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Review article

Post-mortem diagnosis of anaphylaxis: A difficult task in forensic medicine

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ABSTRACT

The lack of reliable laboratory biomarkers and common standard definitions of signs and symptoms represents the main problem for clinicians when a suspected anaphylactic event must be diagnosed, while a post-mortem diagnosis of anaphylaxis is often a very difficult task in forensic medicine.

Significant necroscopic signs as well as the data reported from witnesses or medical records may be absent, biological fluids as blood or urine may be unavailable or under thanatological modifications.

The aim of this review is to focus on the diagnostic difficulties with which coroners and forensic pathologists have to cope when a confirmation of anaphylactic death is required by judicial authorities.

Investigation methods for a prudent forensic diagnosis of anaphylactic death as well as the need of new potential laboratory or histological investigation techniques coming from immunological research are discussed too.

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Anaphylaxis is a severe systemic reaction, which is due to immunoglobulin E (IgE)-mediated release of vasoactive and inflammatory mediators from mast cells and basophils, and occurs after contact with a specific allergenic antigen in previously sensitised subjects. The actual incidence of anaphylaxis ranges from 10 to 20/100,000 people per year [1–4].

Cardiovascular and respiratory effects of extreme forms of anaphylaxis cause death with an incidence of approximately 154 annual fatal episodes per million hospitalised subjects [5].

Lenler-Petersen et al. estimated that a drug-induced fatal anaphylactic shock involves yearly 0.3 cases per million inhabitants and occurs after administration of antibiotics, non-steroidal anti-inflammatory drugs, anaesthetics, contrast reagents and extracts of allergen [6].

Antibiotics, especially the β -lactam ones, are alleged to cause 500–1000 fatal anaphylactic episodes in the United States each year [7].

Anaphylaxis due to anaesthetics occurs in one out of every 3500–25,000 general anaesthetic administrations, with a mortality rate of 6% for all cases of anaesthesia-related anaphylaxis. Muscle relaxants are the most common drugs involved in anaphylaxis during anaesthesia, causing 60–70% of reactions, followed by latex (16.7%), colloids (4.0%), hypnotics (3.4%), opioids (1.3%) or other agents (chymopapain, propacetamol, protamine, methylene blue, ethylene oxide, 1.3%) [8,9].

Latex anaphylactic fatal episodes were reported by the Food and Drug Administration with an incidence of three cases per year involving patients under surgical or medical procedures, health-care workers or general population [10].

About 100 fatalities from food-induced anaphylaxis occur each year in the United States population [11].

Food-induced anaphylaxis is attributable to any food, but peanuts, tree nuts and seafood are frequently involved in these allergic reactions [11].

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Venoms from insects' stings cause at least 50 fatalities annually in the United States population [12].

Fatalities from allergen immunotherapy occur in approximately 1 per 2 million injections based on 33 million administered doses, while fatal reactions to skin testing are rare [13].

All the above epidemiological data suggest the social and clinical relevance of anaphylaxis worldwide. Although anaphylaxis was first described by Portier and Richet, who provoked systemic reactions after attempting to immunise dogs against jellyfish stings using sea anemone extract in the early 1900s, there are still several difficulties in achieving common standard definitions, diagnostic procedures and therapy protocols [14,15].

These problems are due to the enigmatic and variable presentation of the syndrome, to the lack of universal clinical-diagnostic coding criteria used by researchers and clinicians and to a partial knowledge of anaphylactic basic pathophysiology (mediators' effects and interactions between various cell types involved) [15].

Common clinical criteria are currently being improved and new additional biomarkers researched to identify, treat and prevent anaphylactic events. Updated landmarks from scientific societies advise the following diagnostic steps:

- (1) Evaluation of the allergenic history (antecedent atopic or anaphylactic events to known, suspected or unidentified allergens).
- (2) Application of clinical diagnostic criteria as these from US National Institute of Allergy and Infectious Disease (NIAID) and US Food Allergy and Anaphylaxis Network (FAAN), reporting that each one of the following three criteria must be fulfilled over minutes or several hours from the beginning of the crisis:
 - (a) acute onset of an illness involving skin or mucosal tissue or both and including respiratory symptoms or low systolic blood pressure or both;
 - (b) two or more symptoms arising at skin–mucosal, respiratory, emodynamic, gastrointestinal districts after exposure to a likely allergen; and
 - (c) low systolic blood pressure higher than 30% from the person's baseline after exposure to a known allergen.
- (3) Laboratory investigations: total and specific IgE serum levels (radioallergosorbent test–enzyme linked immunosorbent assay (RAST–ELISA procedures), mast cells released factors (tryptase and chymase serum levels, *N*-methylhistamine urinary levels), basophil activation markers CD63–CD203c (flow cytometry procedures), complement system activation markers (C3a–C4a–C5a), eosinophil activation markers (eosinophil cationic protein).
- (4) Allergen skin tests (the procedure is considered safe 3 or 4 weeks after the anaphylactic event) [4,15–17].

An adequate diagnosis and treatment as well as the prevention of anaphylaxis are the main purposes of allergists, intensivists, pulmonologists and internal medicine physicians, while a post-mortem diagnosis of anaphylaxis is a difficult task for forensic medicine investigations to explain the causes of death.

Unlike clinical purposes, a post-mortem diagnosis of anaphylaxis turns out to be very difficult when medico-legal investigations are required by judicial authorities. Coroners and forensic pathologists are well conscious that a post-mortem diagnosis of anaphylaxis hides more problems and technical difficulties than a clinical investigation on an alive atopic patient does.

Medico-legal investigations on a suspected anaphylactic death should be essentially focussed on a scrupulous perusal of the scene and the clinical history, followed by the evaluation of necroscopic and laboratory data [19–22].

1. Scene investigation

Sometimes death occurs at home, at working places, open green spaces (fields, farms) inhabited by numerous insects or other sites, without medical intervention or witnesses. The subject may have ingested foods or drugs or inhaled chemical substances or self-injected drugs. Everything suspected as responsible for allergenic interaction, when found at the scene or near the corpse, must be sampled and analysed. The objects at the scene or near the corpse as well as the subject's clothes must be observed carefully. Subjects wearing bright coloured clothes and using intense perfumes may attract insects more easily. All biological or inorganic stains and tracks must be observed and sampled. Parents, relatives or other witnesses must always be interviewed. The place, month and season at the time of death must be taken into account and compared with the pollens calendar of the local geographical latitude. The presence of animals such as cats, dogs, horses or insects as hymenoptera (one or more insects alive or died) at the scene must be taken into account too.

Special attention should be paid when the scene investigations involve the corpse of a beekeeper. Sometimes death occurs outside a hospital or during an emergency medical transport or at hospital admission. At other times, death occurs inside a hospital during medical or surgery elective procedures or under drug administration. All medical or nursing records available on clinical conditions and therapeutic procedures must be examined. Doctors, nursing operators or other witnesses must be interviewed.

2. Medical history investigation

All the available medical data, written on medical documents or reported by parents, relatives or witnesses on past or recent atopic problems of the subject, must be evaluated, so that each diagnosed or suggested atopic reaction to drugs, foods, insects or others could be investigated. Signs and symptoms, involving cutaneous, cardio-respiratory, gastrointestinal districts or others, written on medical documents or reported by people present at the death, must be carefully evaluated.

Authors reported the frequency of signs and symptoms dealing with a possible anaphylactic event and related to the cutaneous, respiratory, cardiovascular and gastrointestinal districts: urticaria–angio-oedema (88%), upper airways oedema (56%), dyspnoea and wheezing (47%), flush (46%), dizziness, syncope, severe hypotension, shock (33%), nausea, vomiting, diarrhoea, cramping abdominal pain (30%), rhinitis (16%), headache (15%) and pruritus without rash (4.5%) [21,22].

Some of the above signs and symptoms, such as the respiratory ones, may be compatible with specific autopsy findings [21,22].

During the phase of medical history investigations, it is very important that forensic pathologists interact with clinicians or allergist consultants to improve the interpretation of all the collected data.

When a subject, known as atopic, dies in a hospital department or outside a hospital, all medical records must be carefully examined to clarify whether the anti-allergic therapy has been prescribed and assumed correctly. The same attention should be applied in case of death during immunotherapy in atopic subjects. All these evaluations are necessary to support the allergic profile of the subject and also to exclude the eventuality of medical malpractice. All medical emergency or resuscitation procedures applied during the crisis must be evaluated to exclude the eventuality of medical malpractice too.

3. Necroscopic investigation

When anaphylaxis causes death due to serious cardio-respiratory complications such as asphyxia or shock within some minutes after the beginning of the reaction, there may not be sufficient time for specific necroscopical features to appear. Pumphrey et al. reported that significant features suggesting anaphylactic deaths, due to food or venom or drug allergy, are generally present at autopsy only in 59% of cases [20].

The most common detectable findings at autopsy seem to be the respiratory ones. As described by Pumphrey et al., pharyngeal and laryngeal oedema are detectable at autopsy in 49% and 8% of cases [20].

Upper airways oedema is generally detectable in 77% of cases of food anaphylaxis, 40% of venom anaphylaxis and 30% of drug anaphylaxis [20].

Pulmonary congestion and oedema are detectable in 73% of cases, while lung hyperinflation and mucous plugging of bronchial airways, suggesting a respiratory failure due to asthmatic crisis, are detectable in 26% of cases [20].

Respiratory macroscopic and histological investigations may differentiate:

- (1) Swelling of the upper airway lining, laryngeal oedema with total or near-total obstruction of the larynx, vascular laryngeal mucosal congestion, pronounced laryngeal mucosal eosinophilia, no epithelial sloughing and mucous plugging at bronchial mucosae in cases of anaphylaxis with laryngeal occlusion.
- (2) No swelling of the upper airway lining, no laryngeal oedema with total or near-total obstruction of the larynx, vascular bronchial mucosal congestion, pronounced bronchial mucosal eosinophilia, epithelial sloughing and mucous plugging at bronchial mucosae in cases of anaphylactic fatal asthma with significant blood IgE levels.
- (3) Specific signs as bronchial remodelling, ectasia of bronchial gland ducts, Curschmann spirals and Charcot-Leyden crystals in cases of fatal idiopathic asthma without significant blood IgE levels [18].

Eosinophilia is often present at lung, heart and parenchymal tissues after an anaphylactic shock. Mast cells are also detectable at the bronchial mucosae, lung, heart and parenchymal tissues after an anaphylactic shock [20]. Perskvist et al. reported that three significant groups of mast cells are contemporarily present in lungs of anaphylactic death subjects: mast cells containing tryptase and chymase granules, mast cells containing tryptase granules and mast cells containing chymase granules. Only two significant groups of mast cells are contemporarily present in lungs of subjects who died after asthma, both related or unrelated to immune anaphylactic mechanisms: mast cells containing tryptase and chymase granules and mast cells containing tryptase granules [26]. The presence of petechial haemorrhage (periocular, periconjunctival and cardiac wall) in 17% of cases and of brain oedema in 26% of cases suggests an asphyxial mechanism of death too [20]. Cutaneous erythema or angio-oedema is present only in 5% of cases of anaphylactic deaths. Angio-oedema, as well as loss of intravascular fluids, is a typical consequence of peripheral vasodilatation and suggests that a shock occurred. On the other hand, hypoperfusion lesions of spleen, kidneys or other mesenteric districts are typical shock signs too [20–23]. Authors reported that within 10 min an amount of 50% of intravascular fluid may be shifted to the extravascular space when an anaphylactic shock occurs [24,25]. Ischaemic lesions may be found both in normal subjects or cardiological subjects due to myocardial hypoperfusion or release of coronary spasm

factors (histamine, leucotrienes and prostaglandins) after basophils and mast cells degranulation [16,20,32]. During necroscopic procedures, it could be useful to verify and sample all materials present inside the gastric or intestinal cavities in subjects with a suspected or known diagnosis of allergy to foods (i.e., vegetables or fish) or drugs. Samples of blood, bile and urine should be taken for identification, as should dosage drugs also [20]. When a systemic reaction is suspected or reported as due to hymenoptera or other insect stings, it could be useful to search for angio-oedema, erythema, pomphos, papulas or vesiculas on skin or mucosal surfaces and, if possible, the sting. When a sting is found, an entomologist consultant may support investigations and identify the type of insect responsible for the allergic reaction.

4. Laboratory investigation

The main laboratory procedures normally applied on live subjects after an allergic event are not extensively applicable to all died atopic subjects.

Unfortunately, the concentration and stability of many analytes may be modified under the effects of different thanatological processes, which may cause cytolysis and chemical degradation during the post-mortem period. Therefore, biochemical or immunological assays are not reliable when performed on blood or urinary fluids sampled post-mortem.

Despite the lack of exhaustive studies on the real post-mortem stability of IgE immunoglobulins, some authors consider the assay on total and specific IgE serum levels (RAST, ELISA procedures) as a reliable procedure applicable after death [27–29].

Yuginger et al. also suggested the use of the victim's serum containing IgE antibodies to identify allergens in uneaten portions of foods consumed shortly before the anaphylactic event [29].

The presence of medical history, reporting light general symptoms in the absence of significant IgE serum levels, should induce the diagnosis of an anaphylactoid event not only in clinical practice but also in forensic investigations. In cases of drug-induced anaphylactoid crisis, occurring in subjects with significant basic cardiovascular diseases, an initial blood hypotension, due to histamine degranulation from mast cells, may cause lethal cardio-respiratory failure (i.e., anaphylactoid crisis after vancomycin administration in cardiac surgery patients) [30,31].

Serum assays on neutral proteases, as well as mast cells tryptase or chymase, have been studied by authors who reported increased levels in subjects died after anaphylactic events (serum tryptase peaks 60–90 min after anaphylaxis, persisting for up to 5 h in live subjects), but it is well known that the beginning of post-mortem cytolytic processes induce artificial elevations of the values of these analytes [19,30,32,33,34,36].

The intensity and the speed of the cytolytic processes are different in each subject, essentially as a consequence of the time of death, the pre-mortem body temperature and post-mortem room temperature and the endogenous and exogenous bacterial flora of the corpse, so that it is impossible to establish any reference values on the above analytes' levels. Serum from blood samples obtained immediately pre-mortem, that is, during resuscitation procedures, could be useful for laboratory measurements, but blood samples obtained during the first hours after death should not be employed for the assay of neutral protease levels [19,30,32,34,36].

Moreover, increased levels of serum tryptase may occur in some events different from anaphylaxis, such as multiple trauma, asphyxia, myocardial infarction, heroine intoxication, systemic mastocytosis and hypereosinophilic parasitosis, so that any reliable diagnosis of an allergic event should not be based on tryptase measurement in such cases, both during the pre-mortem or post-mortem period [19,34,35].

As reported by Perskvist et al., the typisation of various groups of mast cells containing different amounts of neutral proteases, which allocate in tissues of organs such as the lung parenchyma, could be useful to diagnose an anaphylactic event, but, at the moment, no exhaustive studies are available on these procedures [26].

Urinary measurements of *N*-methylhistamine, the main metabolite of histamine whose half-life lasts 30 min, are useful in live subjects after an anaphylactic event, being detectable up to 24 h after the crisis with a significant peak within the first 3 h [37,38].

Similarly to serum tryptase, also urine *N*-methylhistamine measurements are not reliable after anaphylactic death, due to cytolytic and other different thanatological processes, while urinary samples obtained immediately pre-mortem or post-mortem could be useful for laboratory measurements too.

The same problems reported above involve other analytes, which are usually measured in alive atopic subjects, such as the complement system activation markers (C3a–C4a–C5a) and the eosinophil activation markers (eosinophil cationic protein) [19,38,40].

Flow cytometric procedures used to detect CD63–CD203c basophil anaphylaxis markers represent new analytic techniques recently in use to evaluate live atopic subjects but have not been tested after anaphylactic death yet. On the other hand, no data are currently available on the possible effects on the concentration and chemical stability of these markers, induced by the post-mortem cytolysis and thanatological processes. Future researches may further promote new knowledge on the reliability of the basophil anaphylaxis markers in subjects after fatal anaphylaxis [39,41,42].

To summarise, extensive knowledge related to all physiopathological pathways of anaphylaxis is still an unfinished process. A large number of mediators, such as histamine, neutral proteases, tumour necrosis factor, platelet-activating factor, prostaglandins, leucotrienes, interleukines, complement system and a large number of cells such as mast cells, basophils, eosinophils, monocytes, macrophages, lymphocytes, endothelial cells and antigen-presenting cells, are involved in different mechanisms, which are still completely unknown or perhaps some other mediators have not been identified yet.

Future researches improving the knowledge of the mechanisms of anaphylaxis will obviously improve the diagnostic procedures of this dangerous atopic event.

The development of new laboratory analytic techniques from research is a fundamental need for clinicians to improve both diagnosis and treatment of anaphylaxis, while the main expectation in forensic medicine is to achieve reliable diagnostic laboratory procedures, applicable during the post-mortem period to confirm the eventuality of an anaphylactic event responsible for the death of a subject. At present, the only laboratory assay applicable in forensic medicine is the measurement of serum IgE levels (RAST, ELISA procedures), which are considered as stable post-mortem analytes only in an insufficient number of studies, so that the use of this procedure must be applied with extreme caution.

Coroners and forensic pathologists are conscious that both laboratory or necroscopic investigations may sometimes be inconclusive and the only biomarkers available, although not completely reliable when obtained from post-mortem assays, are the serum IgE levels.

The actual lack of anaphylaxis reliable biomarkers produces great expectations for clinicians and forensic pathologists; most of all, they look forward to the discovery of new stable biomarkers, produced during the crisis and able to maintain their own concentration and chemical stability both in living and in died subjects for as long a period of time as possible. Research aimed at discovering these still unknown biomarkers should be encouraged.

Some interesting diagnostic procedures could be those reported by Perskvist et al. who investigated the morphological and chemical typisation of cells allocated in different tissue districts during the anaphylactic crisis [26].

Similar procedures could be very useful to verify the involvement of skin, mucosal districts (upper airways, bronchial and gastroenteric) and parenchymal districts (heart and splancnic) during the anaphylactic crisis. Research on these techniques should be encouraged too.

The forensic diagnosis of anaphylaxis-related death is, at the moment, a difficult multifactorial diagnosis influenced by the following factors:

- (1) Death due to anaphylaxis often occurs outside hospitals without medical observation or assistance, in the absence of medical records and available data on the atopic history of the subject or in the absence of witnesses.
- (2) Macro-microscopical external or internal signs of anaphylaxis may be minimal or absent or under thanatological modifications and the external examination or autopsy of the corpse may be delayed.
- (3) Biological fluids (blood and urine) may be unavailable for laboratory investigations, while chemical features of analytes may be modified due to cytolysis and thanatological processes.
- (4) The actual lack of reliable laboratory markers in use to diagnose an anaphylactic event is a basic problem in forensic medicine.
- (5) The immunological background and experience of a forensic pathologist may not be adequate to solve a diagnosis of anaphylactic death.

A correct medico-legal diagnosis of anaphylaxis-related death should be produced by a prudent comparison of all scene investigational-, clinical-, necroscopic- and laboratory-collected data and after the objective exclusion of other possible fatal causes different from anaphylaxis [20–22].

Clinicians should be also trained to draw and freeze blood and urine samples during resuscitation procedures or immediately post-mortem, in cases of suspected or diagnosed anaphylactic crisis, to obtain biological data before the beginning of the effects of post-mortem cytolysis and thanatological processes. Such an operative behaviour could be of great help for forensic pathologists.

Finally, the interaction of an expert immunologist or allergist consultant with the forensic team could be mandatory to improve and support the forensic diagnosis of an anaphylaxis-related death [18].

Conflict of interest

None declared.

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