

NSAID Hypersensitivity



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Overall Purpose/Goal: To provide excellent case-based reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Mario Sánchez-Borges, MD, and Hae-Sim Park, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To update the current classification and pathogenic mechanisms of aspirin/nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions.
2. To confirm the diagnosis of each phenotype of NSAID hypersensitivity.
3. To effectively treat the patients with NSAID hypersensitivity.

Recognition of Commercial Support: This CME has not received external commercial support.

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The Difficult Cases Feature is based on the *Difficult Cases* Course presented at the AAAAI Annual Meeting and coordinated by the AAAAI New Allergist-Immunologist Assembly (NAIA). View the entire presentation and obtain CME or MOC credit by visiting the *JACI: In Practice* homepage www.jaci-inpractice.org.

CASE 1

A 21-year-old female patient visited our Allergy Clinic due to recurrent generalized wheals, perioral angioedema of 2 years' duration, and symptom exacerbation during the previous 2 weeks. Her medical history was unremarkable, disclosing only allergic rhinitis and tonsillectomy. She had high serum total IgE and specific IgE to house-dust mites. On further history taking, the patient reported that she experienced exacerbation of wheals and angioedema 30 to 60 minutes after taking aspirin or

ibuprofen. However, she noticed that acetaminophen was tolerated without inducing any adverse effects.

DISCUSSION

First, the diagnosis of chronic urticaria (CU) associated with allergic rhinitis was established. Current guidelines recommend physicians to investigate whether nonsteroidal anti-inflammatory

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drug (NSAID) hypersensitivity is present and, if present, to prescribe avoidance of cyclooxygenase 1 (COX-1) inhibitors in all patients with CU.¹ The presence of urticaria/angioedema exacerbations induced by NSAIDs in patients with underlying CU has been designated as aspirin/NSAID-exacerbated cutaneous disease (NECD), which is a major cutaneous phenotype of NSAID hypersensitivity, whereas some patients develop urticaria and/or angioedema on exposure to NSAIDs with no underlying chronic spontaneous urticaria (CSU; termed NSAID-induced urticaria/angioedema).² Between 10% and 40 % of patients with CSU experience exacerbations of urticaria/angioedema that develop 0.5 to 6 hours after taking NSAIDs. The pathogenesis of these exacerbations is related to COX-1 inhibition with increased production of cysteinyl leukotrienes and decreased production of prostaglandin (PG) E₂, a physiological mechanism for inhibiting mast cell mediator release.³ The diagnosis is made on the basis of typical histories and physical examination, and can be confirmed, if necessary, through an oral provocation test with aspirin.⁴ Atopy is known as a predisposing factor for NECD.³ Management of NECD consists of avoidance of COX-1 inhibitors and the use of alternative NSAIDs (selective COX-2 inhibitors or weak COX-1 inhibitors such as acetaminophen), although a small proportion of these subjects cannot tolerate such alternative drugs,⁴ as well as stepwise pharmacological treatment of CSU according to current international guidelines.¹ Patients with NECD show relatively poor clinical outcomes and higher medication requirements to achieve symptom control or remission compared with those with NSAID-tolerant CSU.³

CASE 2

A 59-year-old female patient presented with uncontrolled asthma and rhinitis with frequent asthma exacerbations (>4 times/y) requiring systemic steroids. She had been diagnosed as having allergic asthma and rhinitis sensitive to house-dust mites and pollens at age 25 years and had been on medications with antiasthmatic drugs including inhaled corticosteroids/long-acting β_2 agonists, intranasal steroids, and leukotriene modifiers. After 10 years, she began to experience exacerbations of upper and lower respiratory tract symptoms that developed 30 to 60 minutes after she took ibuprofen or diclofenac. Computed tomography scan showed findings of chronic rhinosinusitis (CRS) in both maxillary sinuses. In addition, during the previous 3 years, CU had developed, which was not controlled by taking second-generation antihistamines including levo-cetirizine, loratadine, and fexofenadine. Her blood/sputum eosinophil counts and serum total IgE levels were elevated. Her FEV₁ (%) level ranged from 45% (when exacerbated) to 80% (maximum value

in controlled status). Although oral/inhalation challenge tests with aspirin were not performed to confirm NSAID hypersensitivity, it is conceivable that she had aspirin-exacerbated respiratory disease (AERD), CRS, and CU associated with NSAID hypersensitivity based on her recurrent exacerbations induced by NSAIDs and clinical features of asthma and CRS. Oral provocation tests with celecoxib as an alternative drug did not elicit a reaction.

DISCUSSION

This patient was diagnosed as having both AERD (NSAID-exacerbated respiratory disease [NERD]) described in a European Academy of Allergy and Clinical Immunology position paper) and NECD, a major phenotype of respiratory and cutaneous forms of NSAID hypersensitivity.² Clinical features of AERD include female predominance, moderate to severe asthma comorbid with CRS/nasal polyps, and higher eosinophil counts.⁵ Because her respiratory and cutaneous symptoms were not controlled even with maintenance medications for asthma, rhinitis, and urticaria, we added anti-IgE therapy (omalizumab) and found significant reductions in asthma, rhinitis, and urticaria symptoms along with reduction in asthma exacerbations and steroid requirements.⁶ Considering that eosinophils are activated in upper and lower airway mucosa, anti-IL-5 antibody can be beneficial to achieve symptoms.⁷ Further studies to evaluate the effect of biologics are needed for a better clinical outcome in patients with AERD.

REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber Bm, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of urticaria: the 2017 Revision and Update. *Allergy* 2018;73:1145-6.
2. Kowalski M, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013; 68:1219-32.
3. Losol P, Yoo HS, Park HS. Molecular genetic mechanisms of chronic urticaria. *Allergy Asthma Immunol Res* 2014;6:13-21.
4. Park HS, Kowalski M, Sánchez-Borges M. Hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs. In: Franklin Adkinson N, Bochner BS, Wesley Burks A, Busse WW, Holgate ST, Lemanske RF, et al., editors. *Middleton's allergy: principles and practice*. Philadelphia: Elsevier Saunders; 2014. chap80, pp. 1296-1309.
5. Buchheit KM, Laidlaw TM. Update on the management of aspirin-exacerbated respiratory disease. *Allergy Asthma Immunol Res* 2016;8: 298-304.
6. Lee JH, Lee HY, Jung CG, Ban GY, Shin YS, Ye YM, et al. Therapeutic effect of omalizumab in severe asthma: a real-world study in Korea. *Allergy Asthma Immunol Res* 2018;10:121-30.
7. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, et al. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol* 2016;169:135-45.