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Lessons from peculiar cases of anaphylaxis: why allergists should be prepared for the unexpected

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Summary

Anaphylaxis is the most severe systemic hypersensitivity reaction, it can be caused by a number of well identified triggers such as foods, drugs, stinging insects and facilitated by predisposing clinical conditions. However, sometimes anaphylaxis shows up with uncommon or peculiar characteristics which could delay diagnosis and therapeutic treatment. In this report we aimed to describe less accounted/difficult-to-approach shapes of anaphylaxis to facilitate clinicians to suspect these severe reactions even in uncommon conditions. We choose to present data on anaphylaxis regarding simulation, mode of exposure to sensitizing agents, pregnancy, exposure to animals, intimate behaviour, psychological stress, and other situations.

IMPACT STATEMENT

Sometimes anaphylaxis can occur with uncommon or peculiar characteristics which could delay diagnosis and therapeutic treatment. We aimed to describe less accounted/difficult-to-approach shapes of anaphylaxis to facilitate clinicians to suspect these severe reactions even in uncommon conditions.

Introduction

Anaphylaxis is the most severe systemic hypersensitivity reaction, it involves multiple organ systems and can be deadly (1, 2). Anaphylaxis can be caused by a number of well identified triggers such as foods, drugs, stinging insects and clinical conditions (1, 2). However, sometimes anaphylaxis shows up with uncommon or peculiar characteristics which could delay diagnosis and therapeutic treatment. In this brief report we aimed to introduce less accounted/difficult-to-approach shapes of anaphylaxis to facilitate clinicians to suspect these severe reactions even in uncommon conditions.

Simulated anaphylaxis

In rare occasions, it has been reported that anaphylaxis can be mimicked by other clinic conditions (3) such as a diverticular perforation associated with colo-urachal fistula (4) and a massive subcutaneous emphysema presenting as anaphylaxis (5). We have recently shown that in obstetric surgery oxytocin/vasopressin can induce some side effects (negative inotropic and chronotropic effects, low blood pressure, vasodilatation) which can simulate a cardiac anaphylaxis and consequent intraoperative diagnostic problems and risks for the patient (6).

Anaphylaxis and mode of exposure

Inhalation mode

Inhalation of the offending allergens is an uncommon cause of anaphylaxis. Inhalant allergens such as those of some animals (guinea pig, horse, deer and rabbit) (7, 8) and grass pollens (9) can induce anaphylaxis. Food allergens, particularly from milk, in aerosolized form has been associated to anaphylaxis in a dairy worker (10) or in children as component of a medication aerosol (11). Anaphylaxis after occupational inhalation of Cefuroxime in a nurse has been also described (12).

Contact mode

It has been published only five cases of anaphylaxis induced by skin contact with milk or milk-derived foods; some indications on the risk factors to identify susceptible individuals are shown in **table I** (13). Recently a fatal reaction has been registered in a child at school (14) and another recent case report showed a generalized reaction induced by a cutaneous exposure to milk proteins in a colostrum-based cream (15).

Skin prick test (SPT)-related anaphylactic reactions can also be ascribed to the contact mode of exposure, those induced by the use of foods or drugs being the most frequent in clinical practice (16). On the contrary anaphylaxis produced by SPT with standard aero-allergens is extremely uncommon. We described a rare case of systemic life-threatening reaction after a routine SPT in a patient with high allergic sensitization to parietaria and grasses

Table I - Possible predictive risk factors to identify patients with hazard for severe allergic reactions through noningestant routes of exposure.

High serum total IgE level
Strong family history of atopy
Early age of onset of symptoms despite having been breast-fed
Strong reactivity to skin-prick-tests or serum specific IgE evaluation
Clinical history
A disrupted skin barrier (<i>e.g.</i> , from atopic dermatitis, injury)

Modified from Liccardi G, De Falco F, Gilder JA, D'Amato M, D'Amato G. Severe systemic allergic reaction induced by accidental skin contact with cow milk in a 16-year-old boy. A case report. *J Investig Allergol Clin Immunol.* 2004;14(2):168-71.

(17). In the same article we reported a multicentric evaluation of the frequency of SPT-related anaphylaxis in Italy: our case was the only one among 55.105 patients and 684.306 allergens tested (17). Possible risk factors for SPT-related anaphylaxis are similar to those described in **table I**. Moreover, in children we suggest to avoid the contemporary use of inhalant and food allergens, and the use of intradermal skin testing, to minimize the number of allergens to be tested during the SPT procedure, and to check the subjects for at least 20 min after the end of SPT. In some cases, it should be useful to consider the possibility of diluting allergenic extracts before their use (18, 19). It is important to underline that the need to carry out *in vivo* tests (*e.g.*, SPTs, prick by prick) for the diagnosis of food allergy in highly sensitized individuals has been reduced by the growing use and utility of modern laboratory procedures such as Component Resolved Diagnostics (20, 21).

Anaphylaxis and pregnancy

Anaphylaxis is considered uncommon during pregnancy. However, among potential risk factors such as age and history of allergy, caesarean delivery could be recognized as the main culprit condition because the necessity of using anaesthesia, surgical procedures and drugs (22). An amoxicillin-induced anaphylaxis at the end of pregnancy determined newborn death by hypoxic-ischaemic cerebral injuries (23).

As previously reported, delivery, especially when carried out by caesarean section, can determine dangerous systemic reactions. Oxytocin constitute a complex cause of systemic/bronchial reactions as well as equivocal side effects-related- symptoms (negative inotropic and chronotropic effects, low blood pressure, vasodilatation) that mimic cardiac anaphylaxis (6, 24). Another insidious effect derived by a demonstrated homology in the protein sequence of oxytocin and latex allergens Hev b 7.01 and Hev b 7.02 (25).

We have previously described two life-threatening anaphylactic reactions with onset a few minutes after the infusion of oxytocin in two women sensitized to latex allergens during caesarean section under spinal anaesthesia in the delivery room (26). Moreover, it has been also demonstrated that oxytocin, under pro-inflammatory cytokines stimulation, may induce contraction of smooth muscle and airway narrowing suggesting that oxytocin serves as a bronchoconstrictor (27). These data suggest that inflammatory conditions of airways such as those found in asthmatic women (especially those with severe asthma) might constitute an independent (from anaphylaxis) risk factor for airway obstruction after infusion of oxytocin during delivery. The role of oxytocin receptors could also explain the well-known worsening of asthma control in about one-third of pregnant women suffering from asthma. These findings suggest a particular attention in managing delivering women suffering from latex allergy and bronchial asthma. An accurate anamnestic, clinical and diagnostic evaluation, a latex-free setting, the use of oxytocin-alternative agents and, in case of asthma, a drug premedication are likely to reduce the risk of anaphylactic or airway-obstructive reactions in these women (24) (**figure 1**).

Another extremely uncommon condition for anaphylaxis is lactation (28). It is not clear the pathogenesis, a possible role of

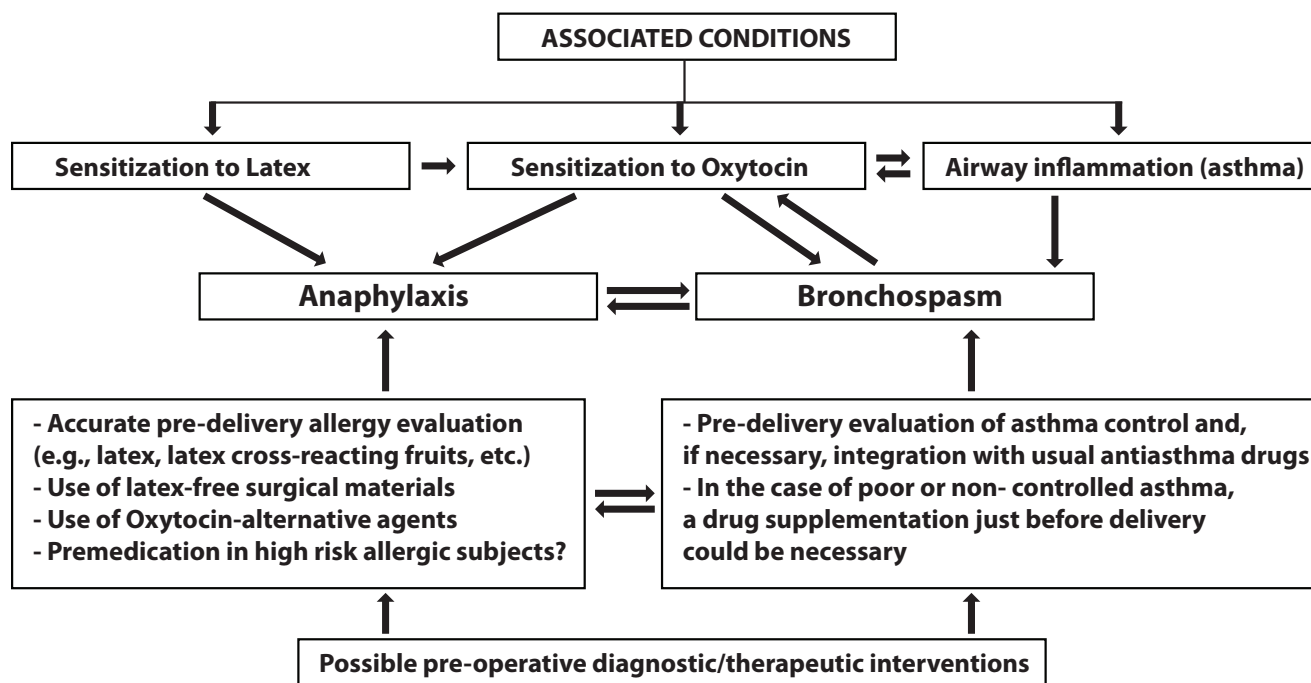
hormones has been suggested (the withdrawal of the stabilising effect of progesterone on mast cells) but also the influence of others (prolactin, oxytocin, adrenocorticotrophic hormone and corticotropin-releasing hormone) (29).

Finally, some case reports have shown that bovine serum albumin may be a causative agent in severe anaphylaxis after standard intrauterine insemination or *in vitro* fertilization if added to the culture medium of spermatozooids (30).

Anaphylaxis and animal exposure

Although respiratory allergy is a common consequence of animal allergens inhalation, in rare occasions a clear clinical picture of anaphylaxis developed after inhalation of guinea pig, horse, rabbit and deer epithelia (7, 8). Another possible modality of inducing anaphylaxis after exposure to animals is their bite. In some rare cases the bites were inflicted by domestic or wild animals such as horse, gerbil, mouse (31-33). However, the risk of anaphylaxis from animal bites is relatively more common in individuals working with laboratory animals, particularly rodents (34). Another topic related to animals regards some food-derived animal substances that can be used in medications at various stages of the

Figure 1 - Possible correlation between latex, oxytocin sensitization and airway inflammatory conditions including suggested pre-operative diagnostic/therapeutic interventions.



Modified from Liccardi G, Bilò MB, Mauro C, Salzillo A, Piccolo A, D'Amato M, Liccardi A, D'Amato G. Oxytocin: an unexpected risk for cardiologic and broncho-obstructive effects, and allergic reactions in susceptible delivering women. *Multidiscip Respir Med* 2013;8(1):67.

manufacturing process. Caglayan-Sozmen *et al.* (35) review the possible roles of medications which may contain egg, red meat, gelatin, and fish allergens in allergic reactions in children with food allergy. The risk of reactions to hidden milk allergens in drugs is particularly important. In fact, dry-powder inhalers may contain lactose as excipient, this product can be rarely contaminated with milk proteins and, consequently, it may induce allergic reactions in patients with cow's milk allergy (36, 37). Reports have described immediate hypersensitivity reactions to methylprednisolone sodium succinate 40 mg injection, a formulation that contains lactose as excipient (38). Some cases of anaphylaxis after receiving diphtheria-tetanus-pertussis vaccine injection (39) or some probiotics (40) in children allergic to milk have been reported. Among food-derived animal substances, also gelatin can induce systemic reactions being contained in medications like plasma volume expanders, erythropoietin, hemostatic products (41), as well as in some vaccines (42, 43). Although dogs can induce respiratory allergy, we would like to cite the potential role of service dogs in certain clinical conditions at high risk of anaphylaxis such as surgical interventions in subjects with high allergic risk. Tew and Taicher documented the first report of a service dog used to detect mast cell mediator release in patients with mastocytosis (44). This service dog was used not only in a family-centered care model, but also as an additional perioperative monitor to predict the eventual occurrence of perioperative mediator release (44).

Anaphylaxis and intimate behaviour

Although rare, the contact with allergens can also be due to a direct contact between two individuals, one of whom carries on his/her body the allergen potentially dangerous for the other individual (or can carry traces of food or drugs in biological fluids) (**figure 2**). This can easily happen during intimate behaviours, such as kisses or sexual intercourses. This topic may be underestimated and under-reported, due to its delicate nature, involving a very intimate aspect of the life (45).

The mechanism by which kissing may induce local or, in some cases, generalized reactions in sensitized individuals is the passive transport of allergenic molecules through saliva, skin or oral mucosa, and the consequent contact of these allergens with the skin or mucosae of the sensitized subjects. The severity of allergic symptoms likely depends on the type of kissing, as the contact with the 'unprotected' oral mucosa may account for a greater penetration of allergens in comparison to intact skin (45).

Foods are the most frequent cause of allergic reactions following a kiss from an individual who have eaten an allergenic food to a patient sensitized to the same allergen (46). Peanuts, walnuts and other tree nuts are the most common foods involved, followed by fruits or vegetables such as apple, carrot, kiwi, fish, shellfish, and milk (47, 48). There are only few reports of oral allergy syndrome and consequent generalized urticaria in drug-sensitized

individuals, a few minutes after passionate kisses given by their partners who had previously used the drug particularly beta lactams (49, 50). Foods (such as Brazil nut) can also penetrate into seminal fluid and induce after vaginal intercourse (51); seminal fluid can also carry antibiotics (such as amoxicillin) and trigger anaphylaxis in an amoxicillin-sensitized woman after oral sex (52). Anaphylaxis after anal intercourse but tolerance after vaginal intercourse has been also described (53).

Seminal plasma hypersensitivity (SPH) is characterized by immediate local or systemic postcoital symptoms following mucosal exposure to seminal fluid. Systemic SPH is a type I, immediate, IgE-mediated hypersensitivity reaction with the well-known symptoms (54).

The prostate-specific antigen (PSA), a 33-34 kDa glycoprotein, better known for its use in monitoring prostate cancer in men, was in fact identified as a major allergen in human seminal fluids. It was found that PSA carries high homology to the canine prostatic kallikrein, which was identified as Can f 5. The clinical relevance of this cross-reactivity was confirmed in a few cases, and investigators have hypothesized that patients who experienced SPH after their first unprotected intercourse could have been sensitized by previous exposure to dogs (54).

We have recently shown the increasing relevance of allergic sensitization to Can f 5 in North East Italy considering both the number of sensitized individuals (69.02% among 268 dog-sensitized ones, and 57.92% as exclusive sensitization) and the level of sensitization (77.6% of individuals showed medium or high values of specific IgE according to manufacturer's specifications) (55). Moreover, our Italian multicenter study has shown that a prevalent exposure to a male dog represents a risk factor for the presence of Can f 5 monosensitization (56). The results of this study emphasize the need of an adequate diagnosis and management of patients suffering from dog allergy, especially those with relevant clinical symptoms following dog exposure in order to prevent systemic SPH (57).

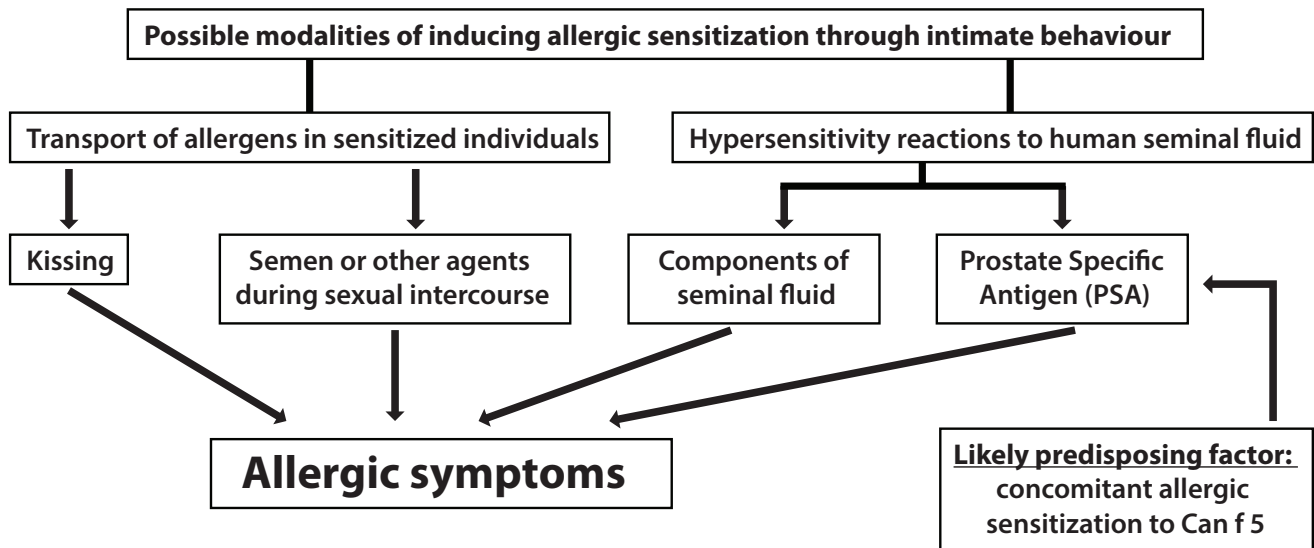
Anaphylaxis and psychological stress

The relationship between anaphylaxis and psychological stress (PS) is an intriguing puzzle, the question being: can the former be the cause or only consequence of the latter or both?

It is well documented that (PS) may enhance allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis through several complex mechanisms like mast cell activation and mediator release, inflammation and imbalance of the autonomic system (58-60).

Stress can activate the hypothalamic-pituitary-adrenal axis through the release of corticotropin-releasing hormone (CRH). Theoharides *et al.* have shown that CRH secreted under stress stimulates mast cell degranulation through activation of CRH receptor-1 (CRHR-1) (61). This effect is augmented by other neuropeptides also released by stress, such as substance P (SP) and neurotensin (NT). In fact, both NT and SP induce the expression of functional

Figure 2 - Possible modalities of inducing allergic sensitization through intimate behaviour.



Modified from Liccardi G, Caminati M, Senna G, Calzetta L, Rogliani P. Anaphylaxis and intimate behaviour. *Curr Opin Allergy Clin Immunol* 2017;17(5):350-5.

CRHR-1 (61). Moreover, the same authors have shown that CRH induces the expression of high-affinity IgE receptor (FcεRI) and augments allergic stimulation of human mast cells (62).

To the best of our knowledge, only two case reports have clearly suggested a relationship between a PS situation and the onset of anaphylaxis (63, 64). The diagnosis of such anaphylaxis has been made essentially through anamnestic criteria and exclusion of other most common triggering agents/situations. We believe that PS alone or as relevant co-factor could induce anaphylaxis more frequently than expected if we consider the aforementioned mechanisms and the high presence of PS in the general population. On the contrary, the role/onset of PS in patients surviving anaphylaxis episodes has been better explored. Baiardini *et al.* (65) studied quality of life and well-being in patients with drug-induced anaphylaxis. Two validated tools were used: The Drug Hypersensitivity Quality-of-Life Questionnaire (DrHy-Q) and the Psychological General Well-Being Index (PGWBI). Compared with the Italian reference population, patients had a significantly reduced PGWBI total and domain score. The authors highlighted for the first time impaired Health Related Quality of Life (HRQoL) and distress commonly feature in survivors to anaphylactic reactions to drug.

Recently Lee *et al.* (66) have evaluated Posttraumatic Stress Disorder (PTSD) arising after anaphylaxis in adults, by investigating the psychosocial burden of recent anaphylaxis in Korean adults. The results of this study indicated that patients who experienced anaphylaxis were likely to develop psychiatric disor-

ders, such as PTSD, anxiety, and depression. The development of PTSD did not appear to depend on the severity of anaphylaxis, although patients with higher Impact of Event Scale-Revised-Korean version (IES-R-K) scores had more severe anxiety and depression. These and previous considerations suggest that the general management (diagnosis/treatment) of anaphylaxis should include a psychological/psychiatric evaluation.

Others

Anaphylaxis after the use of polyethylene glycol (PEG), a water-soluble, organic compound included in a wide variety of products has been described. In the healthcare setting, it is a common ingredient in medications and procedural agents (*e.g.*, for performing ultrasound scans) (67). Anaphylaxis to chlorhexidine (a synthetic bisbiguanide antiseptic agent) has been reported particularly in the perioperative and medical procedural settings (68).

Rare cases of anaphylaxis have been reported also with the use of anti-anaphylaxis agents such as cetirizine and chlorpheniramine (69, 70). Another controversial topic is the possible induction of anaphylaxis by vaccines used to prevent contagious infections, many patients refusing vaccinations for this fear. Mc Neil *et al.* (71) reported only 33 vaccine-triggered anaphylaxis cases that occurred after 25,173,965 vaccine doses (against different infectious agents), the rate of anaphylaxis being 1.31 (95% CI, 0.90-1.84) per million vaccine doses.

Interest in this issue has increased significantly with the recent start of mass vaccination against the Sars-CoV-2 virus. Preliminary reports have been published on anaphylactic events occurring after the administration of the first Sars-CoV-2 available vaccines. Twenty-one cases were determined to be anaphylaxis (a rate of 11.1 per million doses administered) after the use of Pfizer-BioNTech COVID-19 Vaccine (72), while 10 cases were determined to be anaphylaxis (a rate of 2.5 anaphylaxis cases per million Moderna COVID-19 vaccine doses administered) (73). The aforementioned polyethylene glycol (PEG) has been indicated as potential agent of anaphylaxis in these vaccines being an excipient (74-76).

Conclusions

Data reported from our previous studies and from a review of the Literature show that sometimes anaphylaxis can occur with uncommon or peculiar characteristics which could delay diagnosis and therapeutic treatment. We hope that the description of less accounted/difficult-to-approach shapes of anaphylaxis could facilitate clinicians to suspect these severe reactions even in less common clinic presentations.

Previous presentations

Data presented at AAIITO 2020. Online “Il Mese dell’Allergologia AAIITO” 9-26 October 2020.

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Conflict of interests

The authors declare that they have no conflict of interests.

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