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Review

Drug-induced anaphylaxis in children

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Summary. Anaphylaxis represents one of the most frequent medical emergencies in childhood. However, as compared to adults, drugs are less common triggers of anaphylaxis in children, with a frequency which is increasing from infancy to adolescence. Deaths seldom occur, maybe because of the paucity of comorbidities in children. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the main elicitors in drug-induced anaphylaxis in children. Both immune-mediated (mainly IgE-mediated) and non immune-mediated may be involved. IgG-mediated and complement-mediated mechanisms has been also hypothesized. Correct management relies on a right diagnosis and prompt therapy. A proper work-up is also important to prevent further potentially fatal re-exposures to the same drug or other structurally similar molecules but also unnecessary avoidance of medications not representing the culprit of the episode. (www.actabiomedica.it)

Key words: epidemiology, drugs, anaphylaxis, MRGPRX2

Introduction

Anaphylaxis is an acute systemic allergic reaction which could be life-threatening and also fatal. Diagnostic criteria has been established since 2006 but still many cases remain underdiagnosed and undertreated all over the world (1). Food, insect stings and medications are the main triggers across all ages (2-5). Less common triggers include animal dander, latex, contrast media, environmental allergens, and exercise or temperature. In as much as 10-35% of cases a plausible trigger cannot be identified (i.e. in idiopathic anaphylaxis) (1, 5). Differences however exist in anaphylaxis between adulthood and childhood regarding the relative proportion of eliciting triggers, clinical presentation and even mortality. Drugs in adults are the most frequent etiological agents in fatal anaphylaxis in most regions were data are available (3). Data on drug-induced anaphylaxis in children are scarce and mostly limited to case series including adult populations. Aim of the present review is to provide the reader some insights into the etiology, pathophysiological mechanisms and management of drug-induced anaphylaxis in children.

Epidemiology

The frequency of anaphylaxis varies widely across studies, with an incidence ranging from 3 to 112 episodes per 100,000 person-years, and a lifetime prevalence of 0.05 to 5.1%. Such wide variations me be

explained by the strength of the definitions used, genetics, geographical patterns, and other still undefined factors (6, 7). The incidence in children aged 0-4 years is almost 3 times higher than that of other age groups, with higher figures in boys than in girls until age 10-15 years. According to the raising prevalence of atopy, the frequency of anaphylaxis has also been increased since late 1990s, maybe reflecting also a better diagnostic capacity and guidelines implementation among care providers worldwide (6, 8).

Much less is known about the prevalence of drug-induced anaphylaxis. The frequency of self reported drug hypersensitivity is very high in the general population, even in childhood. Systematic reviews and metanalysis report a prevalence of self-reported drug allergy of 10.0% in adults, and 5.1% in children, with a higher frequency in hospital settings (9). However, when properly investigated, only a few of these reactions can be confirmed after a diagnostic work-up (10). Noteworthy, drugs represent one of the "big three" elicitors in etiological ascertained anaphylaxis and the first causative factor in perioperative anaphylaxis (1-3, 5-8). Recent electronic health database reports found an unexpected high prevalence of drug-induced anaphylaxis, occurring in approximately in 1% of adults in the United States (11). Time trend in the same populations seemed to be relatively stable, but year peaks for unexplained reasons were recorded (11).

Drugs are also the main cause of hospital admission for anaphylaxis in adults with an expected rate of 1 in 3.000 hospitalized patients and the leading causative factor in severe or fatal anaphylaxis in adulthood in most regions. Death approximately occurs in 0.3% to 2% of severe anaphylaxis (6). The incidence of fatal drug-induced anaphylaxis may be increasing (12). The patent of many new biotechnological drugs for different human diseases and the approval from regulatory agencies of newly discovered life-saving therapies in critically ill patients could be a major culprit in this expected temporal trend. However, in UK no increase in fatal-anaphylaxis was found for any cause, including drugs, between 1992 and 2012 despite an increase in rate of hospitalization (13). Indeed, in Australia drug-induced fatal anaphylaxis had increased by 300% between 1995 and 2004, despite an increasing rate of hospital admission of only 150% (14). A small but not significant increase of drug-induced fatal anaphylaxis has been also reported in the same country from 2004 onward (15).

Little is known about the epidemiology of drug-induced anaphylaxis in children. The frequency of self-reported drug allergy, including anaphylaxis in children and adolescents is almost half of that reported in adults in most regions of the world (2, 9, 16). As in adults, also in children only a few cases of suspected drug hypersensitivity are really allergic to certain drugs, with the likelihood of a true allergy increasing with the severity of the reaction (17). Medications, including allergen-specific immunotherapy (SIT), have been reported with a proportion ranging from 8%. to 33.1% of all causes in case series of anaphylaxis in children (2, 17-23). However, drugs were the eliciting triggers in only 101 out of 1970 (5%) cases of anaphylaxis registered among patients under 18 years reported in the European Anaphylaxis Registry (24). Of those, 50 out of 101 (50%) were attributed to SIT. In this population sample however only 1.3% patients had grade IV / fatal reactions. It is worth mentioning that the proportion of medication-induced anaphylaxis in adolescence (13-17 years) almost doubled as compared to earlier ages, probably reflecting age-dependent sensitization and/or different attitude to use specific therapeutic products. Indeed, in infants and toddlers the frequency of drug-induced anaphylaxis seems to be to 4- 5-fold lower than in children > 12 months of age (20).

Fortunately, deaths very seldom occur because of drug-induced anaphylaxis in children. In general the mortality because of anaphylaxis is age-dependent and is much less in children than in adults, maybe as an epiphenomenon of the lack of major comorbidites, less use of medications interfering with treatment and high adult supervision (3, 6). In a large French survey on 1603 cases of fatal anaphylaxis (of whom 63% were iatrogenic) only 2.4% occurred in children (25). Further in a pharmacovigilance study from China collecting 91 cases of drug-induced anaphylaxis in children, only one death was recorded, with a frequency of severe anaphylaxis being more then 15 time lower in children 0-5 years than children 13-17 years old (26). However, even if uncommon, drugs account for most of pediatric anaphylaxis fatalities in both Europe and United States (27, 28)

Etiology and risk factors of drug-induced anaphylaxis in children

Anaphylaxis has been described as an adverse affect virtually of all medications, including anti-allergic drugs and corticosteroids across all ages (19, 26, 29, 30). Antibiotics and non-steroidal anti-Inflammatory drugs (NSAIDs) represent the major culprit in almost all studies on drug-induced anaphylaxis in children. NSAIDs, whether or not combined with exercise, are also major potentiating factors in the so called cofactor augmented food-induced anaphylaxis (31). However, specific immunotherapy (SIT) represented the most frequent etiology of medication-induced anaphylaxis in a multi-center data-collection survey from Turkey (19). Other medications, including opiates, anesthetics, hormones, radiocontrast agents, probiotics and chemotherapics may also represent a significant issue. In a recent survey from China, biologics and chemotherapics covered 10% of all cases of drug-induced anaphylaxis in children (26).

In general, asthma and atopy seem not to be a risk factors for drug-induced anaphylaxis (19, 30, 32). However, an atopic status seems to be a risk factor for NSAIDs hypersensitivity reactions (33). Atopy has been also associated to cross-intolerance to NSAIDS, at least in adults (34).

Female sex has been also reported to be associated with a three-fold higher risk of medication-induced anaphylaxis in some studies (19). Other studies have also reported a higher risk of actual drug-induced anaphylaxis in children with a history of systemic illnesses or concomitant regular assumption of other medications (30). High level of exposition and the frequent use of intravenous route as occurs in cystic fibrosis may be also predisposing factors (35).

Mastocytosis may also be a risk factor for drug-induced anaphylaxis, particularly in the perioparative period (36, 37). Triggers may be NSAIDs, opioids, beta-lactams, contrast media, or other medications, including anesthetics. Approximately 4% of children with mastocytosis may develop an episode of mast cell activation with systemic symptoms under different anesthetic procedures (38). However, high levels of basal tryptase are uncommon in drug-induced anaphylaxis and only a minority of cases with medication-induced anaphylaxis are associated with mastocytosis (36).

Mechanisms of drug-induced anaphylaxis in children

Drug-induced anaphylaxis may occur as a consequence of both immune-mediated (mainly IgE-mediated) and non immune mediated mechanisms (7, 35). As many drugs have a low-molecular weight, thay act as aptens, i.e. they require the binding to a high molecular weight protein carrier to be recognized by antigen-presenting cells to induce an IgE or non IgE-mediated immune response. Non immune mechanisms may include direct mast cell activation or an imbalance of eicosanoids metabolism with up-regulation of leukotrienes production and inhibition of prostaglandins synthesis, including prostaglandin E2 (PGE2). PGE2 acts through the EP2 receptor, which stabilizes mast cells, and therefore the decrease in PGE2 occurring as a downstream effect of COX-1 inhibition by NSAIDS might lead to abrupt mediator release from inflammatory cells and the development of systemic symptoms in susceptible subjects (39). Non immune mediate mechanisms seem to be the main mechanism of anahylaxis induced by certain medications such as NSAIDs, opiates, neuromuscolar blockers and some antibiotics, such as vancomicin or fluorochinolones (35, 39, 40). New insights into the pathophysiology of some anaphylactoid (or "psudoallergic") reactions have been provided by the discovery that a single receptor in mouse, named Mrgprb2, the orthologue of the human G-protein-coupled receptor MRGPRX2, can induce direct mast cell activation leading to histamine release, inflammation and airway contraction (41). This receptor seems to be the target for some small-molecule drugs (such as quinolones, neuromuscular blocking agents, and icatibant) and other cationic substances collectively called basic "secretagogues" which can induce adverse reactions by non immune mechanisms. Acetyl salicylic acid has also been shown to facilitate direct mast cell activation by an increase in Syk kinase phosphorylation of the FcεRI signalling complex, with an affect which could have a genetic basis related to FcεRIa subunit gene polymorphisms (42, 43).

Immune mechanisms may be IgE mediated or non IgE-mediated. Under a condition of antigen-excess, as occurs when large amount of drugs are administered by the intravenous route, a IgG-mediated may be involved, with a mechanism which has been described in mouse as «passive systemic anaphylaxis» (40). This has been demonstrated in patients treated with aprotinin, dextran but also in intravenous immunoglobulin-treated IgA-deficient individuals, von Willebrand factor-deficient subjects under substitutive therapy, and also in patients treated with a variety of chimeric, humanized, and even fully human mAb (40, 44). Again, genetic factors may play a role in these non IgE-mediated adverse reactions to medications. For example, some studies haves shown a higher frequency of mutant alleles associated with a gain-of-function of the stimulatory FcγRIIA in patients with hypogammaglobulinemia who developed anaphylaxis because of IgG anti-IgA antibodies after intravenous immunoglobulin infusion (45). Mouse models indicate that probably in drug-induced IgG-mediated anaphylaxis different cell types from mast cells, such as activated monocytes/macrophages, basophils, or neutrophils are involved (40, 44).

Notably, the existence of a complement-mediated anaphylaxis has been also hypothesized, which could explain some non IgE-mediated anaphylaxis triggered by non proteic micellar drugs, lipid carriers, liposomes and polyethylene glicol (40).

Management of drug-induced anaphylaxis

Drug-induced anaphylaxis is an emergency. The median times to cardiorespiratory arrest after a medical intervention-induced anaphylaxis is only 5 minutes, as compared to 30 minutes after food-induced anaphylaxis (1). The premise for proper treatment is a correct diagnosis, which in most cases may be made independently from the confirmation of the etiological role of a drug through a proper diagnostic work-up. Indeed, the diagnosis of anaphylaxis relies on a combination of history and a well defined set of symptoms established from international guidelines (1, 4). According to guidelines, two out of three criteria require the exposure to a likely or known allergen or other trigger. Therefore, unless the first criteria is respected, if a trigger could be not properly identified, by history alone and/or in vivo or in vitro test results, a diagnosis of drug-induced anaphylaxis could not be made. This occurs quite seldom in drug-induced anaphylaxis, as the brief time lapse between exposure to the suspected trigger and the beginning of symptoms makes the cause-effect relationship often undoubtful. Sometimes clinical history is so clear that performing in vivo or in vitro tests aimed to demonstrate an immune or non immune mechanism upon which the suspected drug had induced reported symptoms may be useless or even contraindicated. This is not the case of anaphylaxis occurring during the periperative period, as many drugs and diagnostic or therapeutic interventions are administered at the same time during anesthetic procedures.

An increase of serum tryptase concentrations in comparison with basal levels between 15 min and 2 h after a reaction is highly suggestive of anaphylaxis, but his absence does not exclude it (46). Regarding emergency treatment, guidelines recommend adrenaline intramuscularly as first-line option. Intravenous fluids and bronchodilators may be required. Second-line options include antiH1-antihistamines and glucocorticoids.

The identification of the offending drug is necessary to prevent further, potentially fatal, episodes and unnecessary avoidance of a drug not etiologically related to the episode. Appropriate tests are skin tests and detection of IgE to the suspected drug The drug provocation test is considered the diagnostic gold standard. However, it should be taken into account that risks and benefits must be carefully considered before performing a challenge test to the relevant drug in children with anaphylaxis (35, 47). Further, children with anaphylaxis to drug and their families should be prescribed adrenaline autoinjector and they should be instructed on how they should use it.

Conclusions

Further studies are warranted on the prevalence of drug induced anaphylaxis in childhood. A correct diagnosis is critical for preventing further anaphylactic reactions. Avoidance of the offending drug and knowledge of adrenaline use for treatment of anaphylaxis are the cornerstone of the management of anaphylaxis.

Conflict of interest: None to declare

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