Drug Allergy in Children: What Should We Know?

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Drug adverse reactions are collectively referred to as reactions that occur differently than anticipated by drugs. Among these, IgE may be involved or not involved. Frequently, the involvement of IgE is not distinguished. This review discusses a broad range of drug hypersensitivity reactions in children including even the non-IgE mediated reactions. Since there is not much known about the drug hypersensitivity in children, we will evaluate the epidemiology and major causes of pediatric drug hypersensitivity. Then we will suggest several issues of viral infection as a compounding factor, genetic analysis, and the most vulnerable subjects among children.

Epidemiology

There is not much information about the epidemiology of drug allergy, drug hypersensitivity, and adverse drug reactions in children. The prevalence may be in the range of 0.1%–16.8%. Skin reactions are the most common, followed by digestive symptoms. They can even involve multiple organs at the same time. More than half of the symptoms appear on the day of first medication. In rare cases, however, the drug provocation test was performed to identify the causative agent to the end. Therefore, the drug sensitivity of children may be overestimated. The actual prevalence is estimated to be lower in children.

Besides, it is inevitable to lose information on drug hypersensitivity reactions during the process of collecting and reporting, and it is not known whether these omissions are more common in children. However, the process of collecting and evaluating adverse drug reactions in children is very different from that of adults, and the parents' colored-perception in this collection process is more likely to distort information about causality and response types than facts. Although there are a limited number of studies, the most common drugs in children are beta-lactam

antibiotics, antipyretic analgesics including NSAIDs, and vaccination injections. However, the major causative agents are influenced by the characteristics of the subject group in which the adverse events are collected, and the more commonly used drugs are reported as the major causative agents.

Characteristics of hypersensitivity reactions according to major drugs

The major causes of drug-related adverse reactions in children include beta-lactam antibiotics, NSAIDs, and vaccines. Therefore, it is necessary to investigate the diagnostic algorithm of each agent by each agent as much as these drugs are the most studied.

Beta-lactam antibiotics

Beta-lactam antibiotics are a class of antibiotics that have a beta-lactam ring in their molecular structures. They are classified into two major groups: penicillin and cephalosporin, and also classified into four minor groups: carbapenem, monobactam, oxacephem, and clavulanic acid.

Beta-lactam antibiotics are the most prevalent drug for hypersensitivity reaction in children and are estimated to have a 1%-10% prevalence rate. The 2016 European Guideline recommends a stepwise approach to confirm the beta-lactam antibiotic allergy. A vital point of the guideline was that no blood test or skin prick test alone could predict or confirm a subject's drug allergy. It is necessary to perform a drug provocation test (DPT) to ultimately diagnose or exclude them. In the reports of major domestic institutions, although different protocols were followed for each institution, DPT was conducted as a crucial tool to confirm several true subjects and to exclude many false positive issues. Although the immediate allergic reaction can be provoked by the standard protocols, non-immediate allergic responses are difficult to diagnose: the protocol is not standardized, and in severe cases of the severe cutaneous adverse reaction (SCAR), provocation test is contraindicated. Finally, cross-resistance between beta-lactam antibiotics is very rare: it is recommended to select the causative agent directly or the agent to be applied in future cases.

NSAID

NSAIDs are the most widely used medication for pain, fever, and inflammation in children. In children NSAIDs are safe, but the rate of hypersensitivity reactions ranges from 0.6% to 5.7%. Even in some studies, the reaction to NSAIDs is more prevalent than that to beta-lactam antibiotics. According to the recent European position paper on the diagnosis and treatment of childhood NSAIDs, a precise classification according to the mechanism is very practical although the rating itself is not straightforward. In children under ten years, most responses are non-

immunologic, cross-intolerant, and easily attributed to co-factors such as exercise or infection. Thus they are divided into non-allergic NSAID hypersensitivity and other cases. In children older than 10, on the other hand, the reactions are similar to those of adults: non-allergic reactions are classified into the NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous disease (NECD), NSAIDs-induced urticaria/angioedema or anaphylaxis (NIUAA). Allergic reactions are classified as selective NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), and selective NSAID-induced delayed reactions (SNIDR). In childhood traditional NERD is uncommon. It appears in the form of rhinitis rather than asthma, cross-intolerant reactions are more common than in adults. NSAID-related periorbital swelling is particularly prevalent in the school-aged children, and anaphylaxis reactions are more common, occurring in 9%-40% of NSAID-related cases. Because there are no other suitable markers in the diagnostic process, DPT is essential to establish diagnosis and alternatives. Although selective NSAIDs for COX2 are not approved for this age group, they can be useful in practice. The natural history is not yet known; thus it is recommended to re-evaluate it periodically.

Hypersensitivity reactions to the vaccine

Hypersensitivity reactions to the vaccine are one of the most common adverse reactions seen in caregivers and primary physicians. An Australian study reported that up to 48% of subjects replied an adverse reaction after vaccination: 63% of them were fever and local reactions, 8% were skin reactions, and 0.5% (2 cases) were anaphylactic reactions. Taking good clinical history is essential in assessing the postvaccination hypersensitivity reaction. It is efficient to classify them into a systemic and local reaction, and then reclassify them into immediate and delayed forms. In a systemic allergic reaction, the potential for allergic reactions to preservatives, stabilizers, adjuvants, microbial components, and culture medium components should be carefully considered.

Other Points to Consider

The pattern of ADR becomes similar to that of adults in adolescence. In the younger subjects, it is much different from that of adults. Adverse reactions by the immunologic mechanisms, i.e., ones to beta-lactam antibiotics, the prevalence are similar in all ages. However, other ADRs by non-immunologic mechanisms, i.e., ones to radiocontrast media or NSAIDs, the prevalent age and severities are various and unpredictable.

Viral infections

Viral infections, by themselves, present skin rashes indistinguishable from drug hypersensitivity and also act as a cofactor to drug hypersensitivity reactions. Many of DPT-negative cases are linked to viral infections. Several

specific viruses are more involved in drug hypersensitivity reactions: for example, skin rashes frequently occur when EBV is combined with beta-lactam therapy. Recently certain viruses are suspected of being linked with SCARs: human herpes virus infection is closely related to DRESS syndrome.

Severe cutaneous adverse reactions

Not many SCAR cases are reported in children. Antibiotics and antipyretics are the most important causes of pediatric SCARs in the recent domestic report. In previous studies, SCAR was found to be more common in non-oral drugs, but in Korea, most of them occurred in oral medications. The clinical manifestations of the SCARs are widely variable, and a spectrum of a single disease cannot explain it. However, some findings are consistent across all SCARs: a certain period has passed before the SCARs has full-blown and supportive care with anti-inflammatory medication is the management of choice.

Vulnerable Subjects

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

In a recent study on the profile of spontaneous ADR in a children's hospital dedicated to the chronic complex condition, rankings of causative medications are different. Medicines that are more frequently prescribed for the more extended time results ADRs. Off-label prescription to the younger subjects is prone to cause ADRs. Although the biologics are prescribed these days increasingly, there is no specific report on the prevalence of risk factors of ADRs to these drugs in children yet.

Conclusions

Suspecting the association of medication is the crucial first step of pediatric ADR assessment. The exact prevalence is not known due to the rare and conflicting epidemiological data. One thing is sure that only part of the subjects takes the full evaluation. ADR to Beta-lactam antibiotics, NSAIDs and vaccines are unique in their presentation; therefore thorough assessment and management is warranted when they were probably suspected. Hypersensitivity reaction to other medications are rare in pediatric populations, but they can be a significant problem in vulnerable subjects, especially the alleged drugs are irreplaceable control their underlying issues.

Therefore, a thorough evaluation is again essential to recommend adopting desensitization or avoidance.

References

1. Holten KB, Onusko EM. Appropriate prescribing of oral beta-lactam antibiotics. Am Fam Physician 2000;62:611-20.
2. Bergmann M, Caubet JC. Specific Aspects of Drug Hypersensitivity in Children. Curr Pharm Des 2016;22(45):6832-51.
3. Gomes ER, Brockow K, Kuyucu S, Saretta F, Mori F, Blanca-Lopez N, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016;71:149-61.
4. Dibek Misirlioglu E, Guvenir H, Bahceci S, Haktanir Abul M, Can D, Usta Guc BE, et al. Severe cutaneous adverse drug reactions in pediatric patients: a multicenter study. J Allergy Clin Immunol Pract 2017;5:757-63.
5. Graham F, Caubet JC. Diagnosis of drug causality in non-immediate drug hypersensitivity in children. Expert Rev Clin Pharmacol 2018;11:655-8.
6. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β-lactam antibiotics. Expert Opin Drug Saf 2018;17:499-508.
7. Kim DW, Choi YC, Lee YS, Nam YH, Jung JA. Analysis of pediatric adverse drug reactions reported to regional pharmacovigilance center of a single university hospital. Allergy Asthma Respir Dis 2018;6:263-9.
8. Park GM, Park JH, Jung JW, Han HW, Kim JY, Lee E, et al. Pediatric adverse drug reactions collected by an electronic reporting system in a single tertiary university hospital. Allergy Asthma Respir Dis 2016;4:354-9.
9. Na HR, Lee JM, Jung JW, Lee SY. Usefulness of drug provocation tests in children with a history of adverse drug reaction. Korean J Pediatr 2011;54:304-9.
10. Yu YM, Shin WG, Lee JY, Choi SA, Jo YH, Youn SJ, et al. Patterns of Adverse Drug Reactions in Different Age Groups: Analysis of Spontaneous Reports by Community Pharmacists. PLoS One 2015;10:e0132916.
11. Choi J, Lee JY, Kim KH, Choi J, Ahn K, Kim J. Evaluation of drug provocation tests in Korean children: a single center experience. Asian Pac J Allergy Immunol 2016;34:130-6.
12. Sim DW, Park KH, Park HJ, Son YW, Lee SC, Park JW, et al. Clinical characteristics of adverse events associated with therapeutic monoclonal antibodies in Korea. Pharmacoepidemiol Drug Saf 2016; 25:1279-86.
13. Baek HJ, Cho YS, Kim KS, Lee J, Kang HR, Suh DI. Multidisciplinary approach to improve spontaneous ADR reporting in the pediatric outpatient setting: a single-institute experience in Korea. Springerplus 2016;5:1435.
14. Kim B, Kim SZ, Lee J, Jung AH, Jung SH, Hahn HJ, et al. Clinical profiles of adverse drug reactions spontaneously reported at a single Korean hospital dedicated to children with complex chronic conditions. PLoS One 2017;12:e0172425.
15. Oh HL, Kang DY, Kang HR, Kim S, Koh YI, Kim SH, et al. Severe Cutaneous Adverse Reactions in Korean Pediatric Patients: A Study From the Korea SCAR Registry. Allergy Asthma Immunol Res 2019;11:241-53.