Single Non-steroidal Anti-inflammatory Drug-Induced Hypersensitivity Reactions in Children: Case Report

Çocuklarda Tek Non-steroid Anti-inflamatuar İlaç ile Oluşan Hipersensitivite Reaksiyonları

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ABSTRACT Non-steroidal anti-inflammatory drug (NSAID) hypersensitivity is one of the most common drug-related reactions in children. According to European Network for Drug Allergy, NSAID hypersensitivity is mainly divided into two groups: single drug induced IgE or T cell-mediated reactions and cross-reactive reactions due to inhibition of cyclooxygenases. These major groups are classified in phenotypes according to the clinical findings and the presence of the underlying diseases. However, it may not sometimes be so easy to classify each patient according to these phenotypes. In this presentation, three children who had single NSAID-induced reactions but different clinical presentations have been described. Also, two of these children had some manifestations common to cross-reactive types of NSAID hypersensitivity which further complicated phenotyping.

Key Words: Drug hypersensitivity; anti-inflammatory agents, non-steroidal; phenotype; child

ÖZET Non-steroid anti-inflamatuar ilaç (NSAİİ) hipersensitivitesi çocuklarda ilaç ilişkili reaksiyonların en sık nedenlerinden biridir. Avrupa İlaç Allerji Topluluğu (European Network for Drug Allergy)'na göre, NSAİİ hipersensitivitesi iki ana gruba ayrılır: Tek ilaçla oluşan IgE veya T hücre aracılı reaksiyonlar ve siklooksijenaz inhibisyonuna bağlı çapraz reaksiyonlar. Bu iki ana grup NSAİİ hipersensitivitesi, klinik bulgulara ve altta yatan kronik hastalıklara göre fenotiplendirilir. Her olguyu önceden belirlenmiş fenotiplere göre sınıflandırmak bazı durumlarda kolay olmayabilir. Bu sunumda, tek NSAİİ ile oluşan reaksiyonları olan farklı klinik görünümlerde 3 olgu anlatılmıştır. Bu olgulardan ikisi, çapraz reaksiyonlarda gözlenen bazı klinik özellikleri de göstermektedir. Bu durum fenotiplendirmeyi güçleştirmektedir.

Anahtar Kelimeler: İlaç aşırı duyarlığı; anti-inflamatuar ajanlar, steroid olmayan; fenotip; çocuk

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Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) is one of the most common drug related adverse reactions in children.[1,2] Classification of NSAID hypersensitivity is based on the presence of cross-reactivity, the clinical manifestations and the presence of an underlying disease.[3] According to the mentioned criteria, five major clinical phenotypes of can be differentiated.[4] However, all patients with NSAID hypersensitivity may not fit into this classification. Therefore, advanced phenotyping within these major groups is thought to be possible with better characterization of clinical features of patients.[5]

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In this report, we presented three cases with single NSAID-induced hypersensitivity. Two of them did not fit into the classification recommended by European Network for Drug Allergy (ENDA) and had co-existing features pertaining to cross-intolerant types of NSAID hypersensitivity. We reported these cases to call attention to the different phenotypes that did not match to the classification published by ENDA.

CASE REPORTS

CASE REPORT 1

Case 1 is a four year-old boy who developed angioedema approximately six hours after ibuprofen intake on two separate occasions. Both reactions confined to his lower lip without urticaria and respiratory symptoms or any other organ system involvement. His parents described no previous reaction with any other NSAID. He did not have any atopic disease and had no history of NSAID hypersensitivity in his family. Skin prick test including common aeroallergens was found negative. Oral provocation test (OPT) with ibuprofen caused angioedema in his lips and cheeks within one hour of 20 mg ibuprofen intake. OPT with acetyl salicylic acid (ASA) at a total cumulative dose of 40 mg/kg/day revealed no reaction. Therefore, a diagnosis of single NSAID-induced (possibly IgE mediated) angioedema was considered.

CASE REPORT 2

Case 2 is a 12 year-old boy who presented with lip edema one hour after taking a 25 mg dexketoprofen tablet. He had no history of previous reactions with any other NSAIDs. He described urticarial lesions since his seventh birthday with an increased severity for the last one year on 2-3 days in a week which was not related with NSAID intake. On physical examination, he was diagnosed as having an asthma exacerbation. Pulmonary function test revealed 14% reversibility in FEV_1 after inhalation of a dose of 400 μg/day salbutamol. He had no history of atopic diseases other than asthma. His grandfather had symptoms after intake of more than one, chemically non-related NSAIDs and could only use acetaminophen safely. Skin prick test to house dust mites was found positive. OPT with dexketoprofen caused lip and periorbital edema within one hour of last dose. The reaction eliciting dose of dexketoprofen was 67.5 mg. OPT with ASA was negative at a total cumulative dose of 40 mg/kg/day.

CASE REPORT 3

Case 3 is a 15 year-old boy who had been followed with a diagnosis of asthma and allergic rhinitis since his fifth birthday. He had atopic sensitization to grass pollens. He used strong and weak inhibitors of cyclooxygenases from several classes without any reaction in the past. Interestingly, one week before his admission, he developed urticaria eight hours after taking ibuprofen. Later in the same day, angioedema occurred in his hands. He had no history of NSAID hypersensitivity in his family. During OPT with ibuprofen, he developed itching on his face and edema on his hands one hour after 10 mg ibuprofen intake. Although he had no dyspnea or other respiratory symptoms, forced expiratory flow in one second decreased by 12%. OPT with ASA was found negative. Therefore, a diagnosis of single NSAID-induced anaphylaxis was thought.

DISCUSSION

In this report, we described three children who had OPT confirmed diagnosis of single NSAID-induced hypersensitivity. The cross reactive type of NSAID hypersensitivity are excluded by OPT with a strong inhibitor of cyclooxygenase, ASA. The reactions were thought to belong to the group of single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA). Case 1 is the prototypical patient of SNIUAA group who reacts to a single drug or class of chemically related drugs and usually does not have a history of chronic urticaria or asthma. Case 2 and 3 did not fit into the classification recommended by ENDA and had co-existing features pertaining to cross-intolerant types of NSAID hypersensitivity.[5,6] Case 2 is an asthma and chronic urticaria patient with a recent increase in activity of both diseases. He presented with recently started NSAID reactivity, but interestingly found not to be a cross-reactor of NSAIDs. Case 3 had ibuprofen-

induced anaphylaxis. He had underlying asthma, allergic rhinitis and atopic sensitization, but interestingly a single NSAID was discovered to be the culprit for the reaction. Although the underlying diseases in Case 2 and 3 are usually seen in cross reactive type of NSAID hypersensitivity, these patients demonstrated to have single NSAID induced reactions.

The single NSAID-induced IgE mediated reactions may be urticaria/angioedema (Case 1 and 2) or anaphylaxis (Case 3). Patients single NSAID induced reactions usually do not have an underlying chronic cutaneous or respiratory disease, but may have a history of hypersensitivity to food or other drugs.[7] In contrast to single NSAID induced reactions, a chronic respiratory disease (asthma/rhinosinusitis/nasal polip) or cutaneous disease (chronic spontaneous urticaria) exists in patients with NSAID-exacerbated respiratory disease or NSAIDs-exacerbated cutaneous disease which are both cross-reactive type of NSAID hypersensitivities. Case 2 and Case 3 are noteworthy for their underlying chronic diseases but single NSAID induced reactions. House dust mite sensitization which is also found in Case 2 is the main sensitization in multiple NSAIDs-induced urticaria/angioedema patients.[1] Case 2 and 3 may also resemble to NSAID-exacerbated respiratory disease patients with their underlying asthma, bronchial and cutaneous symptoms in OPT. Grass pollen sensitization which is found in Case 3 were previously reported as the main sensitization in non-erosive reflux disease (NERD) patients.[5] In contrast to NERD patients considering severity of asthma, both cases are well-controlled with low dose inhaled corticosteroids.

In conclusion, classification of NSAID hypersensitivity according to the underlying diseases may not be so discrete in some patients. We reported these cases to call attention to the different phenotypes that did not match to the classification published by ENDA. To advance the phenotyping of patients, there may be need to better understand the pathophysiology of chronic underlying diseases in NSAID hypersensitivity.

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