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Anaphylaxis biomarkers: present and future

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Key words

Biomarkers; anaphylaxis; allergy; predictors; tryptase.

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Summary

Anaphylaxis is a severe, rapidly developing, and life-threatening systemic hypersensitivity reaction. The diagnosis of anaphylaxis is primarily clinical. Numerous studies on the mechanisms and the biomarkers of the disease are initiated every year. The biomarkers of anaphylaxis may become an important tool for the diagnosis, prevention, repeated risk assessment, severity stratification, and new therapeutic strategies for treatment of the disease. Various immune and non-immune mediators produced and released by effector cell populations are currently considered as biomarkers of anaphylaxis. Here, we review the current data on potential biomarkers of anaphylaxis and the possibilities and perspectives for their use in future clinical practice.

Impact statement

Specific, nonspecific and genetic biomarkers of anaphylaxis have been characterized. In addition to tryptase and sIgE, promising and practically applicable new biomarkers of AF are chymase, carboxypeptidase A3, CCL2 and basogranulin. Genetic biomarkers can predict AF severity and identify high-risk patients.

Introduction

Anaphylaxis (AF) is a severe, rapidly developing, and life-threatening systemic hypersensitivity reaction (1-3). The diagnosis of AF continues to be primarily clinical and is verified by one or more clinical systemic criteria of AF (1-3). The search for AF biomarkers remains one of the most relevant research areas in the AF field, since these biomarkers may reflect the pathogenetic mechanism of AF, allow to confirm the diagnosis of AF, evaluate the need for epinephrine injection, and predict the risk of AF development, severe course, and fatal outcome (4-7).

AF poses several features for the search for biomarkers and their practical use. The involvement of body systems (respiratory, cardiovascular system, gastrointestinal tract, skin, central nervous system) in the AF varies significantly, and symptoms can range widely. For example, skin lesions may be absent or delayed, be first sign of the AF, vary from moderate erythema to giant urticaria and life-threatening angioedema. The existing diagnostic criteria for AF are not always unambiguous, especially for mild and moderate disease, complicating the timely identification of this group of patients. A patient with AF may have a varying pattern of symptoms and threshold level of trigger exposure, exposure to cofactors, *etc*. When provoked by the same trigger in the same patient, the symptoms may also vary. The concentration of potential biomarkers in the body fluids varies depending on the stage of AF, the profile and rapidity of the development

of the symptoms (first minutes or hours after contact with the allergen or delayed reactions), the exposure to the trigger, and many other factors. This leads to obvious problems in standardizing the conditions for obtaining the biological material and interpreting the test results in wide clinical practice. In addition, the busy emergency environment limits the scope of a diagnostic workout. It is extremely difficult to find a universal and practically applicable AF biomarker. Given the various underlying mechanisms of the AF, measuring only one biomarker may not be sufficient to verify the diagnosis.

Biomarker is defined primarily as the quantitative data of physical exam and/or laboratory parameters with the defined "normal" and "pathologic" limits (8). The optimal biomarker should be highly specific, sensitive, predictive, fast, easy to use, affordable, and as non-invasive as possible. Many cell populations participate in the development of AF, with the largest role of mast cells and basophils: though other cell populations may dominate in various endotypes of AF. AF biomarkers include specific immunoglobulins of class E (sIgE), key actors in the development of immune IgE-mediated AF, and several nonspecific biomarkers (histamine, lipid mediators of inflammation, chemokines and cytokines, proteases, *etc*.), produced and released by various populations of effector cells and involved in the pathogenesis of immune and non-immune systemic reactions. In addition, genetic AF biomarkers have several advantages and a high potential to group patients with a high risk of AF and its severe course, and are currently being actively studied and identified.

Materials and methods

To discern anaphylaxis biomarker studies for this review, we conducted a literature search in August 2023 using PubMed, Scopus, eLIBRARY databases. The keywords used in the search were: anaphylaxis biomarkers, biomarkers of anaphylaxis severity, plasma/serum anaphylaxis biomarker, genetic anaphylaxis biomarkers, histamine in anaphylaxis, tryptase in anaphylaxis, carboxypeptidase in anaphylaxis, neutrophil anaphylaxis biomarkers, platelet activation factor in anaphylaxis, angiotensin converting enzyme in anaphylaxis, heparin in anaphylaxis, cytokines in anaphylaxis, mastocytosis in anaphylaxis. Based on the search more than 6,000 articles were retrieved. Articles with the following characteristics were selected for final analysis: original research investigating specifically the contribution of various biomarkers to the pathogenesis of AF and its severity for the period 1990-2023; studies conducted using cell cultures, animal models, or human subjects. Articles with the following characteristics were rejected: articles not relevant to the study of the role of various biomarkers in the pathogenesis of AF and its severity, period up to 1990, conference abstracts, letters or commentary, editorial and opinion articles lacking original data; articles written in a language other than English or Russian. The search was executed by two authors (AP and NE), using both databases and the keywords listed. The inclusion of an article was based on consensus by both authors. If no consensus could be obtained, the opinions of other authors were sought after (EF and SZ) to determine the outcome of the article. Based on the search and selection process, 58 studies on various anaphylaxis biomarkers were final selected and analyzed for this review.

Results and discussion

Specific class E immunoglobulins

The mechanism of IgE-mediated AF is based on a typical allergic immediate-type reaction caused by the interaction of sIgE antibodies with relevant allergens. Serum sIgE testing in suspected AF to identify possible clinically significant sensitization and the trigger of systemic reaction is an important and integral stage of allergic examination. Specific IgE level is evaluated against allergen sources (*i.e*., walnut, cashew, egg white, egg yolk, *etc*.) and/or molecular components (preferably recombinant ones). The listed tests are useful mostly in diagnosing food AF, and also in drug, insect, and other types of AF (food-dependent exercise-induced, idiopathic) (4, 9, 10). sIgE to the relevant allergen is found in almost all children with food AF induced by a specific food product. We observed only a few patients with food AF with reference level of specific IgE to the relevant allergen, but as a rule, over time, the level of specific IgE is determined above normal. The concentration of the biomarker in children with AF varies significantly and does not always correlate with the severity of the reactions (11, 12). The high sensitization (> 100 kU/L) to fish/seafood was associated with inhalation hypersensitivity to the allergen and determined the elimination measures (excluding being in a room where fish/seafood is fried, boiled, or butchered) to prevent repeated AF in this group of patients (12, 13). Specific IgE for molecular components of the allergen are relevant for identifying high-risk patients for the development of systemic (including cross, and severe) reactions or tolerance to the allergen. High sensitization to milk casein (Bos d 8) (17), to egg white ovomucoid (Gal d1) (18) and sensitivity to recombinant peanut allergens (Aga h1, Aga h2, Aha h3, Aha h6, Aha h9) (19, 21) are predictors of severe and systemic reactions, as well as markers of a long period of development of tolerance or its absence. Garib *et al*. found sIgE to at least one casein, especially to α-casein, in all children with severe (grade 4-5) AF caused by cow milk proteins. In patients with less severe AF (grade 1-3), only 12 out of 21 patients were found to have sIgE to caseins (21). Sensitization to omega-5-gliadin is specific in wheat-dependent physically induced AF, it was found in 80-90% of the patients, whereas sIgE to wheat flour extract was found only in 20-30% of the patients (4). Sensitization to nonspecific lipid transporter proteins (nLTPs) of different plant food allergens (*e.g*., peach (Pru p3), apple (Mal d 3) and apricot

(Pru ar 3), *etc*.) may determine not only a high cross-allergy between different plant species, but due to the physicochemical properties of the allergen (resistance to heating and hydrolysis) a higher risk of systemic reactions. In patients with a history of AF, a significant decrease in sIgE to a causally significant food allergen and its specific components allows introducing the product by conducting a provocative test.

Specific IgE are undoubtedly the key biomarkers of IgE-mediated AF. They are used for differential diagnostics, diagnostics, identification of the trigger of a systemic reaction, determination of the overall risk and severity of AF, prognosis of the tolerance development to the allergen, and evaluation of the possibility of introducing of causally significant product into the patient's diet/life. However, various questions remain about the relationship between IgE-mediated sensitization and AF. It is not known why AF develops only in some patients sensitized to a particular allergen, what is the reason for the poor correlation of sIgE concentration with the severity of the systemic reaction, *etc*. These and other clinically significant observations highlight the role of not only sIgE but also of other factors in the development of AF.

Non-specific biomarkers for diagnosis and evaluation of severity of anaphylaxis

Nonspecific AF markers are released by the effector cells (mast cells, basophils, macrophages, neutrophils, *etc*.) during the acute systemic reaction (**table I**). The mediators have different clinical significance (diagnostic value, stratification of the severity, risk of AF, and response to therapy), half-elimination from the body, features of collecting biomaterial for analysis and subsequent interpretation of the results, significantly affecting their use in real clinical practice.

Tryptase is a neutral serine protease contained in the secretory granules of mast cells. Tryptase is produced mainly by mast cells, being a key plasma biomarker of their activation, including the activation during acute AF; basophils can also release tryptase, but in much smaller quantities. Two main isoforms of tryptase are described, α and β. The first one (α-tryptase) is released constantly and increases with an increase in the number of mast cells, as in mastocytosis. Mast cells activation (degranulation) upon AF releases β-tryptase (6). The mast cells of various organs contain a different amount of tryptase, which can determine the dependence of the severity of an acute reaction on the allergen entry route. Commercial tests are available to determine total tryptase (α/β-tryptase), which allows us to evaluate this biomarker in clinical practice. The method of measuring serum tryptase is stable, reliable, and easy, but limited by the timing of biomaterial obtainment. The basal serum tryptase level in healthy people ranges from 1 to 11 ng/ml (ImmunoCAP).

From the first minutes of the AF development, the serum tryptase increases sharply, peaking within 60-90 minutes, followed by a steady decline and disappearance within a few hours (5). If AF is suspected, guidelines recommend blood sampling for the tryptase determination twice: first, in the first 15 minutes to 3 hours after the onset of the first AF symptoms, and second, 24 hours or more after the AF symptoms disappearance to determine the basal level of the marker (1, 2). Measuring the basal level of tryptase outside an acute AF is especially relevant for patients with the tryptase within the reference values, even during the acute systemic reaction. When the tryptase level exceeds the values obtained using the formula *1.2 × baseline + 2 ng/ml*, it can be diagnostically significant for AF (1, 2).

Studies showed the clinical significance of tryptase in AF for diagnosis, evaluation of the risk of development, and stratification

Table I *- Characteristics of nonspecific anaphylaxis biomarkers.*

Biomarker of acute AF	Characteristic	The period of detection from the AF onset / peak time
Tryptase in plasma/serum (1*, 2*, 5, 22-28)	Stable, highly specific for type 1 hypersensitivity. It is used in the diagnosis of AF, with the concentration positively correlating with the plasma/serum histamine and the severity of AF	15 min-3 h/0-90 min **The study of basal tryptase level outside the AF is recommended*
Histamine in plasma/serum (26, 27, 32, 33)	High specificity for type 1 hypersensitivity, correlation with the plasma/serum tryptase and AF severity	5-30 min/5-15 min
Urine histamine metabolites: N-methylhistamine, N-methylimidazole acetate (26, 28, 33)	High correlation with the plasma/serum histamine, correlation with AF severity	Within 24 hours or more/unknown
Chymase in plasma/serum (34, 35, 36)	Potentially stable, may correlate with the plasma/serum tryptase	Within 24 hours or more/unknown
Carboxypeptidase A3 in plasma/serum/saliva (37, 38)	It is found in serum and saliva; limited data on an increase in plasma/serum despite the normal tryptase level	Within 8 hours or more/unknown

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Biomarker of acute AF	Characteristic	The period of detection from the AF onset / peak time
The major factor of basophil chemotaxis (CCL2) in plasma/serum (39, 40)	May correlate with the AF severity	Within 2 hours/unknown
Neutrophil myeloperoxidase in plasma/serum (41, 42)	Correlates positively with the AF severity	Within 5 hours/unknown
Platelet activation factor (PAF) in plasma/serum (44, 45, 46)	Correlates with the AF severity	3-15 minutes/less than 5 minutes
Platelet Activation Factor-acetyl hydrolase (PAF-AH) in plasma/serum (44, 45, 46)	The concentration of the marker correlates negatively with the severity of AF	Unknown
Angiotensin Converting Enzyme (ACE) (47, 48, 49)	The concentration of the marker correlates negatively with the severity of AF	Unknown
Dipeptidyl Peptidase 1 (DPP1) in plasma/serum (36, 50)	Data are limited, a potential role in the chymase activation	Unknown
Basogranulin in plasma/serum (51)	Data is limited. A unique secretory marker of basophils	Presumably 5-30 min, similar to histamine/unknown
Heparin in plasma/serum (28, 52)	Data is limited. Potential correlation with the AF severity	Unknown
Leukotriene E4 (LTE4) in urine (53)	Data is limited	Unknown
11-beta-prostaglandin F2-alpha in urine (54)	Data is limited	Unknown
Plasma/serum cytokines: interleukins (IL-2, IL-4, IL-5, IL-6, IL-10, IL-13), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) (26)	Data is limited. Potential correlation with the AF severity	Within 10 hours/unknown (for some cytokines, 100 minutes)

of the severity; however, the tryptase level depends on several factors (trigger, age of the patient, symptoms). Tryptase increases most often in the insect and medicinal AF, while in the food AF the biomarker in question is less representative and often remains normal, even if blood is sampled at the optimal time. In the perioperative AF in children, the high concentration of blood tryptase is observed in more than half of patients (22, 23); in the drug-caused AF, an increase may be more significant and prolonged (24). Ruëff *et al*. found an increased risk of AF developing during allergen-specific immunotherapy (ASIT) in patients with insect allergy and high basal tryptase (25). Serum tryptase levels positively correlate with histamine concentration, AF severity, severe hypotension, and skin symptoms (erythema and urticaria) (24, 26). In some acute AF patients, the lack of tryptase increase combined with a histamine increase may show the predominant involvement of basophils in the development of a systemic reaction (27). When interpreting the tryptase level, it is important to consider the normal or slightly elevated concentration in 36-40% of acute AF cases, which does not exclude this diagnosis (26, 28). In young children, the basal level of tryptase is elevated initially and reaches the adult norm only by 9-12 months (29), tends to increase with age (30); some data show it is higher in men than in women (31). Tryptase may increase in patients with an acute isolated skin allergic reaction, chronic urticaria, mastocytosis, primary activation syndrome of mast cells, including α-tryptasemia, idiopathic activation syndrome of mast cells and several other conditions not related to AF (oncohematological diseases, helminthiasis, eosinophilic gastrointestinal diseases, chronic renal failure, myocardial infarction) (24).

Tryptase is a recognized factor in pathogenesis, accessible, and routinely used diagnostic biomarker of AF, with a certain predicting ability regarding the severity and risk of AF development. It's challenging to use the marker because of its low sensitivity and blood sampling restrictions.

Histamine is the next important mediator of IgE-mediated allergic reactions, released from granules of mast cells and basophils. Histamine effects most AF symptoms (edema, hyperemia, urticaria, itching, *etc*.) and correlates with the severity of AF (26), but the role of plasma histamine and/or its urine metabolites (N-methylhistamine and N-methylimidazole acetate) as biomarkers of AF remains questionable. Upon the development of AF, the plasma histamine peaks 5 minutes after exposure to the allergen and returns to basal values after 15-30 minutes (32). Therefore, the use of histamine as a nonspecific marker of AF is possible only when collecting blood samples within the first 15 minutes from the start of the reaction, which is extremely difficult. Histamine disappears rapidly from the plasma via methylation by N-methyltransferase to form N-methylhistamine, deaminated by diamine oxidase into N-methylimidazole acetate. The resulting metabolites are stable and can be detected in the urine for 24 hours or more from the onset of AF symp-

toms; some data show their correlation with its severity (28). Commercial kits are available for the study of urine histamine metabolites, however, the use of those kits is not popular. The normal level of these markers does not exclude the diagnosis of AF, and false positive test results are possible, associated with the consumption of histamine-liberators or with systemic mastocytosis (33).

Chymase is a relatively new and still poorly studied biomarker of AF. Chymase is a serine protease found in the secretory granules of mast cells. This marker is quite stable in blood serum and was detected in 8 cases of fatal AF at autopsy; its concentration correlated with the serum tryptase (34). In a similar work, Osawa *et al*. identified chymase in lung mast cells during autopsy of 3 fatal AF cases; the control autopsy cells without AF had no chymase (35). The serum chymase in the patients with food, drug, and insect-caused AF increased compared to control within 8 hours of the first AF symptoms and remained high for at least 24 hours (36).

Carboxypeptidase A3 is a potential mediator of AF released by activated mast cells. Brown *et al*. analyzed the levels of carboxypeptidase A3 in the blood and saliva of 33 patients with suspected drug allergy undergoing provocative tests (37). Baseline basal serum and saliva levels of carboxypeptidase A3 were higher in the patients with positive provocative tests and a history of severe allergic reactions with cardiovascular and/or respiratory symptoms. When analyzing this marker directly at the moment of provocation, its level increased only in the saliva of patients with a positive test. Zhou *et al*. found high levels of carboxypeptidase A3 in plasma/serum samples of patients collected within 8 hours after the onset of a systemic allergic reaction; 70% of these patients had normal tryptase concentration (38). The stability of carboxypeptidase A3, the ability to test it over a wide time range, and the noninvasiveness of testing it in saliva make it a good candidate for further study.

Besides mast cell mediators, C-C motif chemokine ligand 2 (CCL2), the major factor of basophil chemotaxis attracting basophils to the focus of inflammation after exposure to an allergen, is promising. Korosec *et al*. studied the potential of CCL-2 as an AF biomarker in blood samples taken directly during the AF episode, 7, and 30 days after the systemic reaction (39). The study showed the significantly lower absolute number of circulating basophils in the acute AF compared to the non-reaction period. CCL-2 was significantly higher in the acute AF compared with samples taken outside the reaction, with the decrease of CCL-2 to baseline within 2 hours after the onset of AF symptoms. The test had 94% and 96% sensitivity and specificity, respectively. A similar study showed not only a serum CCL-2 increase in the acute systemic reactions, but also its significant positive correlation with their severity (40).

The role of neutrophils in the development of AF has been shown to be activated in the early stages of the reaction, independent of mast cell activation. The main enzyme stored in neutrophils is myeloperoxidase, the level of which in the blood increases at the time of development of clinical symptoms of AF and may correlate with its severity. Francis *et al*. reported that this enzyme was 2.9-5 times higher in patients with severe and moderate AF compared to healthy controls, it remained stable during the first 5 h after the onset of symptoms (41). In an experimental model of AF, an increase in myeloperoxidase levels is detectable 2 minutes after exposure to the trigger (42). There are also reports of increased neutrophil elastase values in the development of drug-induced AF during angiography with ioxaglate (43).

Lipid mediators are synthesized and released from effector cells upon their activation, including that in AF. The role of platelet activation factor (PAF), eicosanoids, and sphingosine-1-phosphate in the AF development has now been proven. Several studies showed a key role of PAF and its cleavage enzyme, platelet activation factor-acetylhydrolase (PAF-AH), in the pathogenesis of AF. PAF is a pro-inflammatory phospholipid synthesized and secreted by mast cells, monocytes, and tissue macrophages. PAF determine the cardiovascular symptoms of AF (hypovolemia, increased vascular permeability, myocardial dysfunction, *etc*.). Series of studies demonstrated high serum PAF and low PAF-AH in an anaphylactic attack, correlating with the severity of AF (44-46) better than tryptase and histamine. Basal PAF-AH in patients with insect-induced AF (outside acute reaction) showed similar results. An important disadvantage of PAF is the extremely short period of life (3-15 minutes) from the AF symptoms development, precluding its clinical use.

Angiotensin converting enzyme (ACE) showed the protective role in the development of life-threatening edema in AF (47, 48). Summers *et al*. noted significantly lowered basal serum ACE in patients with a history of severe swelling of the pharynx and larynx upon the development of acute allergic reactions to food allergens, relative to patients with no such history (49). The relative risk of severe, life-threatening edema of the pharynx and larynx was increased 10-fold upon the decrease in serum ACE concentration in these patients.

Dipeptidyl peptidase 1 (DPP1) is a less studied marker of the acute AF, the level of this peptidase positively correlates with the chymase level, since this enzyme is supposed to activate the chymase (36, 50). Basogranulin, a functionally similar protein of basophil granules, is actively studied as an alternative to histamine serum marker of AF (51). The pathogenesis of anaphylactic reaction involves endothelial cells and various ways of heparin release, activating the complement system (the formation of anaphylatoxins C3a and C5a) and factor XII, the proteolysis of kininogen, and the release of nitric oxide (NO) and bradykinin; the complement activation and the bradykinin level correlate with the severity of AF (28, 52). Urine leukotriene E4 (LTE4) and 11-beta-prostaglandin F2-alpha are of potential significance

in AF (53). The plasma level of several inflammatory mediators, such as IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), may increase in AF and correlate with its severity, but their sensitivity and specificity as biomarkers has not yet been established (26). Some data show the negative correlation of several cytokines, such as transforming growth factor-β (TGF-β), IFN-γ, and apolipoprotein B (apoB), with the severity of food-caused AF in the pediatric population (54).

Genetic biomarkers of risk and severity of anaphylaxis

Most of the nonspecific acute AF biomarkers described above have significant disadvantages of only relative stability and a limited time frame for biomaterial collecting, which complicates their application and interpretation. Potential genetic biomarkers of AF are sufficiently stable, not time-limited, and valuable outside the acute AF. Therefore, they are potentially useful for the prevention of systemic reactions and the selection of groups of patients with a high risk of severe AF (**table II**). In particular, mutations of the *C-KIT* gene regulating mast cell function were associated not only with mastocytosis but also with idiopathic AF (55). Replication of the *TPSAB1* gene encoding α-tryptase is associated not only with hereditary α-tryptasemia, characterized by an increase in basal tryptase levels, but also with the severity of hymenoptera venom-induced AF (56). Górska *et al*. identified a link between increased tumor necrosis factor receptor-associated factor 4 (*TRAF-4*) gene expression in blood with the development of food-caused AF in patients with mastocytosis (57). Some studies demonstrated the connection of AF with changes in the functioning of genes encoding interleukins, which are crucial in regulating the balance of Th1/Th2 cellular response. Single nucleotide polymorphisms of genes encoding IL4 and IL-10 were detected in patients with AF to penicillin (58, 59). We found a significant decrease in the expression of the platelet activation factor acetylhydrolase gene (*PLA2G7*) in blood of children with food AF (outside the acute episode) compared to the control group without AF (60). The AF severity correlated negatively with the expression of the gene under study, which decreased significantly with the development of AF in patients with a history of cardiovascular symptoms (drop in blood pressure, pronounced tachycardia/bradycardia). We have also obtained interesting data on the angiotensin converting enzyme (*ACE*) gene expression in blood (60). In AF patients, the expression was significantly higher in those with a history of mild, localized, or no edema, compared with those with life-threatening edema of the tongue and soft tissues of the oropharynx.

Signal transducer and activator of transcription 6 (STAT6) is a transcription factor playing a central role in the pathophysiology of allergic inflammation. Sharma *et al*. report rare monoallelic variants of STAT6 in 16 patients suffering from severe and therapy-resistant allergy, with a history of AF in 9 of them (61). Functional studies have established a phenotype with stable phosphorylation of STAT6, increased expression of the target gene STAT6, and a bias towards the Th2 response. According to the authors, the identification of these STAT6 variants should be regarded as a new autosomal dominant allergic disorder.

Recently, anecdotal reports described the role of microRNAs in the molecular mechanisms of AF in humans. MicroRNAs are small non-coding RNAs that regulate gene expression, usually by suppressing transcription. Rodriguez Del Rio *et al*. found in 2021 an increase of several serum micro-RNAs (miR-21-3p and miR-487b-3p) in children upon the development of food AF. The authors proposed its potential in the diagnosis of AF (62). In 2022, Francuzik *et al*. identified hsa-miR-451a in patients with a history of anaphylaxis (63). However, the need to evaluate these markers in dynamics and methodological features of the study (multidirectional changes in tryptase concentration, different triggers, small sample size, *etc*.) show the role of Micro-RNA in the pathogenesis of AF rather than its significance as an objective biomarker of AF.

Table II - *Characteristics of genetic anaphylaxis biomarkers.*

Biomarker	Characteristic
Polymorphism of the *C-KIT* gene (55)	Polymorphism of the gene was detected in mastocytosis and idiopathic AF
Replication of the *TPSAB1* gene (56)	Replication of the *TPSAB1* gene detected in hereditary α-tryptasemia is associated with the severity of hymenoptera venom-induced AF
Expression of the tumor necrosis factor receptor-associated factor 4 (TRAF-4) gene in blood (57)	Increased gene expression is associated with the development of food-caused AF in mastocytosis
Polymorphisms of IL-4 and IL-10 genes (58, 59)	Polymorphism of the gene was detected with drug AF to penicillin
Expression of platelet-activating factor acetylhydrolase (*PLA2G7*) gene in blood (60)	Basal gene expression (outside acute reaction) negatively correlates with the severity of AF
Expression of the angiotensin converting enzyme (*ACE*) gene in blood (60)	The basal gene expression (outside acute reaction) negatively correlates with the frequency of severe AF symptoms

Conclusions

Many studies show that anaphylactic reactions involve a complex and diverse range of immune cells and mediators. The search for new biomarkers of anaphylaxis (AF) is important for verification of diagnosis, its prevention, evaluation of the risk of recurrence and of life-threatening/lethal systemic reactions, stratification of severity, and treatment of AF.

Tryptase is the most useful biomarker for identifying an acute allergic reaction. Measuring sIgE levels to the suspected trigger can help identify high-risk groups for cross- and severe reactions and help with elimination measures. Chymase, carboxypeptidase A3, CCL2, and basogranulin alternative to histamine are the promising new biomarkers for the diagnosis of acute AF, due to their rather long-lasting life span. Further research should show that genetic biomarkers can predict the severity of AF and identify high-risk individuals before AF develops.

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Contributions

AP: conceptualization, writing – original draft, funding aquisition. AP, NE, EF, SZ: writing – review & editing. AP, SZ: supervision.

Conflict of interests

The authors declare that they have no conflict of interests.

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