DRUG ALLERGY IN CHILDREN

Toshkent tibbiyot akademyasi
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Abstact: The drug allergy "label" may have a lifetime of consequences for a child. Many children with alleged drug allergies are proven to be tolerant to the culprit medication when challenged. The field of drug hypersensitivity is a recently evolving field of research, but studies on its epidemiology and diagnostic tools are lacking in children. Clinical history is significant in the diagnosis and classification of drug hypersensitivity in children. Diagnostic tools have been evaluated in a limited number of children; therefore, the guidelines are mainly in line with those for adults. Here, we review the clinical characteristics, main drugs, risk factors, and diagnosis of drug hypersensitivity to aid in its accurate diagnosis in children.

Key words: Adverse drug reaction, Drug allergy, Drug hypersensitivity, Drug provocation test

Introduction

Reactions to at least one drug have been reported in 2.9%–16.8% of pediatric patients.14) However, only a few selfreported drug reactions are confirmed drug hypersensitivities (DHs).5,6) The drug allergy (DA) "label" of children, an alleged DA diagnosis with or without a proper evaluation, can result in use of less alternative therapies, increasing the risk of antibiotic resistance and higher lifetime medical costs.7) Therefore, when Dis reported in pediatric patients, physicians must provide appropriate diagnosis and management or refer them to a pediatric allergy specialist. Here, we review the terminology, epidemiology, clinical manifestations, main causative agents, diagnosis, and risk factors of DA in children.

Definition and classifications Adverse drug reaction (ADR) is defined by the World Health Organization as "a response to a drug which is noxious, and unintended, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."8) As shown in Fig. 1, ADRs are traditionally divided into type A and type B reactions. Type A reactions are dosedependent predictable consequences of the known pharmacological action of the drug that account for 80% of ADR cases. Type B reactions are less common, dose-independent, unpredictable, and unrelated to the drug's pharmacological action.9) DHs, part of type B reactions, are adverse effects of drugs that clinically resemble allergic reactions. DAs are DHs for which a definite immunological mechanism has been demonstrated (Fig. 1). When DA is suspected, DH is the preferred

term.10)Clinically, DHs are classified as immediate DH, which occur within 1–6 hours after the last drug administration, and nonimmediate DH, which occur at any time from 1 hour after the initial drug administration.11) DAs are classified according to the Gell and Coombs system of hypersensitivity into type I (drugspecific immunoglobulin E antibodies), type II (cytotoxic reactions mediated by drugspecific immunoglobulin G antibodies), type III (immune complex reactions), and type IV reactions (delayedtype hypersensitivity reactions mediated by cellular immunity).

12) Epidemiology Accurate data on the epidemiology of ADR, DH, and DA are rare in children, with most epidemiologic data including both type A and B reactions.1,3,13) The prevalence of reported ADR in children is lower than that in adults in the range of 2.9%–16.8% according to different reports (Table 1).1,35,13,14) However, among the reported ADRs, the proportion of confirmed DA is as low as 4% after diagnostic evaluation.5,6,15) According to a nationwide Korean questionnaire, the prevalence of DA symptoms in school children was 4.4%, but the prevalence of diagnosed DA was only 1.1%.4) In a Turkish survey, the incidence of the parent-reported immediate type DH was 7.87%; however, after diagnostic workup, the true frequency was 0.11%.6) In contrast to DH in adult patients, the process of collecting and reporting DH largely depends on the parents' perception, and it is not evident whether the missing rate is higher in children. The common culprit drugs causing DHs in children are antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), antiepileptic drugs (AEDs), and vaccines.1618) However, the characteristics of the subject group can largely affect adverse reaction frequency and type. Clinical manifestations In children, cutaneous symptoms, especially maculopapular eruptions (MPEs), are the most frequently reported reactions, followed by gastrointestinal symptoms.5,6,14,1720) Cutaneous symptoms include urticaria, angioedema, and for some drugs, such as sulfonamides, fixed drug eruptions.16,18,21) Gastrointestinal symptoms included nausea, vomiting, diarrhea, or constipation (Table 2). Isolated respiratory reactions are mostly restricted to NSAIDs but may also present as a part of anaphylaxis. The frequency of drugrelated anaphylaxis is 5%–25% of all anaphylaxis cases according to different reports,22) including a multicenter retrospective review of anaphylaxis in Korea revealing that 10% of anaphylaxis triggers are drugs.23) The rate of druginduced anaphylaxis is increasing: A United States retrospective analysis showed a 212% increase in drug-related anaphylaxis (479%, age 0–4 years; 140%, age 5–17 years) from 2005 to 2014.24) Other symptoms include headache, lethargy, cough, palpitations, and ocular issues. Severe cutaneous adverse reactions (SCARs) are a group of rare but potentially lifethreatening reactions including acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS), StevensJohnson syndrome (SJS), and toxic epidermal necrolysis (TEN).25,26) SCARs show widely

variable clinical manifestations, such that the pathogenesis is not clear but is thought to involve cytotoxic Tcell activation. However, some findings are consistent across all SCARs: a certain period must pass before SCARs become fullblown, and early drug withdrawal and supportive care with antiinflammatory medication is the management of choice.26,27) In our previous study based on the Korean SCARs registry, we analyzed 47 pediatric cases of DRESS, SJS, and TEN from 15 tertiary hospitals.27) The latency period between drug exposure and symptoms was longest in DRESS patients (mean, 23.5 days) and shorter in SJS and TEN patients (mean, 4 and 6.5 days, respectively). Cutaneous lesion extent was largest in DRESS cases without mucosal involvement in most cases and without permanent sequelae in all cases. In SJS and TEN patients, the area of skin involvement was smaller but showed slower recovery; a few cases had skin or skin appendage sequelae, while most SJS and TEN patients had mucosal involvement. Finally, 1 of the 4 TEN patients died. The culprit drugs were commonly used, including antibiotics and antipyretics, or uncommon but chronically used drugs, including AEDs, which was comparable to other different pediatric SCAR research.25,27)

Major culprit drugs The major causes of DH in children include betalactam antibiotics, NSAIDs, and vaccines (Table 2). Studies on the incidence of DH according to specific drugs is sparse, but it can be estimated from domestic epidemiologic studies on ADRs.28,29) Beta-lactam antibiotics Beta lactam antibiotics, a class of antibiotics that have a betalactam ring in their molecular structures, are classified into 2 major groups (penicillin and cephalosporin) and 4 minor groups (carbapenem, monobactam, oxacephem, and clavulanic acid). Beta-lactam antibiotics are the most prevalent drugs that induce hypersensitivity reactions in children at an estimated 1%–10% prevalence rate.2,3033) According to domestic reports, drug provocation tests (DPT) could be safely performed in pediatric patients with higher diagnostic accuracy.34,35) Crossreactivity between betalactam antibiotics is due to the side chain R1 in amoxicillin, ampicillin, and cefaclor, which have identical or almost identical side chains, have been shown to have crossreactivity by skin testing; and in ceftriaxone and cefotaxime, which have identical side chains and also show skin test crossreactivity. It is recommended that we evaluate medication side chains to safely challenge betalactams with different side chains.18,36) Finally, a study on the natural history of betalactam DH in children demonstrated results suggestive of tolerance acquisition.37) Nonsteroidal anti-inflammatory drugs NSAIDs are widely used for pain relief, fever control, and anti-inflammation in children.3840) The prevalence of DH to NSAIDs is 0.6%–5.7% in the general population, while the exact prevalence is not reported in children.41,42) In an older report, the prevalence of aspirin intolerance in children was 0.3%; recently, in asthmatic children, the prevalence of NSAID hypersensitivity is 0.9%.43) In some studies, the reaction to NSAIDs may exceed that to betalactam antibiotics, especially

in severe reactions.4446) In a tertiary hospital in Korea, NSAIDs were the second most common culprit agent in patients who underwent DPT, following beta-lactams.47) As depicted in Fig. 2, the DH to NSAIDs is classified according to the crossreactivity and symptoms and further by mechanism, timing, and underlying allergic diseases: nonallergic, crossreactive reactions are classified into NSAIDexacerbated respiratory disease, NSAIDexacerbated cutaneous disease, NSAIDinduced urticaria/angioedema or anaphylaxis, and allergic, singlereactor reactions are classified into selective NSAIDinduced urticaria/angioedema or anaphylaxis, and selective NSAIDinduced delayed reactions.48,49) According to the recent European position paper on childhood NSAIDs, in children under 10 years of age, most responses are nonimmunologic, crossintolerant, and easily attributed to co-factors such as exercise or infection.50)Thus, they are divided into nonallergic NSAID hypersensitivity and other cases. In children older than 10 years, on the other hand, the reactions are similar to those of adults. According to recent guidelines, DPT is essential ino diagnosing NSAID hypersensitivity in children.16,50) For the management of NSAID hypersensitivity, confirmed diagnosis and classification are required and an alternative NSAID other than the culprit drug is needed. However, because the majority of children under 10 years of age have crossreactive forms of reactions, DPT of alternative NSAIDs are recommended.50) Although selective NSAIDs for COX2 are not approved for this age group, they have been used safely in practice.51,52) Vaccines ADR after vaccination must be differentiated between aller gic and nonallergic reactions. Immediate nonallergic reactions include local injection site reactions (swelling, redness, or soreness) and constitutional symptoms such as fever. These are not contraindications to future vaccine doses.53) Hypersensitivity to vaccine can present as immediate allergic reactions occurring within minutes to 4 hours including urticaria, angioedema, and anaphylaxis, and delayedtype reactions such as rashes occurring hours to days after injection.54) Delayedtype reactions usually do not require allergic evaluation, are selflimiting, and do not contraindicate further doses.55) Immediate hypersensitivity to vaccine in the pediatric population is estimated as 1 per 50,000 to 1 per 1,000,000 doses for most vaccines to 1 per 50,000 doses for diphtheriatetanuspertussis vaccines, while vaccinetriggered anaphylaxis is reported to be 1.45 per 100,000 doses.56) Vaccine allergies are rarely triggered by the microbial antigen; rather, they are more commonly induced by other components such as egg protein, stabilizers such as gelatin or milk protein, antibiotics, preservatives, adjuvants, and latex.54)The management of vaccine hypersensitivity starts with verifying immediate allergic reaction through careful history taking and progresses to skin testing with fullstrength vaccine and, if available, vaccine components or diluted vaccine in a positive history of anaphylaxis.53) In a patient with history of immediate allergic reaction and a positive skin test result, additional doses of vaccine or other vaccines with com NSAID DiagnosisDH is generally diagnosed, as described

in Fig. 3. On the basis of a detailed history taking, appropriate diagnostic testing should be performed as indicated to confirm the causality of the DH. History taking A detailed comprehensive history is essential in the diagnosis of DH.16,58) History taking in pediatric patients often occurs through the caregivers, who may provide exaggerated or biased descriptions.16) The following items should be evaluated with aid from hospital records at the time of event or pictures if possible: exact name of the medication, time elapsed since event (some allergies wane over time), involved systems (pictures), time between medication use and symptom onset, reason for medication, concurrent medication, diagnostic testing, therapeutic management, same or similar medication before and after reaction, same or similar symptoms without medication, and underlying conditions that may affect or be mistaken for drug reactions.11) Based on the patient's history, if DH is suspected, a specific allergy workup should be performed 4–6 weeks after the resolution of clinical symptoms and signs.10) Skin test Skin testing in DH consists of skin prick tests (SPTs), intradermal tests (IDTs), and patch tests.16) Sequential SPT and IDT can safely diagnose suspected IgEmediated reactions, but the diagnostic value in children is evaluated in a limited number of studies.18,5962) Penicillin and minor determinants are the only commercial agents for SPT, but even these are not available in Korea, and other skin tests must be prepared according to guidelines.63)Delayed reading of IDT at 48–72 hours and patch testing can be used to evaluate nonimmediate reactions and SCARs.64) However, a negative skin test cannot rule out DH and DPT remains the gold standard in diagnosing DH in children. 18,60,65) Due to the pain and difficulty of IDT in children, experts are leaning toward DPT before IDT, especially in cases of nonimmediate reactions.16,66) In vitro test The only commercially available *in vitro* tests of DH are ImmunoCAP (ThermoFisher, Uppsala, Sweden) assays for a limited number of drugs. Ideally, *in vitro* tests of specific DHs may be useful in settings of patients taking multiple drugs simultaneously and in those of severe DH in which skin test is not available or inconclusive and DPT is contraindicated.10) *In vitro* studies may identify the culprit drug and characterize the active phase of DH.67) To identify the culprit drug of immediate DH, specific IgE measurement and basophil activation test can be used with low sensitivity and high specificity in adults for both assays.6769) For nonimmediate DH, the lymphocyte transformation test and enzymelinked immunosorbent spot assays of cytokines and cytotoxic markers (granzyme B, granulysin, interferonγ) enable the identification of the specific drugassociated, but the sensitivity is yet limited.67,7072) The measurement of tryptase and histamine release and determination of cellular phenotype in a skin biopsy or the peripheral blood can aid in the characterization of the active reaction phase.67) Drug provocation test DPT can be performed to confirm or exclude DH and identify safe alternative treatments in confirmed DH patients.73) The different routes of DPT (oral, parenteral,

topical, and cutaneous) vary depending on the culprit agent.18,58) Several protocols were proposed for children, including single, graded, or multipleday challenges, but there is no single standardized protocol.7376) The recent European Academy of Allergy and Clinical Immunology guideline suggests starting with 1/10 of a single age/weightappropriate dose and proceeding to a half and then a full dose; for patients with severe reactions, the starting dose may be as low as 1:10000 to 1:1000.16) DPT is contraindicated during pregnancy and in cases of acute infection, uncontrolled asthma, or underlying diseases, in which a response to provocation may be noncontrollable with the exception of special circumstances.73) DPT should not be performed for patients who have experienced severe lifethreatening reactions such as anaphylaxis or SCARs. 10,73) DPT should be performed under safe conditions with trained staff and emergency resuscitative equipment available. 10,16,73) Factors that may affect DH in children

1. Age In the general population, age extremes are considered risk factors of ADR.77) However, the incidence of ADR or DH by age varies among studies. In an Italian ADR monitoring study in children 0–14 years, the incidence of ADR was the highest in infants <1 year with a trend of a higher to lower incidence from younger to older age groups.78) In a study of pediatric admissions due to ADR, the median age of children admitted due to ADR was higher than for those admitted for other reasons.79) In an international study that aimed to determine the risk factors associated with ADR in hospitalized children, subjects older than 11 years showed a significantly higher incidence of ADR than those 2–11 years.80) A national surveillance of emergency department visits for ADR in the US showed a higher incidence of ADR in children <1 and 1–4 years old, but the majority of ADR in younger children was unintentional overdose and no significant trend among age groups was shown when only allergic reactions were considered.13) Viral infections Viral infections, by themselves, present skin rashes that are indistinguishable from DH and act as a cofactor to DH reactions. Many DPTnegative cases are linked to viral infections.32 Several specific viruses are more closely involved in DH reactions e.g. skin rashes frequently occur when patients with the EpsteinBarr virus are treated with betalactam antibiotics.81,82) Certain viruses were recently suspected of being linked with SCARs e.g. human herpes virus infection is closely related to DRESS syndrome.82)

Genetic predisposition In adults, specific alleles of the human leukocyte antigen (HLA) gene act as risk factors for DHs. HLA B*57:01 and HLA A*31:01 are related to DRESS or an MPE, while HLA B*15:02 is associated with SJS or TEN. However, it does not show consistent results across all races.

Other points to consider For children with chronic complex conditions, the clinical profile and causative medications of spontaneous ADR are different i.e., medicines that are more frequently prescribed for a more extended time result in

higher incidence of adverse reactions.21) A high frequency of offlabel prescriptions to younger subjects is prone to cause adverse reactions.1,80,83) Polypharmacy is a constant risk factor of ADR.1,16,79,80) Female sex is a risk factor of ADR in adults but not in children.77,79,80) Although biologics are increasingly prescribed these days, there is no specific report to date on the prevalence of risk factors of ADRs to these drugs in children.

Conclusion

Suspecting the association of medication to an unexpected symptom is the crucial first step of assessment in children. The exact prevalence is not known due to rare and conflicting epidemiological data. We do know that few subjects with DH claims actually undergo a full evaluation to confirm DA. ADR to betalactam antibiotics, NSAIDs, and vaccines present uniquely; therefore, a thorough assessment and careful management are warranted in suspected cases. Hypersensitivity reactions to other medications are rare in pediatric populations, but they can be a significant problem in vulnerable subjects, especially when the alleged drugs are irreplaceable for controlling their underlying diseases. Therefore, a thorough evaluation is essential for recommending drug desensitization or avoidance. Conflicts of interest No potential conflict of interest relevant to this article was reported.

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