ABSTRACT. Objective. Nonsteroidal antiinflammatory drugs (NSAIDs), mainly ibuprofen, are used extensively among children as analgesic and antipyretic agents. Our initial survey in the Kendang Kerbau Children’s Hospital in Singapore showed NSAIDs to be the second most common adverse drug reaction-causing medications among children of Asian descent. We attempted to characterize the clinical and epidemiologic profile of NSAID reactions in this group of patients.

Methods. A retrospective case series from a hospital-based pediatric drug allergy clinic was studied. A diagnosis of NSAID hypersensitivity was made with a modified oral provocation test. Atopy was evaluated clinically and tested with a standard panel of skin-prick tests. We excluded from analysis patients with any unprovoked episodes of urticaria and/or angioedema, patients <1 year of age, and patients who refused a diagnostic challenge test.

Results. Between March 1, 2003, and February 28, 2004, 24 patients, including 14 male patients (58%) and 18 Chinese patients (75%), with a mean age of 7.4 years (range: 1.4–14.4 years), were diagnosed as having cross-reactive NSAID hypersensitivity. A family history consistent with NSAID hypersensitivity was elicited for 17% of patients. None of the patients reported any episodes of angioedema/urticaria unrelated to NSAIDs. The median cumulative reaction-eliciting dose was 7.1 mg/kg. Facial angioedema developed for all patients (100%) and generalized urticaria for 38% of challenged patients, irrespective of age. There was no circulatory compromise, but respiratory symptoms of tachypnea, wheezing, and/or cough were documented for 42% of patients. A cross-reaction hypersensitivity response to acetaminophen was documented for 46% of our patients through their history and for 25% through diagnostic challenge. Compared with patients with suspected adverse drug reactions to antibiotics, patients in the NSAID group were older (7.4 vs 4.8 years) and more likely to have a diagnosis of asthma (odds ratio: 7.5; 95% confidence interval: 3.1–19).

Conclusions. Early presentations of facial angioedema and urticaria are key features of dose- and potency-dependent, cross-reactive reactions to NSAIDs in a subpopulation of young, Asian, atopic children. Significant overlap with acetaminophen hypersensitivity, especially among very young patients, for whom the use of a cyclooxygenase-2-specific medication may not be feasible, severely limits options for medical antipyretic treatment. PEDIATRICS 2005; 116:e675–e680. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0969; nonsteroidal antiinflammatory drug, children, urticaria, atopy, angioedema.

ABBREVIATIONS. NSAID, nonsteroidal antiinflammatory drug; COX, cyclooxygenase; ADR, adverse drug reaction; AERD, aspirin-exacerbated respiratory disease.

A

Acetaminophen, the most ubiquitously used antipyretic medication for children worldwide, is an "old" medication whose mechanism of action has been defined recently. Acetaminophen has no significant action on peripheral COX-1 and COX-2, but its antipyretic effect is consistent with a central nervous system-mediated activity at a new, previously unknown, enzyme, i.e., COX-3, which is found in the brain and spinal cord and is distinct from the 2 already known COX enzymes.1 It is now thought that this selective inhibition of the enzyme COX-3 in the brain and spinal cord explains the effectiveness of acetaminophen in relieving pain and reducing fever without unwanted gastrointestinal side effects. Although it has almost no antiinflammatory effects (even at high doses) and thus is not a NSAID, acetaminophen, like aspirin and the NSAIDs, is an inhibitor of prostaglandin synthesis. This may explain the published incidence of sensitivity to acetaminophen among patients with cross-reactive NSAID hypersensitivity, i.e., an average of ~7% (0–16%).2

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NSAIDs are a common factor in adverse drug reactions (ADRs) among adults. The average relative risk of urticaria/angioedema in a large cohort of patients exposed to these agents was between 1.1% (for those who used NSAIDs chronically) and 3.6% (for those who took NSAIDs intermittently, for treatment of acute pain). NSAID hypersensitivity reactions are probably less common among children. In a population-wide screen, the estimated incidence of ADRs attributable to NSAIDs among children was 0.3%. In fact, ibuprofen (a propionic acid-derivative NSAID) suspension was approved in 1995 for non-prescription use for children, after a thorough review of a stellar safety profile in the United States. Nevertheless, in their report from a survey of 36 years of suspected ADR-associated fatalities among children in the United Kingdom, Clarkson and Choonara showed that NSAIDs were implicated in ~3% (12 cases) of the 390 fatality cases reviewed.

There is a known increased incidence of ADRs among patients with a history of drug hypersensitivity, with increased age, with the presence of an associated chronic disease, with the use of multiple medications, and with female gender in the older age group. Traditionally, atopic patients are not at increased risk of developing ADRs, although, if a penicillin allergy develops, then asthmatic individuals are more likely to experience a severe or life-threatening reaction. NSAID hypersensitivity, however, seems to be associated positively with the presence of atopy. Among highly selected children with difficult-to-treat asthma, the incidence of aspirin-exacerbated respiratory disease (AERD) is almost 30%, mostly among female patients with associated sinusitis and early onset of disease and in the context of the triad of AERD, nasal polyps, and severe asthma. There is, however, significant controversy regarding the importance of these challenge-derived findings for selected patients in the routine treatment of children with asthma. Lesko et al. showed a decrease in outpatients visits for asthma exacerbations among asthmatic children after short-term use of ibuprofen and definitely no increase in the rate of hospitalization for these children. A recent review of the subject even suggested that ibuprofen, as an anti-inflammatory medication, may be of use in the treatment of acute exacerbations among asthmatic children.

In recent years, a new classification of NSAID hypersensitivity has been proposed and extended to the pediatric age group. Basically, reactions are either dose dependent and likely related to the anti-COX-1 effect of the medication (ie, AERD, urticaria/angioedema among patients with chronic urticaria, urticaria/angioedema among patients without chronic urticaria, and mixed/anaphylactoid reactions) or activity independent and most likely immunologically mediated; the latter reactions are drug specific and require a period of sensitization before the reaction can be elicited.

AERD has been studied extensively, with advances being made in the understanding of the putative mechanism of first-exposure reactions to chemically dissimilar drugs, the genetic back-ground, and the rationale for the relatively safe use of specific COX-2 inhibitors among such patients. Classically, patients with AERD and the aspirin triad (asthma, nasal polyps, and aspirin hypersensitivity) are nonatopic adults with difficult-to-control asthma, persistent sinusitis, and nasal polyps. Protocols for oral and inhalational provocation tests are in use for the diagnosis of AERD, and the incidence of AERD established with such tests was ~21% among adults and 0% to 5% among nonselected children with asthma. The same systematic review established that most patients with AERD also reacted to ibuprofen, naproxen, and diclofenac, whereas the incidence of cross-reactivity to acetaminophen among such patients was only 7% (range: 0–16%). The likelihood of acetaminophen cross-reactivity seems to be related inversely to the reaction-eliciting aspirin dose.

Urticaria and angioedema have been documented as associated reactions among patients with AERD, but they are not the hallmarks of these reactions. Urticaria and angioedema with multiple NSAIDs are observed among patients with chronic urticaria, but usually these are not associated with respiratory disease. The incidence of facial angioedema and NSAID hypersensitivity among atopic children was studied by Capriles-Behrens, et al. in a 10-year, retrospective, random chart review of patients attending an allergy clinic for treatment of asthma and/or allergic rhinitis. In this group of children, 41 of 1007 (4.1%) experienced documented facial angioedema in response to NSAIDs, with the incidence increasing significantly with age, ie, 2% at <5 years of age, compared with 21% (7 of 32 patients) in the 16- to 21-year-old group. The exact mechanism of aspirin-induced urticaria and angioedema is unknown, but the difference between patients who develop AERD and those who develop urticaria is not explained easily by metabolic differences in the production of different eicosanoids.

To date, there have been no publications regarding the incidence and reaction profile of aspirin or NSAID hypersensitivity among Asian children but, interestingly, 5-lipoxygenase-related genetic markers associated strongly with AERD in a Korean population were not found to be significant in a study performed in the United States. In our population, 2.7% of pediatric patients admitted to the Kendang Kerbau Children’s Hospital in Singapore reported histories of ADRs, mostly cutaneous. The most frequently involved drugs in this patient group were beta-lactam antibiotics. In this same survey, NSAIDs were the second most common ADR-causing medications among children of Asian descent. To define more clearly the clinical characteristics and associated risk factors for NSAID hypersensitivity in our population, we performed a retrospective review of data for patients from our drug allergy outpatient clinic from March 2003 to February 2004. We report on a group of 24 young children with cross-reactive urticaria/angioedema anaphylactoid reactions to multiple NSAIDs who were examined within 1 year in the pediatric allergy clinic of the Kendang Kerbau Children’s Hospital in Singapore.
Patients

The study involved a retrospective case series from the pediatric drug allergy clinic at Kendang Kerbau Children’s Hospital in Singapore. Between March 2003 and February 2004, all patients referred to the pediatric allergy outpatient clinic at Kendang Kerbau Children’s Hospital in Singapore with suspected hypersensitivity to NSAIDs were evaluated by an experienced pediatric allergist and offered an oral provocation test as needed. Information on early birth and exposure data, social, economic, and maternal factors, additional diagnoses and medication usage, family history of allergic disease, and exposure to house pets and passive smoking was recorded in each patient’s chart.

Patients were included in the analysis if they had confirmed hypersensitivity to NSAIDs. Diagnosis of NSAID hypersensitivity was made either with a clear history of recurrent reactions to multiple NSAIDs or with a modified oral provocation test. Atopy was confirmed with skin-prick tests with a standard panel of respiratory allergens. Additional provocation tests with COX-2-specific NSAIDs were performed as needed. Demographic and clinical data were compared with those for a group of patients referred in the same time period because of ADRs to a β-lactam antibiotic. We excluded from analysis patients with any unprovoked episodes of urticaria or angioedema, patients <1 year of age, and patients who refused a diagnostic challenge test.

Oral Provocation Tests

Aspirin oral provocation tests were performed in the outpatient clinic of the Kendang Kerbau Children’s Hospital. Before test administration, patients were examined and interviewed and vital signs, including heart rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation, and peak flow measurement, were recorded. All patients with a prior diagnosis of asthma underwent a pulmonary function test, and challenge was performed only if the forced expiratory volume in 1 second was >80% of the predicted value. Asthmatic patients continued to use all inhaled medications in their scheduled regimen. Challenge was not performed if the patient required orally administered steroids or other orally administered medications. Administration of all antihistamines was stopped 1 week before testing. The recommended schedule (to be used in patients with nonspecific NSAID-induced urticaria and angioedema without evidence of chronic urticaria) of doubling the initial 30-mg dose every 30 minutes caused quite severe reactions to develop, mostly after the end of the challenge. Therefore, we modified the regimen so that the initial dose was 50 mg of orally administered aspirin and subsequent doses of 50 mg each were administered at hourly intervals, after monitoring of all listed vital signs, if no clinical signs of an ADR appeared. The maximal cumulative dose was 10 mg/kg body weight. Patients were monitored in the clinic for ≥2 hours after the last ingested dose.

Oral provocation tests with ibuprofen and/or acetaminophen were performed as needed for diagnostic purposes, with similar protocols. Oral provocation tests with COX-2-specific inhibitors (12.5 mg of rofecoxib or 10 mg of valdecoxib) were administered with 1 dose, with similar follow-up and evaluation protocols. Patients remained under observation for ≥4 hours after challenge.

Skin-prick Tests

All tests were performed in the respiratory laboratory by an experienced technician, with commercial allergen extracts and the GreerPick skin-prick test device (Greer Laboratories, Lenoir, NC), and were evaluated by an experienced pediatric allergist. A wheal diameter of ≥3 mm, in excess of the negative control finding, was considered a positive test result. The allergens included in our panel were produced commercially by Greer Laboratories, except for the Blomia tropicalis extract, which was produced by the Al- lergy and Molecular Immunology Laboratory, National University of Singapore. The standard skin-prick test panel included house dust mite mixture (Dermatophagoides farinae, 5000 allergic units/mL, plus Dermatophagoides pteronyssinus, 5000 allergic units/mL, standardized), Blomia tropicalis (0.2 mg protein/mL, 50%, vol/vol, glycerol), cockroach mixture (Periplaneta americana and Blattella germanica), mixed feathers (chicken, duck, and goose), canary feathers (Serinus canaria), kapok seeds, Alternaria alternata, Curvularia spicifera, Cladosporium herbarum, Aspergillus fumigatus, Candida albicans, cat hair (standardized cat hair, Felis catus [dometics]), 10 000 biological allergic units/mL, dog epithelia (Canis familiaris), grass mixture (9-grass mixture, standardized), acacia, melaleuca, beefwood (Australian pine), oil palm, mango blossom, sage mixture, and weed mixture.

Statistical Analyses

Simple analysis of variance was used for comparison of continuous data such as age and blood pressure. Logistic regression analysis was used for comparison of dichotomous values such as the presence or absence of associated allergic rhinitis and asthma, and nonparametric tests (Kruskal-Wallis and Mann-Whitney tests) were used for comparisons between small groups of patients. SPSS for Windows, version 11.5 (SPSS, Chicago, IL), was used for all statistical computations.

RESULTS

Between March 1, 2003, and February 28, 2004, 24 patients, including 14 male patients (58%), 18 Chinese patients (75%), and 6 Malay patients, with a mean age of 7.4 years (range: 1.4–14.4 years; first quartile: 4.9 years) were diagnosed in the pediatric allergy clinic with cross-reactive NSAID hypersensitivity. Clinically significant allergic disease was associated for 83% of patients; 58% had allergic rhinitis, 46% had asthma, and 29% had atopic dermatitis. A diagnosis of asthma was more likely in the older age group. A positive family history of atopy-related disease was present for 83% of patients, whereas 17% reported cross-reactive NSAID hypersensitivity among closely related family members. Skin-prick tests were positive for ≥1 aeroallergen for 88% of patients, mostly for the house dust mites. The clinical and demographic data for the patients according to age group are detailed in Table 1. The clinical sever-

<table>
<thead>
<tr>
<th>TABLE 1. Demographic and Clinical Data for the Patient Cohort</th>
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<td>No. of Patients (%) (N = 24)</td>
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<td>&lt;5 y (n = 7)</td>
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<tr>
<td>Male/female ratio</td>
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<tr>
<td>Chinese</td>
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<tr>
<td>Asthma</td>
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<td>Allergic rhinitis</td>
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<tr>
<td>Facial angioedema</td>
</tr>
<tr>
<td>Urticaria/rash</td>
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<tr>
<td>Respiratory symptoms</td>
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<td>Inciting medication</td>
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Patient data are shown for 3 age groups, ie, <5, 5 to 10, and >10 years. Chinese indicates patients of Chinese descent; NS, not significant. Presenting complaints were facial angioedema, urticaria/rash, and respiratory symptoms (wheezing, shortness of breath, or cough).
ity of the atopic disease was mild to moderate for the majority of diagnosed patients. A diagnosis of asthma was significantly more likely in the older age group (odds ratio: 2.4; \( P < .05 \)). There were no patients with severe or difficult-to-control asthma.

The presenting complaints were periorbital angioedema (88%), urticaria (50%), wheezing (33%), perioral angioedema (21%), rhinorrhea (13%), facial swelling (8%), and a maculopapular rash (for 1 patient, 4%), developing 30 minutes to 4 hours after ingestion of the offending drug. Respiratory symptoms were more likely to be reported by patients in the older age group, but the level of significance reached with this small group of patients was only \( P < .1 \) (Table 1). The medications involved were ibuprofen (63%), acetaminophen (46%), diclofenac (25%), and other NSAIDs (9%).

Most of our patients (92%) presented to and were referred from the children’s emergency department. Of 22 patients who presented to the emergency department with an acute ADR to a NSAID, 14 (64%) required hospitalization, with an average hospital stay of 2.4 days (range: 1–4 days).

Of 24 patients, 5 had clear histories of repeated reactions to ≥2 chemically unrelated antipyretic agents (NSAIDs and/or acetaminophen) documented in a medical setting. Nineteen patients underwent a diagnostic oral provocation test, 9 (47.4%) with aspirin, 4 with ibuprofen, and 6 with acetaminophen. The reactions to aspirin and ibuprofen were very similar in all measured parameters and therefore are reported together. The median cumulative reaction-eliciting dose was 7.1 mg/kg (range: 2.7–13.2 mg/kg), and the median reaction time from the start of the challenge test was 60 minutes (range: 30 minutes to 3 hours). All patients (100%) developed periorbital angioedema, 38% frank wheezing, 38% urticaria, and 23% rhinorrhea. Respiratory symptoms of tachypnea, wheezing, and cough developed for 3 (37.5%) of 8 patients with prior diagnoses of asthma and for 2 (40%) of 5 nonasthmatic patients challenged (\( P > .1 \)).

The median cumulative reaction-eliciting dose among patients challenged with acetaminophen was 16.4 mg/kg (range: 9.6–25.3 mg/kg), whereas 1 patient who was challenged inadvertently with diclofenac as an inpatient reacted at a dose of 0.6 mg/kg. A cross-reactive hypersensitivity response to acetaminophen was documented for 46% of our patients through their history and for 25% through diagnostic challenge.

Only 1 patient developed significant laryngospasm, with respiratory distress and difficulty swallowing, and required intramuscularly administered epinephrine and oxygen therapy. None of our patients developed hypotension or symptoms of circulatory compromise. All patients received a dose of 1 mg/kg orally administered prednisone, as well as inhaled salbutamol as needed, with resolution of respiratory symptoms within 120 minutes. All patients were discharged from the outpatient clinic and none required additional treatment or hospitalization after a challenge. Patients were examined again 1 week after the challenge, and no delayed reactions were reported.

Compared with patients referred to our clinic because of suspected ADRs to antibiotics, patients in the NSAID group were older (7.4 vs 4.8 years; \( P < .005 \)) and more likely to have a diagnosis of asthma (odds ratio: 7.5; 95% confidence interval: 3.1–19; \( P < .05 \)). When interviewed, patients related the onset of NSAID hypersensitivity several months to years before their referral and diagnostic procedure, with 1 patient’s parent reporting the development of mild angioedema with the first exposure to acetaminophen at the age of 2 months.

**DISCUSSION**

We have described a series of 24 children with confirmed cross-reactive NSAID hypersensitivity diagnosed during a 12-month period in the Kendang Kerbau Children’s Hospital in Singapore. Because there are no in vitro tests to establish the diagnosis of NSAID hypersensitivity, a diagnostic oral provocation test was offered to the family when diagnosis was not possible on the basis of clinical indications alone (ie, recurrent episodes of immediate reactions on initial exposure to multiple drugs). None of our patients had any known previous exposure to aspirin or chemically similar medications; therefore, elicited reactions could not be explained on the basis of previous sensitization or immunologically mediated cross-reactivity.

The most common presenting complaints were periorbital edema (88%), urticaria (50%), and wheezing (33%). Bronchoconstriction (clinically ascertained on the basis of the presence of tachypnea, prolonged expiratory phase, and wheezing) developed for 38% of patients challenged with aspirin or ibuprofen, irrespective of the presence or absence of clinical asthma. None of these children suffered from severe or difficult-to-control asthma, and overall their atopic complaints were mild.

The mean age at diagnosis was 7.4 years, but 25% of our children were <5 years of age. Because of ethical considerations, patients <1 year of age were not offered a diagnostic challenge as part of their drug hypersensitivity evaluation and therefore were not included in this study. This relatively young age at presentation seems to be a cardinal feature of this type of reaction among Asian children. Because facial angioedema developed for all of our challenged patients, irrespective of their young age, this also seems to be a hallmark of NSAID hypersensitivity in this group.

Challenge-ascertained cross-reactivity with acetaminophen was present for 25% of our patients. In their histories, similar but usually milder reactions to acetaminophen were reported by 46% of patients. This in contrast to the published 7% prevalence (range: 0–16%) reported in previous studies. This finding may stem from a referral bias, whereby young children who experience hypersensitivity reactions to ibuprofen but who are well able to tolerate acetaminophen for antipyretic use are less likely to be referred for allergy investigations by their pediatricians. An additional bias stemmed from our own
challenge practices; for young children with questionable reactions to ibuprofen but a history of good acetaminophen tolerance, routinely we offered a challenge with acetaminophen, to prove its continued safety, and deferred the diagnostic challenge with aspirin to a later date. Such patients were not included in this study because a diagnostic challenge was not performed.

There was no gender preference. Compared with patients referred to the same clinic with suspected ADRs to antibiotics, patients in the NSAID group were older (7.4 vs 4.8 years; \( P < .005 \)) and more likely to have a diagnosis of asthma (odds ratio: 7.5; 95% confidence interval: 3.1–19; \( P < .05 \)). The association of NSAID hypersensitivity with atopy and asthma is consistent with previous publications.\(^9,10,32\)

We made clinically dictated modifications in the oral provocation protocol because of the accumulated experience with the first few patients. The original protocol for urticaria and angioedema reactions among normal individuals, adapted from the published data,\(^33\) called for a small initial dose with doubling every 30 minutes (similar to oral provocation protocols with antibiotics). Provocation protocols for AERD use smaller incremental doses given at longer (3–4-hour) intervals over 2 to 4 days.\(^34\) For a typical 25-kg pediatric patient, the classic provocation protocol would call for a schedule of 25 mg, 50 mg, 100 mg, and 200/250 mg at 30-minute intervals. Both patients challenged in this manner developed severe urticaria, angioedema, and concomitant bronchospasm ~1 hour after ingestion of the final dose, with no reaction elicited by the previous doses. The doubling schedule necessitated giving as the final dose the total 10 mg/kg challenge, whereas the total accumulated previous doses were ~5 mg/kg, a level usually not associated with clinical reactivity in our patient population. With our modified schedule, a constant dose of 50 mg was given at 1-hour intervals, with challenge end point at a total cumulative dose of 10 mg/kg. Most patient exhibited a reaction within 30 to 60 minutes after a cumulative dose of >5 mg/kg was achieved, but the overall severity of reactions, especially the severity of respiratory distress, was decreased significantly.

The exact mechanism of aspirin-induced urticaria and angioedema is unknown. The observation that premedication with antihistamines may prevent the development of urticaria among patients with AERD after aspirin challenge,\(^35\) while not affecting the induced bronchospasm, supports the hypothesis that the skin manifestations of NSAID hypersensitivity are histamine mediated, whereas the respiratory effects are secondary to increased production of proinflammatory leukotrienes. For our patients, treatment with a fast-acting antihistamine (such as loratadine) after development of a challenge-induced reaction did not prevent the manifestation of periorbital angioedema and urticaria. Systemic corticosteroid treatment did seem to enhance resolution of symptoms, compared with the previously reported NSAID-induced reactions for the same patient.

After evaluation, 14 of 24 children were advised to use low-dose (5–10 mg/kg) acetaminophen as the sole antipyretic agent; this was based on our observation that the minimal reaction-eliciting dose of acetaminophen was 9.6 mg/kg in the whole group of challenged patients. For 6 of the older children, we performed a clinic-based challenge with a COX-2-specific inhibitor (either rofecoxib or valdecoxib). The use of COX-2-specific NSAIDs seemed, as documented,\(^23,36–38\) to be significantly safer for these children but did result in mild periorbital edema for 2 of 4 patients and mild but generalized urticaria for 1 of 4 patients challenged with valdecoxib. The dose- and potency-dependent response means that even patients with exquisite sensitivity may tolerate low (up to 5 mg/kg) doses of acetaminophen without adverse effects. Because there are no COX-2-specific inhibitors that are licensed for use among children <12 years of age and no liquid preparations, the use of low-dose acetaminophen may be the only practical option for antipyretic treatment that can be used safely. For patients with skin manifestations alone, the use of fast-acting antihistamines in combination with the antipyretic treatment requires additional evaluation.

For the purposes of classification, we think that these patients’ reactions belong to the described type 3 reaction group (ie, urticaria and angioedema among patients with nonchronic urticaria) or type 4 (ie, mixed reactions).\(^14\) The fact that our young patients had strong personal and family histories of atopy, most with clinical manifestations of mild/moderate allergic respiratory disease, as well as their ethnic origin, the time frame for the appearance of clinical reactions after exposure, and the ubiquitous presentation of facial angioedema irrespective of age, defines these children as a subgroup in this classification; their pathophysiologic features and the natural history of their disease require greater elucidation.

**CONCLUSIONS**

Facial angioedema and urticaria are key features in dose- and potency-dependent, cross-reactive reactions to NSAIDs in a subpopulation of young, Asian, atopic children. For very young patients, for whom the use of a COX-2-specific medication may not be feasible, limited options for medical antipyretic treatment remain.

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Early Presentation With Angioedema and Urticaria in Cross-reactive Hypersensitivity to Nonsteroidal Antiinflammatory Drugs Among Young, Asian, Atopic Children
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