



Review article

Markers of anaphylaxis – a systematic review

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ABSTRACT

Anaphylaxis is defined as severe, life-threatening, systemic or general, immediate reaction of hypersensitivity, with repeatable symptoms caused by the dose of stimulus which is well tolerated by healthy persons. The proper diagnosis, immediate treatment and differential diagnosis are crucial for saving patient's life. However, anaphylaxis is relatively frequently misdiagnosed or confused with other clinical entities. Thus, there is a continuous need for identifying detectable markers improving the proper diagnosis of anaphylaxis. Here we presented currently known markers of anaphylaxis and discussed in more detail the most clinically valuable ones: tryptase, platelet activating factor (PAF), PAF-acetylhydrolase, histamine and its metabolites.

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Contents

1. Introduction	265
2. Material and methods	266
3. Results and Discussion	266
3.1. Anaphylaxis – definition, clinical manifestations, differential diagnosis	266
3.1.1. Role of mast cells in anaphylaxis	267
3.2. Tryptase	269
3.3. Histamine	271
3.3.1. Histamine and myocardial dysfunction	272
3.4. Platelet-activating factor (PAF)	273
3.5. Genetic markers of anaphylaxis	274
4. Conclusion	274
Conflict of interest	274
Financial disclosure	274
References	275

1. Introduction

Anaphylaxis is defined as severe, life-threatening, systemic or general, immediate reaction of hypersensitivity, with repeatable symptoms caused by the dose of stimulus which is well tolerated

by healthy persons [1]. Mast cells are the most important cells, involved in anaphylactic reactions. The mediators of these cells are: histamine, tryptase, serotonin, proteoglycans, proteases, chemotactic factors and *de novo* synthesized lipid mediators: prostaglandin D2 (PGD2), leukotriene B4 (LTB4), platelet activating factor (PAF), cysteinyl leukotrienes (LTC4, LTD4, LTE4), cytokines (TNF-alpha, IL-4, IL-5, IL-6, IL-8) [1–4]. Therefore, the proper diagnosis, immediate treatment and also differential diagnosis are crucial for saving patient's life. The measurements of potential markers of anaphylaxis could be helpful in this situation. In present, the measurements of tryptase levels are used in clinical practice [1–4]. Scientific reports revealed, that the

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activity of this enzyme, which is characteristic for mast cell granules, correlates well with the severity of anaphylactic reactions [1–4]. The measurements of levels of platelet activating factor (which causes the increase in vascular permeability) and PAF-acetylhydrolase, as well as histamine and its metabolites, could be also the valuable tool in cases of anaphylaxis.

Here we presented currently known markers of anaphylaxis and discussed in more detail the most clinically valuable ones: tryptase, platelet activating factor (PAF), PAF-acetylhydrolase, histamine and its metabolites.

2. Material and methods

A search was started on 01.04.2015. using the MEDLINE/PubMed database (United States National Library of Medicine National Institutes of Health). The key words, used in the process of searching data; were as follows: anaphylaxis; mast cells; histamine; histamine receptors; tryptase; PAF. In order to select the data available in the literature, we performed the searching of the data using the following strategy: anaphylaxis – 19786; anaphylaxis AND clinical trial – 693; anaphylaxis AND review – 3012; anaphylaxis AND case report – 4764; anaphylaxis AND guidelines – 576; mast cell – 35164; mast cell AND anaphylaxis – 2418; histamine – 67318; histamine AND review – 8456; histamine AND anaphylaxis – 3474; histamine AND clinical trial – 6330; histamine AND anaphylaxis AND clinical trial – 96; histamine AND anaphylaxis AND case report – 351; histamine receptor – 21173; histamine receptor AND anaphylaxis – 535; tryptase – 3990; tryptase AND review – 569; tryptase AND anaphylaxis – 518; tryptase AND mast cell – 3342; tryptase AND clinical trial – 198; tryptase AND case report – 366; PAF – 10460; PAF and review – 830; PAF AND anaphylaxis – 280; PAF AND clinical trial – 297; PAF AND clinical trial AND anaphylaxis – 0; PAF AND case report AND anaphylaxis – 0. Filters: published since 1972 (in 1972 PAF was discovered). In January 2017, when we started the manuscript preparation, full-text articles were assessed for eligibility. In order to select the data available in the literature, we performed the searching of the data using the following strategy: anaphylaxis – 990; anaphylaxis AND clinical trial – 405; anaphylaxis AND review – 2263; anaphylaxis AND case report – 2304; anaphylaxis AND guidelines – 551; mast cell – 19803; mast cell AND anaphylaxis – 1347; histamine – 21096; histamine AND review – 3610; histamine AND anaphylaxis – 990; histamine AND clinical trial – 2157; histamine AND anaphylaxis AND clinical trial – 30; histamine AND anaphylaxis AND case report – 157; histamine receptor – 8551; histamine receptor AND anaphylaxis – 202; tryptase – 3132; tryptase AND review – 460; tryptase AND anaphylaxis – 464; tryptase AND mast cell – 2570; tryptase AND clinical trial – 128; tryptase AND case report – 287; PAF – 4046; PAF and review – 347; PAF AND anaphylaxis – 68; PAF AND clinical trial – 297; PAF AND clinical trial AND anaphylaxis – 0; PAF AND case report AND anaphylaxis – 0. Filters: published in last 17 years; full text.

From those full-text articles, 285 were selected for further analysis. In the final version of the manuscript, 168 articles were cited (5 clinical papers, 37 papers on mast cells and their functions in anaphylaxis, and papers on tryptase, histamine and PAF (n = 31, n = 34, n = 61, respectively)).

The search was mainly limited to studies written in English. 166 from 168 citations were found in MEDLINE. In the part of the manuscript, concerning clinical signs and symptoms, two Polish authors of chapters in textbooks were cited (Refs. [2,55]). Three citations, concerning tryptase in diagnostics of allergic diseases, anaphylactic reactions to low-molecular weight chemicals, and idiopathic anaphylaxis, were written in Polish in original versions (Refs. [14,17,163], respectively).

The process of searching for data is presented graphically according to PRISMA 2009 flow diagram in Fig. 1.

3. Results and Discussion

3.1. Anaphylaxis – definition, clinical manifestations, differential diagnosis

The European Academy of Allergy and Clinical Immunology (EAACI) describes anaphylaxis as a severe, life-threatening, systemic or generalized, immediate hypersensitivity reaction. It is, in other words, a manifestation of objective, repeatable symptoms caused by an exposure to a stimulus of a strength that would be well tolerated by healthy individuals [1].

Anaphylaxis is not usually treated as a specific disease, but as a set of symptoms characterizing a specific reaction of people who are hypersensitive to various factors [2]. In the International Statistical Classification of Diseases and Related Health Problems ICD-10, it most closely matches an anaphylactic shock (T78.2). Clinical manifestations of anaphylaxis depend on the organs or systems affected. The clinical symptoms of hypersensitivity reactions, defined as anaphylaxis, can have a mild course and be of a local nature (hives, swelling) or give severe reactions with symptoms of shock (ie. a significant decrease in blood pressure, symptoms of airway obstruction) [2].

If one of the following criteria is fulfilled, the characteristic symptoms are very likely to be described as anaphylaxis [3]:

- 1 Respiratory reactions (shortness of breath, wheezing, stridor, hypoxemia);
- 2 Decrease in blood pressure and related symptoms from the other systems (syncope, fainting, coma, urinary incontinence);

Two or more of the following symptoms which occur suddenly after exposure to a probable triggering factor:

- symptoms of an acute nature, when the causative agent is unknown (duration from a few minutes to several hours) on the skin, mucous membranes (generalized itching, redness of the skin, swelling of the lips, tongue, uvula);
- respiratory symptoms (shortness of breath, wheezing, stridor, hypoxemia);
- decrease in blood pressure and related symptoms from other systems (syncope, fainting, coma, urinary incontinence);
- persistent symptoms from the gastrointestinal tract (abdominal pain, nausea, vomiting).

- 3 Decrease in blood pressure that occurs after exposure to a specific, known factor:

- infants and children: low systolic blood pressure (appropriate for the age group <70 mmHg for ages 1 month – 1 year; <70 mmHg + (age x 2) for group 1 year–10 years, <90 mm Hg for 11–17 years) or a decrease of systolic blood pressure over 30% of the initial value in relation to the value usually observed for that patient;
- adults: lower systolic blood pressure <90 mmHg or a decrease in systolic blood pressure over 30% of the initial value in relation to the value usually observed for that patient. The frequency of specific signs of anaphylaxis is shown in Table 1.

Symptoms suggesting anaphylaxis must be differentiated from other diseases of individual organs and systems [2]:

- skin and mucous membranes: chronic, transient physical urticaria; oral allergy syndrome,
- respiratory system: acute laryngitis and tracheitis; airway obstruction (foreign body, failure of the vocal cords),
- asthma attack (asymptomatic from other systems and organs),

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