

Localized unilateral periorbital edema induced by aspirin

Kursteen S Price, MD and David M P Thomson, MD

Background: Aspirin intolerance manifested as bronchospasm or urticaria/angioedema has been observed since the beginning of this century.

Objective: To report a novel case of intolerance to aspirin ingestion.

Methods: Case report; routine skin testing; pulmonary function testing; aspirin challenge.

Results: A 30-year-old man with a history of left ocular trauma at the age of 10 noted a 3-year history of left periorbital angioedema after aspirin but not other nonsteroidal anti-inflammatory drugs. Incremental oral aspirin challenge resulted in this unilateral symptomatology at a dose of 673 mg.

Conclusion: To the best of our knowledge, this is the first reported case of unilateral periorbital edema following aspirin ingestion.

Ann Allergy Asthma Immunol 1997;79:420-22.

INTRODUCTION

Aspirin intolerance has been reported since its synthesis and widespread medicinal use began more than 90 years ago¹; however, the mechanism(s) of aspirin sensitivity remains unknown. Recognized clinical manifestations of aspirin intolerance include angioedema, urticaria, rhinoconjunctivitis, asthma, and anaphylaxis. These symptoms may occur in isolation or in any combination and are estimated to occur in up to 90% of the general population and up to 30% of asthmatic patients.^{2,3}

Controlled oral challenge is the only definitive means by which aspirin sensitivity can be determined.⁴ Challenge studies suggest that patients with aspirin sensitivity be subgrouped according to symptom expression, coexistence of atopy, and nonsteroidal anti-inflammatory drug cross-intolerance.⁵ Patients with aspirin-induced asthma are typically nonatopic and often suffer from chronic rhinitis, sinusitis, and nasal polyposis. They are generally intolerant to other nonsteroidal anti-inflammatory drugs that inhibit cyclo-

oxygenase and are able to ingest these drugs once desensitized to aspirin.³ In contrast, patients with cutaneous reactions to aspirin ingestion typically exhibit pre-existing urticaria and atopy that is exacerbated by aspirin resulting in systemic urticaria or angioedema but may also manifest localized reactions.⁶ Based on these observations it has been suggested that the mechanism responsible for aspirin-induced urticaria and angioedema may be different from that responsible for nasal and respiratory aspirin reactivity. Cases of aspirin intolerance manifest as initial periorbital angioedema followed by acute asthma attack are reported and such patient subgrouping may be misleading.^{5,7}

We present the case of a young man with a history of repeated unilateral periorbital angioedema following aspirin ingestion. Hypothesized mechanisms of aspirin tolerance are discussed.

CASE REPORT

A 30-year-old man of Italian descent was referred to our Allergy/Immunology service because of a 3-year history of repeated left periorbital angioedema lasting 24 hours following ingestion of aspirin for occasional headaches. Prior to this, the patient had tolerated aspirin

and other nonsteroidal anti-inflammatory drugs. The patient was otherwise healthy and denied symptoms of bronchospasm, cutaneous eruptions, systemic or other forms of localized urticaria/angioedema after aspirin ingestion or otherwise. The patient had undergone two surgeries to remove a foreign body from the left eye following trauma at the age of 10. The patient's mother had had seasonal allergic rhinitis.

Incremental oral aspirin challenge was conducted under constant supervision with vital signs and pulmonary function monitoring at half-hour intervals. A starting dose of 1 mg was used followed by doses of 2, 5, 10, 50, 100, 200, and 325 mg at half-hour intervals. Thirty minutes after the ingestion of 325 mg or a total of 673 mg of aspirin, the patient experienced pruritus of the left eye. The upper and lower eyelids were found to be hyperemic but no edema was observed at that time. Over the next hour the patient developed marked periorbital edema of the left eye. Blood pressure, heart rate, respiratory rate, and spirometric parameters remained stable and within normal limits throughout the challenge test. The right eye was unaffected.

Skin prick testing with aeroallergens, saline and histamine controls revealed strongly positive responses to the pollen of lamb's-quarters, mixed grasses, and trees. He had weak responses to salmon, shellfish, and milk.

DISCUSSION

We describe the case of a healthy 30-year-old male who presented with a 3-year history of repeated left periorbital edema following aspirin ingestion. The patient had no underlying respiratory or cutaneous disease and had tolerated aspirin and nonsteroidal anti-inflammatory drugs, prior to this

From the Division of Allergy & Clinical Immunology, Department of Medicine, Montreal General Hospital, McGill University, PQ.

Received for publication December 17, 1996.

Accepted for publication in revised form April 25, 1997.

time. The reaction described by the patient was observed during aspirin challenge in our clinical and proves his sensitivity to this drug. In fact, oral challenge is the only definitive diagnostic test for aspirin intolerance irrespective of the presenting clinical symptoms.^{4,8}

Intolerance to aspirin is manifested as variable combinations of angioedema, urticaria, rhinoconjunctivitis, asthma, and/or anaphylactoid shock.⁹⁻¹² To our knowledge there is only one previous report documenting two patients with localized periorbital edema after aspirin ingestion.⁶ In that study, terfenadine enabled the patients to tolerate aspirin with no side-effects.⁶ Unlike those cases of isolated bilateral periorbital edema our patient manifested his aspirin intolerance as repeated unilateral periorbital edema of the left eye exclusively. Unfortunately, the patient was unwilling to undergo further challenge with aspirin or other nonsteroidal anti-inflammatory drugs, and we were unable to determine cross-reactivity or establish whether premedication with an H₁-blocker would prevent his reactions to aspirin.

The mechanism accounting for aspirin intolerance is unclear. Immune recognition of aspirin seems unlikely. Mast cell degranulation has been shown to occur in aspirin-induced urticaria and angioedema, and there is one case report of transient levels of aspirin specific IgE antibodies in the serum of a patient with angioedema.¹³ In support of a fluctuating expression of immune mediators, other investigators have observed temporary refractory periods to aspirin, and changing thresholds to challenge in patients with documented aspirin intolerance.¹⁴ In addition, the fact that an H₁-blocker can prevent angioedema in aspirin-sensitive patients is suggestive of a central role for histamine in cutaneous aspirin intolerance.⁶ Whether specific immune recognition plays a role in aspirin intolerance remains to be determined. Mast cells may be activated by 5-lipoxygenase products or by aspirin directly to release inflammatory mediators including tryptase and histamine. In this case, the patients' tolerance of

other nonsteroidal anti-inflammatory drugs suggests that specific immune mechanisms are involved.

There is more clinical evidence to support an important role for aspirin as an augmentor of eicosanoid mediators in aspirin-induced asthma.^{1,3,6,8} Aspirin may act through the removal of prostanoid metabolites that regulate lipoxygenase or through inhibition of the cyclooxygenase pathway with preferential production of leukotrienes by 5-lipoxygenase causing pseudoallergy. Leukotrienes as potent simulators of chemotaxis, bronchoconstriction, and mucous secretion are thought to play a role in respiratory intolerance. Further, elevated levels of LTC₄, histamine, and PGE₂ are observed in the nasal washings of aspirin-sensitive asthmatic patients following oral challenge.⁸ In addition, aspirin appears to increase target-organ sensitivity to leukotrienes in aspirin-sensitive asthmatic patients. In those studies, desensitization to aspirin decreased the airway responsiveness to LTE₅. Compelling evidence that 5-lipoxygenase products mediate the full spectrum of aspirin-induced reactions in aspirin-sensitive asthmatic patients is seen in the work with 5-lipoxygenase inhibitors such as zileuton which ablate nasal, pulmonary, and dermal reactions to aspirin in such subjects.³

Population studies of aspirin-sensitive and aspirin-tolerant subjects with asthma using serologic techniques showed a significant association between aspirin-sensitive asthma and the major histocompatibility antigen HLA-DQw2.¹⁵ Subsequent investigations using sequence-specific oligonucleotide probes, however, did not confirm this association but found that both aspirin-sensitive and aspirin-tolerant asthmatic patients lacked DPB1*0401, suggesting that expression of that class II molecule protects against immune hyperresponsiveness.¹⁶ Our understanding of the role of immunogenics in asthma and atopy remains cursory. Further investigation into HLA antigen associations and immune responsiveness is needed.

In summary, we document a case of aspirin intolerance manifest as unilateral left periorbital edema in the absence of underlying respiratory or cutaneous disease. The unilateral nature of this patients' aspirin intolerance is intriguing. One could speculate that remote left ocular trauma and surgery which left the patient blind in that eye may have rendered this tissue more susceptible to the action of inflammatory mediators. Perhaps altered innervation changing the chemical microenvironment could explain this phenomenon. Such a case raises the question of whether separate mechanisms account for cutaneous and respiratory aspirin sensitivity or whether the variable expression of clinical symptoms represents a spectrum of disease severity determined by specific genetic susceptibilities and environmental influences.

REFERENCES

1. Vane JR. The mode of action of aspirin and similar compounds. *J Allergy Clin Immunol* 1976;58:691-712.
2. Seena GE, Passalacqua G, Andri G, et al. Nimesulmide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* 1996;14:94-103.
3. Lee HT. Mechanism of bronchospasm in aspirin-sensitive asthma. *Am Rev Respir Dis* 1993;148:1422-3.
4. Stevenson DD. Challenge procedures in detection of reactions to aspirin and nonsteroidal antiinflammatory drugs. *Ann Allergy* 1993;71:417-8.
5. Quirarte J, Blanco C, Castillo R, et al. Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients. *J Allergy Clin Immunol* 1996;98:678-85.
6. Katz Y, Goldberg N, Kivity S. Localized periorbital edema induced by aspirin. *Allergy* 1993;48:366-9.
7. Chan TYK. Angioedema and acute asthma attack due to the unexpected occurrence of aspirin in an over-the-counter cold preparation. *Br J Clin Pract* 1996;50(7):412-3.
8. Manning ME, Stevenson DD. Pseudoallergic drug reactions. *Immunol Allergy Clin N Am* 1991;111:659-78.
9. Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-

-
- edema. *Br J Dermatol* 1969;81:588-97.
10. Faich GA. Adverse drug-reaction monitoring. *N Engl J Med* 1986;314:1598-92.
11. Samter M, Beers RF. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968;68:975-83.
12. Szczeklik A. Adverse reaction to aspirin and nonsteroidal anti-inflammatory drugs. *Ann Allergy* 1987;59(Part 2):234-8.
13. Blanca M, Perez E, Garcia JJ, et al. Angioedema and IgE antibodies to aspirin: a case report. *Ann Allergy* 1989;62:295-8.
14. Sheldon L, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;64:500-6.
15. Mullarkey MF, Thomas PS, Hansen JA, et al. Association of aspirin-sensitive asthma with HLA-DQw2. *Am Rev Respir Dis* 1986;133:261-3.
16. Lympay PA, Welsh KI, Christie PE, et al. An analysis with sequence-specific oligonucleotide probes of association between aspirin-induced asthma and antigens of the HLA system. *J Allergy Clin Immunol* 1993;92:114-23.
- Request for reprints should be addressed to:*
Kursteen S Price, MD
McGill University
McIntyre Medical Sciences Bldg; Rm 1108
3655 Drummond St
Montreal QC
Canada H3G 1Y6
-