*: 19.07.2012.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2012; 122 (9): 422-427