Annals of Clinical & Experimental Immunology

Short Communication

The significance of absent skin symptoms during severe anaphylaxis

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Abstract

Anaphylaxis represents the most serious immediate allergic reaction and the need for early symptom recognition has led to the compilation of different clinical classifications. The most critical symptoms involve cardiovascular and respiratory systems. Suggesting an integrated clinical classification, this work considers severe hypotensive events lacking skin symptoms after exposure to culprit allergen(s) more severe cases as compared to identical reactions with skin symptomatology, because the abrupt hypotension may lead to failure on fluid extravasation and lack of mediators' concentration outside the circulatory system. The potential incorporation of this instrument in the future severity assessment systems may help specialized caregivers to better recognize severe anaphylactic reactions and therefore help them to avoid unnecessary fatal outcomes.

Keywords: Abrupt hypotension; Anaphylaxis; Classifications; Lack of skin symptoms

Introduction

Anaphylaxis, the most serious and life-threatening allergic reaction, is generally a systemic immunoglobulin E (IgE)-mediated reaction resulting from the sudden release of multiple inflammatory mediators from mast cells and basophils [1-3]. This acute pathology can involve several organ systems, particularly the skin, respiratory tract, gastrointestinal tract, and cardiovascular system, where mast cell concentrations are highest [3-7]. The action of mast cell and basophil mediators such as histamine, leukotrienes, and platelet-activating factor leads to smooth muscle contraction, vascular muscle relaxation, and an increase in vascular permeability, causing bronchiolar constriction, abdominal cramps, localized angioedema, hypoxia, great loss of intravascular volume and shock in a short time [2,7-9].

Early symptoms' recognition together with prompt therapy institution is central to a successful outcome because delays in epinephrine administration have been associated with fatalities [1,9,10]. These factors together with symptoms variability have led to the compilation of different clinical classifications [3-5,10-21]. Proposing an actualized and practical tool on the severity assessment for anaphylactic reactions, this work is focused on the phys-pathological importance of absent skin symptoms during severe events. The contribution is addressed to medical personnel that manages critical allergic reactions, such as allergists, specialists of emergency medicine, and intensive care units (ICU) to recognize the importance of this circumstance on the severity of anaphylaxis.

Submitted: 01 June 2021 | **Accepted:** 22 June 2021 | **Published:** 24 June 2021

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Citation: BAKIRI A, MINGOMATAJ EÇ (2021) The significance of absent skin symptoms during severe anaphylaxis. SM J Med Plant Stud 3: 4.

Anaphylaxis severity and lack of skin symptoms

Aiming to be a useful instrument on the severity assessment of anaphylactic reactions, the proposed classification in this work harmonizes both traditional and recent anaphylaxis classifications [5,14-17,20]. Two formats are envisaged: 1) a numerical classification giving a continuum from mild to severe reactions that are clinically meaningful and useful for allergy healthcare professionals, and 2) a four-grade-based ordinal format that is simple enough to be used and understood by other professionals and patients. Similar to other tools, the overall severity either is defined by the highest numerical value of non-mandatory symptoms, i.e. most severe clinical symptoms [13,17]. Despite the objective inconsistency on the forming of a basis for grading an immediate allergic reaction, we have included neurological symptoms to cope with the whole spectrum of symptoms that vary from warmth and agitation to anxiety or panic, cold extremities, paleness, and muscular cramps, and finally to physical inactivity, collapse and loss of consciousness [15,16,19].

Severe anaphylaxis involves vital systems, such as the cardiovascular one. The principal implication of this system during anaphylaxis may lead to severe systolic hypotension, inadequate organ perfusion, collapse, and circulatory arrest [1,9,22-25]. Meanwhile, skin manifestations are also common symptoms in anaphylaxis [7-9]. Although urticaria as a usual symptom is found to be at significantly high risk for moderate to severe anaphylaxis, about 7% of cases in adults occurred without

skin manifestations [26,27]. Stoevesandt et al. reported that venom immunotherapy build-up cycles complicated by moderate to severe anaphylaxis occurred more rapidly than mere urticaria, whereas Manivannan et al. mentioned that patients who experienced repeated epinephrine administration were likely to present with wheezing, cyanosis, arrhythmias, hypotension, shock, stridor, laryngeal edema, cough, nausea or emesis, and less likely to have urticaria [28,29]. Additional causes of severe anaphylaxis without skin manifestations are cardiac anaphylaxis (Kounis syndrome) and mastocytosis [30-32]. The shock in such critical situations corresponds to a combination of problems with cardiac function (the pump), intravascular volume (the tank), or systemic vascular resistance (the pipes), which lead to acute circulatory failure, decreased organ perfusion, inadequate delivery of oxygenated blood to tissues and resultant end-organ dysfunction [33,34]. The suddenly-released inflammatory mediators due to circulatory basophils and abundant mast cells in anaphylaxis-involved organs/systems can lead to abnormal coronary spasms, myocardial depression and dysfunction, general vasodilation, and increased vascular permeability, causing great loss of intravascular volume in a short time and, in unfortunate individuals, fatal outcome [2,7,9,31,35,36].

The above-mentioned clinical and pathophysiological data indicate that anaphylaxis-related hypotension or cardiovascular collapse in absence of skin manifestations should be considered as a more severe episode compared to anaphylaxis cases announced by urticaria or local angioedema (grade 3B vs. grade 3A respectively, see Table 1). Apart from diagnostic difficulties with concern to absent skin manifestations, the abrupt hypotension may lead to the failure of fluid extravasation despite the endothelial barrier breakdown, therefore being the cause of missed mediators' concentration outside the vascular system and consequently, the reason for the inability to develop the initial urticaria or angioedema [9,17,24]. The eventual occurrence of skin symptoms only during/after a successful treatment agrees with the above-mentioned argument. Consequently, the lack of skin affection in the case of anaphylactic shock can be considered a signal of more severe disease as compared to the cases with skin symptoms, and a more serious situation that needs appropriate intervention and considering of ICU personnel

Table 1: Severity classification of immediate allergic reactions [5,14-17,20].

Affected Systems and Anamnestic Data	Mild or Local Allergic Reactions	Moderate Systemic Anaphylactic Reactions	Severe Systemic Anaphylactic Reactions or Anaphylactic Shock		Clinical Death
	Grade 1	Grade 2	Grade 3A	Grade 3B	Grade 4
Skin and Subcutis	Itching, flushing, rash, hives, local angioedema	Any of the left, accompanied by prodromal paresthetic sensations on palms and soles, as well as feeling of warmth	Any of the left, plus pallid face, cold extremities, sweat outbreak	Any of the Grades 2 or 3A, plus decreased body temperature; Grade 1 skin symptoms manifested ONLY during/ after successful patient reanimation!	Any of the left
Abdominal Organs	-	Nausea, abdominal cramps (uterine, gastrointestinal, etc), anticipated by prodromal metallic taste, labial paresthesia	Any of the left, plus vomiting, involuntary defecation, or mission	Any of the left, plus organ bleeding	Any of the left
Respiratory Tract and Eyes	Sneezing, runny nose, nasal congestion, or ocular injection, itching, lacrimation	Any of the left, plus cough, wheezing, shortness of breath (eg, less than 40% PEF drop, responding to an inhaled bronchodilator), itchy throat	Any of the left, plus shortness of breath (40% PEF drop, NOT responding to an inhaled bronchodilator), dyspnea, tightness, laryngeal or uvular edema	Any of the left, plus stridor, difficulty swallowing, hypoxia, cyanosis, asthma, respiratory failure,	Respiratory arrest
Cardiovascular System	-	Mild tachycardia (increase ≥20 bpm), and hypotension (drop SBP by ≥ 20 mmHg)	Evident tachycardia (increase ≥40 bpm), and hypotension (drop SBP by ≥ 40 mmHg)	Severe hypotension, dysrhythmia, bradycardia, shock, syncope, palpitations	Cardiovascular arrest
Nervous and Musculoskeletal Systems	Mild agitation, limited hyperactivity	Evident agitation, hyperactivity, weakness, headache	Exacerbated agitation, anxiety, dizziness, fainting, muscular cramps	"Lightheadedness", feeling of "pending doom", lack of muscular activity	Loss of consciousness

Explanatory notes: These symptoms are not mandatory. The overall severity either is defined by the highest numerical value, i.e. most severe symptoms. Respiratory and cardiovascular symptoms are decisive in the assessment of anaphylaxis severity. Neurological symptoms (as an epiphenomenon of cardiovascular compromise) are of less significant importance; however, it should be considered a risk factor for inefficient initial treatment, complications, and a warning signal to ask ICU personnel for assisting the treatment team. Hypotensive reactions lacking skin symptoms after exposure to culprit allergen(s) should be considered as more severe than other reactions. Similar to cardiovascular diseases, headache in a subject with urticaria or angioedema should be considered a potential sign of arterial hypo/hypertension. Organ bleeding is a rare non-immune symptom of the anaphylactic reaction (mostly uterine) that may affect every inner organ (such as lungs, brain, etc).
NB Any medical personnel helping a patient with anaphylaxis should be on alert for a rapid progression of the above-mentioned symptoms and signs to be ready for rapid counteraction!

assistance. These can include (multiple) uses of adrenergic therapy, abundant liquid infusion, oxygen therapy, increased doses of glucocorticoids, etc. Hopefully, testing of reliability and validity for this approach in a range of settings and populations will allow eventual implementation in a standardized scoring system during clinical studies and routine practice.

Founding resources

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contribution

Mingomataj EÇ ideated the work and drafted the manuscript; Bakiri A assisted with literature collection and helpful discussions.

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